REVIEW

Aging Cell WILEY

Thyroid hormones in diabetes, cancer, and aging

Benoit R. Gauthier[1,2] | Alejandro Sola-García[1] | María Ángeles Cáliz-Molina[1] |
Petra Isabel Lorenzo[1] | Nadia Cobo-Vuilleumier[1] | Vivian Capilla-González[1] |
Alejandro Martin-Montalvo[1]

[1]Department of Cell Therapy and Regeneration, Andalusian Center for Molecular Biology and Regenerative Medicine-CABIMER, Junta de Andalucía-University of Pablo de Olavide-University of Seville-CSIC, Seville, Spain

[2]Biomedical Research Network on Diabetes and Related Metabolic Diseases-CIBERDEM, Instituto de Salud Carlos III, Madrid, Spain

Correspondence
Alejandro Martin-Montalvo, Department of Cell Therapy and Regeneration, Andalusian Center for Molecular Biology and Regenerative Medicine-CABIMER, Junta de Andalucía-University of Pablo de Olavide-University of Seville-CSIC, Seville 41092, Spain.
Email: alejandro.martinmontalvo@cabimer.es

Summary

Thyroid function is central in the control of physiological and pathophysiological processes. Studies in animal models and human research have determined that thyroid hormones modulate cellular processes relevant for aging and for the majority of age-related diseases. While several studies have associated mild reductions on thyroid hormone function with exceptional longevity in animals and humans, alterations in thyroid hormones are serious medical conditions associated with unhealthy aging and premature death. Moreover, both hyperthyroidism and hypothyroidism have been associated with the development of certain types of diabetes and cancers, indicating a great complexity of the molecular mechanisms controlled by thyroid hormones. In this review, we describe the latest findings in thyroid hormone research in the field of aging, diabetes, and cancer, with a special focus on hepatocellular carcinomas. While aging studies indicate that the direct modulation of thyroid hormones is not a viable strategy to promote healthy aging or longevity and the development of thyromimetics is challenging due to inefficacy and potential toxicity, we argue that interventions based on the use of modulators of thyroid hormone function might provide therapeutic benefit in certain types of diabetes and cancers.

KEYWORDS
cancer, diabetes, health span, hyperthyroidism, hypothyroidism, life span, thyroid hormones

1 | INTRODUCTION

Thyroid hormone (TH) production is a tightly regulated process controlled by a classic negative feedback loop involving the hypothalamus, the pituitary, and the thyroid, which has led to the common name hypothalamus–pituitary–thyroid axis (Figure 1).

The thyrotropin-releasing hormone (TRH) is produced in the hypothalamus. Once released, TRH reaches the pituitary gland and binds to the TRH receptor and stimulates the production and secretion of thyroid-stimulating hormone (TSH), also known as thyrotropin (Liu et al., 2019). In the thyroid, TSH binds to the TSH receptor (TSHR) and induces TH production. When needed,
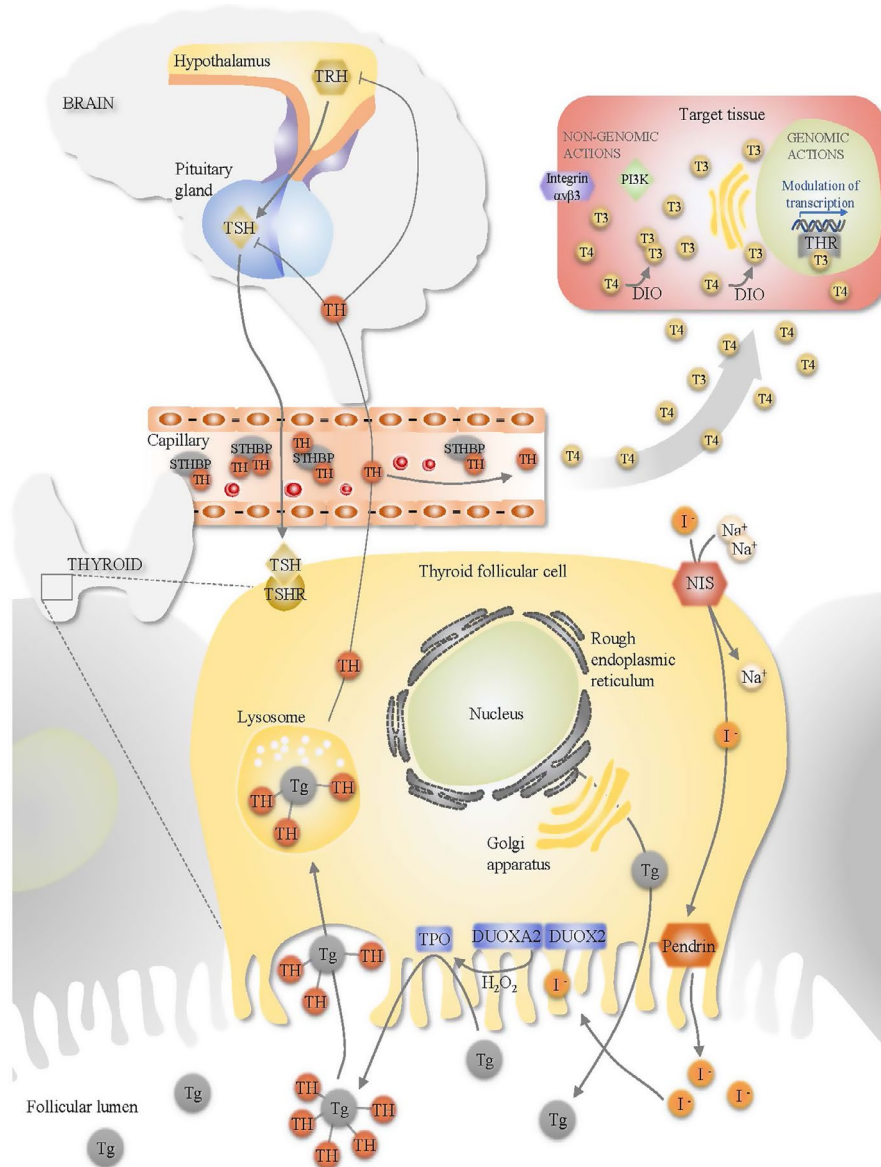
FIGURE 1 Scheme summarizing TH synthesis. TRH is produced by a specific group of neurons located in the paraventricular nucleus of the hypothalamus. When TRH reaches the pituitary gland, it binds to the TRH receptor expressed in the thyrotrophs, stimulating the expression and secretion of TSH into the circulation. TSH reaches the thyroid gland and binds to the TSHR located in the cell membrane of the thyroid follicles, setting in motion TH production in a process that includes the induction of iodine uptake by the NIS. Iodide is mobilized to the colloid via Pendrin action, and it is then oxidized by the thyroid peroxidase (TPO) using H_2O_2. Iodination of tyrosine residues forms monoiodotyrosines and diiodotyrosines that are coupled to form T3 and T4. T3 and T4 bound to TG are released in the colloid of the follicle. When needed, iodinated TG is catabolized in thyroid follicular epithelial cells to produce T3 and T4, which are then released into the circulation. In the bloodstream, THs can be found either free or bound to serum TH-binding proteins (STHBP), such as thyroxine-binding protein, transthyretin, and albumin. Free THs are able to enter into target cells in target tissues via membrane transporters. In target cells, deiodinases generate T3 from T4 by removing the iodine located at the 5′ position of T4. Intracellular T3 acts via genomic actions binding to the THR, where modulate gene expression, or via non-genomic actions affecting signaling pathways such as integrin αvβ3 and PI3 K. THs also act via the nuclear THRβ in the hypothalamus and the pituitary to inhibit TRH and TSH production and secretion, completing a negative feedback loop that maintains physiological levels of THs. DIO: deiodinase. DUOX2: dual oxidase 2. DUOXA2: dual oxidase maturation factor 2. I⁻: iodide. STHBP: serum TH-binding proteins. Na⁺: sodium. NIS: sodium-iodide symporter. T3: triiodothyronine. T4: thyroxine. Tg: thyroglobulin. TH: thyroid hormone. THR: thyroid hormone receptors. TPO: thyroid peroxidase. TRH: thyrotropin-releasing hormone. TSH: thyrotropin. TSHR: thyrotropin receptor

triiodothyronine (T3) and tetraiodothyronine (T4), also known as thyroxine, are released into the circulation. In the hypothalamus and the pituitary, THs act *via* the nuclear TH receptor β (THRβ) to inhibit TRH and TSH production and secretion, completing a

negative feedback loop that maintains the physiological levels of TRH, TSH, and THs.

In target cells, deiodinases (DIO2 and DIO3) generate T3 from T4 by removing the iodine located at the 5′ position of T4. The

expression of the different deiodinases is cell-type and tissue-specific, which provides a mechanism to control TH actions irrespective of circulating TH levels (Gereben et al., 2008; Schweizer et al., 2008). Intracellular T3 acts via binding to the TH receptor α (THRα) and THRβ, which display high affinity for DNA sequences called TH response elements (TREs). Upon ligand binding, THRs assemble into a co-activator complex with histone acetyltransferase activity that is recruited to stimulate transcription (Lonard & O'Malley, 2007; Perissi et al., 2010). Moreover, THR interacts with other nuclear hormone receptors, such as peroxisome proliferator-activated receptors, retinoid X receptors, retinoic acid receptors, and liver X receptors that allow binding to a wide repertoire of nucleotide sequences that contribute to regulate different metabolic pathways, including cholesterol, glucose, and fatty acid metabolism in different tissues (Brent, 2012; Kouidhi & Clerget-Froidevaux, 2018). In addition, THs also modulate molecular pathways via protein–protein interactions such as PI3 K-AKT-FOXO1 and mTOR-p70S6 K signaling, which further modulate transcription (Cao et al., 2005; Davis et al., 2016; Flamant et al., 2017; Mullur et al., 2014). In the presence or absence of THs, THRs modulate the expression of more than 80 genes, mainly involved in mitochondrial biogenesis, oxidative phosphorylation, tricarboxylic acid cycle, de novo lipogenesis, and fatty acid catabolism (Flores-Morales et al., 2002; Jackson-Hayes et al., 2003; Singh et al., 2018). Overall, THs enhance oxygen consumption and ATP hydrolysis and reduce the coupled state of the mitochondria inducing the catabolism of all types of energy sources (Johannsen et al., 2012; Weinstein et al., 1991). At the organismic level, THs increase the basal metabolic rate, which is defined as rate of energy expenditure per time at rest.

THs are required for the development and maturation of several tissues and general well-being (Ng et al., 2013; Nunez et al., 2008). Hollowell et al. have defined the normal reference ranges of total T4 at 57.9–169.9 nM and TSH at 0.39–4.6 mIU/L (Figure 2) (Hollowell et al., 2002). It is estimated that in the general population the prevalence of TH alterations is ~0.5%–4% in areas with sufficient iodine exposure. There are different types of TH alterations (hyperthyroidism, subclinical hyperthyroidism, subclinical hypothyroidism, and hypothyroidism) that lead to different clinical symptoms (Figure 2) (Hollowell et al., 2002). Recent epidemiological meta-analyses have determined a clear association of TH alterations with mortality risk in the general population (Brandt et al., 2011; Kovar et al., 2015; Thvilum et al., 2012).

Clinical hypothyroidism, also known as overt hypothyroidism, is associated with metabolic deregulations, such as hypercholesterolemia, and increased low-density lipoprotein (LDL) levels, that increase the risk of developing diabetes mellitus (DM) and cardiovascular complications (Cappola & Ladenson, 2003; Duntas, 2002; Gao et al., 2013; Sawin et al., 1985; Taylor et al., 2013; Wang et al., 2012). Subclinical hypothyroidism has also been associated with serious complications such as improper neurocognitive health, unbalanced bone metabolism, propensity to develop type 2 DM (T2DM), cardiovascular-associated risk factors, such as high LDL and very-low-density lipoprotein (VLDL) levels, hypertriglyceridemia, hypertension, atrial fibrillation, and obesity, as well as low levels of high-density lipoprotein (HDL) and
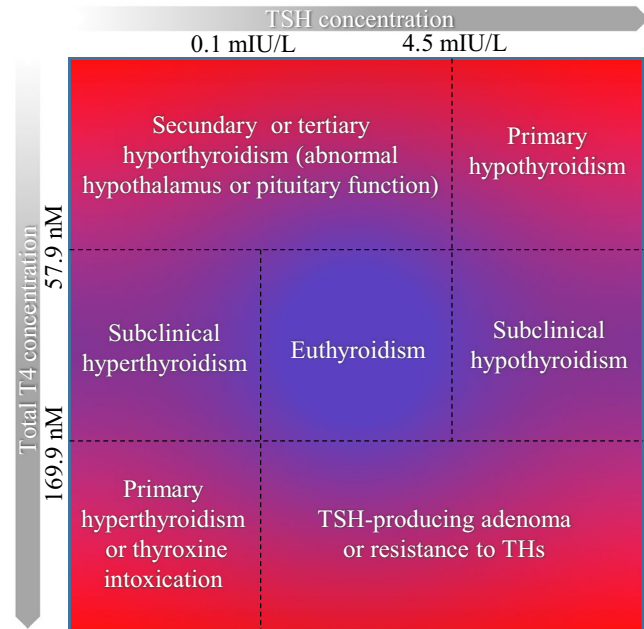

FIGURE 2 Reference ranges and medical conditions associated with thyroid dysfunction. This figure defines reference ranges for primary hypothyroidism, secondary hypothyroidism, tertiary hypothyroidism, subclinical hypothyroidism, euthyroidism, subclinical hyperthyroidism, primary hyperthyroidism/thyroxine intoxication, and TSH-producing adenoma/resistance to THs. TSH and T4 levels were defined as Hollowell et al. Total thyroxine can be converted from nM to µg/dl, dividing by 12.87. THs: thyroid hormones. TSH: thyrotropin

premature mortality (Auer et al., 2001; Biondi & Cooper, 2008; Biondi et al., 2002; Ceresini et al., 2013; Han et al., 2015; Pearce, 2012; Taylor et al., 2013). On the other side of the spectrum, hyperthyroid individuals also have increased risk of developing DM and cardiovascular complications that can cause premature death (Brandt et al., 2013; Franklyn et al., 2005). However, cardiovascular complications are not associated with hypercholesterolemia in hyperthyroid patients, and they normally exhibit reduced circulating cholesterol levels (Kim et al., 2020). In the case of subclinical hyperthyroidism with severely decreased TSH, clinical data indicate an increased incidence of dementia and neurocognitive dysfunction (Aubert et al., 2017; Bensenor et al., 2010). Overt hyperthyroidism and even subclinical hyperthyroidism increase the risk of bone fractures (Blum et al., 2015; Nicholls et al., 2012; Vestergaard & Mosekilde, 2003). Altogether, clinical data clearly indicate that in the general population TH alterations are associated with poor quality of life.

1.1 | Thyroid hormones in aging

1.1.1 | The regulation of thyroid hormones in aging and their role in longevity

Early observations have established that restricted thyroid function is associated with longer life span in small and large mammals,

including humans (Bowers et al., 2013; Buffenstein & Pinto, 2009; Jansen, et al., 2015). Accordingly, higher serum TSH levels and/or low serum free T4 levels have been associated with longer life expectancy, indicating an important role of THs in aging (Beld et al., 2005; Gussekloo et al., 2004, 2006; Rozing, et al., 2010). Although aging may not be considered a disease, it can be argued that the aging process is not a homogeneous physiological process. From an evolutionary point of view, natural selection optimizes mechanisms and processes that allow functionality and survival until the end of the reproductive life. However, at post-reproductive age in the majority of species, there is little natural selection to fight against mechanisms that produce unhealthy aging and death. Notwithstanding, in certain species such as humans, where familial and social interactions can be relevant for the survival of young individuals, natural selection might still have a significant role to promote longevity (Tully & Lambert, 2011). Given these interesting facts, it is difficult to define whether changes that occur in thyroid function in aged individuals are adaptive or maladaptive.

Although T4 secretion has been shown to be slightly reduced in aged individuals, the capacity to metabolize T4 by deiodination mediated by DIO1 and DIO2 is decreased in certain tissues of aged individuals, and healthy aged individuals exhibit normal T4 levels (Duntas, 2018; Mazzoccoli et al., 2010; Michalakis et al., 2013). In this line, old rats exhibiting comparable TSH levels to young ones have lower DIO1 activity and separated studies in rodents have demonstrated that hepatic levels of the TH transporter MCT8 are reduced in aged individuals, indicating that TH responsiveness changes with advancing age (Chaker et al., 2018; Donda & Lemarchand-Beraud, 1989). Moreover, there are evidences indicating that THs might have reduced capacity to activate certain post-receptor mechanisms of thyroid function in aged individuals (Morley, 2003).

The incidence of both hyperthyroidism and hypothyroidism in the older population has continuously risen in the past decades (Boelaert, 2013; Duntas, 2018; Surks & Hollowell, 2007). The diagnosis of hypothyroidism in elderlies is difficult since older people exhibit milder and fewer symptoms of TH deregulation. Moreover, symptoms experienced in these patients are readily interpreted as signs of the aging process, such as fatigue and neurological disorders, which difficult the diagnosis of these alterations (Martinez-Iglesias, Garcia-Siva, Regadera, et al., 2009). Prevalence of subclinical hypothyroidism affects ~6% of the population aged between 70 and 79 years, rising up to 10% in individuals aged over 80 years (Boelaert, 2013; Simonsick et al., 2009). Noteworthy, despite the association of subclinical hypothyroidism with several serious diseases and overall mortality in the general population, a study focused on older individuals with subclinical hypothyroidism has refuted these associations (Simonsick et al., 2009). Actually, epidemiological studies in humans have even associated subclinical hypothyroidism with a reduced risk of all-cause mortality in individuals older than 65 years of age (Selmer et al., 2014). Furthermore, several reports have indicated that old individuals, of at least 70 years of age diagnosed with subclinical hypothyroidism (TSH levels in the range of 4.5–10.0 mIU/L), might even have certain physical function advantages and lower mortality when compared to individuals with normal thyroid function (Simonsick et al., 2009, 2016). Supporting the pro-longevity benefits of reduced thyroid function in the elderly, thyroxine replacement therapy was not efficient in improving cognitive function in old patients with subclinical hypothyroidism (Park et al., 2010).

The prevalence of hyperthyroidism in individuals older than 60 years ranges from 1% to 15% (Bannister & Barnes, 1989; Chiovato et al., 1997; Samuels & Feingold, 2000), being autoimmune Graves' disease is the most common etiology of hyperthyroidism in aged individuals. The majority of prospective studies associate higher TH concentrations with increased frailty and decreased functional capacity in old patients (Ceresini et al., 2011; Chaker et al., 2018; Simonsick et al., 2009). In this line, low levels of TSH or elevated levels of free T4 have been linked to compromised quality of life and increased mortality risk in the aged population (Gussekloo et al., 2004, 2006; Kramer et al., 2009; Parle et al., 2001; Singer, 2006; Waring, et al., 2012). The pro-aging effects of THs have been studied and active T3 binding to the THRβ isoform is known to produce DNA damage and premature senescence, making a causal connection with molecular processes of accelerated aging (Zambrano et al., 2014). Moreover, the detrimental effects of chronic hyperthyroidism in life expectancy have been observed in mice and rats (Lopez-Noriega et al., 2019; Ooka & Shinkai, 1986). In this sense, wild-type mice exposed to T4 leading to a twofold increase in circulating T4 levels exhibit an ~50% reduction in mean and maximal life span (Lopez-Noriega et al., 2019).

Several studies have indicated that different TH levels within the normal range could also have physiological relevance. In this regard, high–normal free T4 levels are considered a risk factor for poor outcomes for cardiovascular disease and mortality (Hogervorst et al., 2008; Simonsick et al., 2016). Several reports have determined the effect of variations of TH levels within euthyroidism on gait speed in older people, indicating that higher TH levels are associated with slower gait speed (Bano, et al., 2016; Chaker et al., 2018; Simonsick et al., 2016). Remarkably, data in the literature indicate that subjects with low–normal free T4 levels or with high–normal TSH levels were expected to live up to 3.7 years longer than individuals with high–normal free T4 levels or low–normal TSH levels (Bano et al., 2019; Chaker et al., 2018). Moreover, lower free T4 levels have been associated with better functional mobility and fitness in healthy euthyroid individuals with ages ranging from 68 to 97 years, which has led to propose low–normal free T4 levels as a marker for healthy aging (Rozing et al., 2010; Rozing et al., 2010; Simonsick et al., 2016). In this line, lower metabolic cost of walking in adults is associated with greater gait speed and a slower decline (Schrack et al., 2012, 2016). Overall, these data are in agreement with the rate of living theory of aging, suggesting that a lower metabolic demand predisposes to longer health span and life span.

1.2 | The special case of centenarians

There is strong evidence indicating that a genetic component predisposes to longevity, which is supported by studies indicating that

long-lived parents have long-lived offspring (Gudmundsson et al., 2000; Kerber et al., 2001; Rozing, et al., 2010). Individuals with exceptional long longevity in the Ashkenazi Jewish population and their families have been studied to determine factors that could be associated with this trait. Several reports have indicated that the offspring of Ashkenazi Jewish centenarians have higher TSH levels than the offspring of non-centenarians and, even nonagenarians and their offspring, have increased TSH levels and/or decreased circulating T3/free T4 levels than their partners (Atzmon et al., 2009; Jansen, et al., 2015). The Leiden longevity study has also supported the association between low thyroid function with lower risk of death from cardiovascular disease and longer life spans (Rozing et al., 2010; Rozing et al., 2010; Westendorp et al., 2009). In this line, nonagenarians with the lowest family mortality history score had the highest TSH levels and slightly lower levels of free T4 and free T3 (Rozing et al., 2010). Interestingly, TSH levels were found to be higher and free T3 levels were slightly lower when the offspring was compared to their partners (Rozing et al., 2010). The Leiden longevity study also analyzed nonagenarians with at least one nonagenarian sibling, their offspring, and their partners (Westendorp et al., 2009). Remarkably, authors determined that offsprings of nonagenarian siblings had lower mortality rate, and lower propensity to develop cardiovascular disease and DM than their partners. These observations have led to the conclusion that increased TSH levels are associated with exceptional longevity, which has been further supported by studies in the oldest individuals of the general population demonstrating the association of higher TSH levels with reduced old age mortality (Atzmon et al., 2009; Gussekloo et al., 2004). An elegant work by Jansen et al. has determined TH levels and TSH secretion over 24 hours in the offspring from long-lived families and their partners, since these hormones are known to have intra-day oscillations due to circadian rhythms. The objective was to evaluate alterations in energy metabolism. Results obtained led to the conclusion that familial longevity is characterized by higher TSH secretion, in the absence of alterations on TH levels or energy metabolism (Jansen et al., 2015). The lack of differences in TH levels and energy metabolism is in sharp contrast with several theories of aging postulating that reduced energy metabolism promotes longer life expectancy.

Interestingly despite the fact that centenarians and their offspring tend to have lower TH function, the offspring of centenarians has a significantly lower body mass index when compared to the normal population and reduced risk of age-related diseases, further indicating a genetic component of longevity (Terry et al., 2003). Further investigations in the Ashkenazi Jewish population have also determined that a genetic background might be responsible for increased life span, since two specific single nucleotide polymorphisms in the TSHR gene (rs12050077 and rs10149689) were linked to higher TSH levels in centenarians and the offspring of centenarians of this population (Atzmon et al., 2009). Based on the Leiden study and others, one can assume that in the general population of the oldest old, high levels of TSH usually are associated with healthy aging (Gussekloo et al., 2004). The fact that TSH levels and not only TH levels are associated with extended survival suggests that modulations in the

negative feedback loop controlling TH production might contribute to this phenotype (Atzmon et al., 2009).

1.3 | The molecular mechanisms of exceptional longevity

An intense area of research has been focused to identify the genetic predisposition to maximal longevity in animal models. Mutations in the DAF2 gene, homolog of the insulin-like growth factor 1 receptor (IGF-1R) in Caenorhabditis elegans and in the IGF-1R in Drosophila melanogaster, are known to extend life span (Arantes-Oliveira et al., 2003; Tatar et al., 2001). Remarkably, the longest living laboratory mice exhibit severely reduced thyroid function as observed in the Laron (growth hormone receptor knockout), Ames (Prop1-mutated), and Snell (Pit1-mutated) dwarf mice (Table 1) (Brown-Borg 2007, 2009; Brown-Borg et al., 1996). These murine models show a healthy aging phenotype that includes, besides the restriction on thyroid function, the preservation of neurocognitive and muscular function, lower incidence of cancers, enhanced insulin responsiveness, and improved glucose tolerance (Brown-Borg, 2009; Brown-Borg et al., 1996; Ikeno et al., 2003; Wiesenborn et al., 2014). At a molecular level, these mice exhibit reduced signaling through the insulin and IGF-1 pathways, which leads to restricted phosphorylation of downstream targets such as the serum/glucocorticoid-regulated kinase and AKT. Restricted activity of these kinases promotes the translocation of FOXO transcription factors into the nucleus, where it modulates the transcription of genes that promote longevity (Brown-Borg et al., 1996; Russell & Kahn, 2007). However, these beneficial effects on health span and/or life span might rely specifically on growth hormone production and/or sensitivity. In this context, we recently determined the direct effect of TH modulation in health span and longevity using the PAX8 knockout murine model and wild-type mice treated or not with T4 (Lopez-Noriega et al., 2019). PAX8 is the master transcriptional regulator of thyroid organogenesis required for TH production (Mansouri et al., 1998). Using these mice, we determined the effects in health status and life expectancy in mice suffering severe hypothyroidism, mild hypothyroidism, and severe hyperthyroidism compared with control healthy mice. T4-treated hyperthyroid mice exhibited reduced body weight, increased food intake, and short life expectancy, indicating that elevated TH levels result in life-threatening toxicity. Not surprisingly, the complete lack of TH production resulted in perinatal mortality (Lopez-Noriega et al., 2019). The direct modulation of TH levels using PAX8 heterozygous knockout mice, which suffer a mild hypothyroidism due to a direct defect in the thyroid gland, while exhibiting normal circulating levels of α-GSU of pituitary hormones in adulthood, did not result in improved health span or longer life span. As opposed to other experimental models of hypothyroidism (Hine et al., 2017; Umezu et al., 2020), we found that the PAX8 heterozygous mice faithfully recapitulate the phenotype of humans with hypothyroidism, including insulin resistance, increased white adipose tissue (WAT) mass, and increased triglyceride content in skeletal

muscle and liver (Lopez-Noriega et al., 2019). Similar to humans, these mice also exhibit reduced basal metabolic rate and obesity while maintaining normal energy intake. Moreover, PAX8 heterozygous mice exhibit poor performance in functional physical tests and accumulated oxidative damage, indicating that even mild alterations on TH levels (mild hypothyroidism) have profound effects in health span. These results indicate that low TH levels in exceptional long-living dwarf mice are not responsible *per se* of longevity benefits. Our data support the notion that humans with exceptional longevity must have a specific genetic and/or epigenetic signature required to achieve longevity benefits (Bowers et al., 2013; Gesing et al., 2012; Jansen, et al., 2015). In addition, our data also indicate that a delicate control of TH levels and function is required to sustain health and survival and that interventions based on the modulation of THs should not be targeted to improve the quality of life or life expectancy in healthy individuals.

1.4 | The effect of nutritional and pro-longevity interventions in thyroid function

Several animals, including humans under calorie restriction, a variety of nutritional interventions that extend health span and lifespan, have low T3 and/or high TSH levels in the blood (De Andrade et al., 2015; Fontana et al., 2006; Muller et al., 2015; Ravussin et al., 2015). Remarkably, a recent report evaluating the effects of 4-week alternate day fasting has clearly demonstrated a reduction in T3 levels in individuals adhered to the intervention, which is accompanied by improvements in markers of cardiovascular health (Stekovic et al., 2020). In this line, a caloric restriction mimetic, resveratrol, rises TSH levels and has profound effects in the thyroid gland, decreasing sodium-iodide symporter (NIS) and thyroglobulin (TG) expression (Giuliani et al., 2017). Calorie restriction produces effects at all compartments of the HPT axis, as well as in TH target tissues. In particular, reduced hypothalamic TRH expression, reduced pituitary TSHβ expression, reduced expression of TG and secretion of T3 and T4 in the thyroid gland, and reduced hepatic DIO1 expression have been described upon different forms of caloric restriction (Boelen et al., 2008; De Andrade et al., 2015; Palkowska-Gozdzik et al., 2017). Different nutritional interventions are also known to alter TH levels. In this regard, adult dogs consuming a low-carbohydrate high-protein high-fat diet exhibited greater circulating T4 levels than dogs fed with a high-carbohydrate low-protein low-fat diet (Chiofalo et al., 2019). Interestingly, Carew et al. evaluated the effect of individual essential amino acid restriction on plasma TH concentrations in chickens (Carew et al., 1997). Results indicated that changes in circulating levels of T3 under protein deficiency may be a consequence of selected amino acid deficits, since only isoleucine deficiency resulted in an elevation in plasma T3, while restrictions on other essential amino acids did not alter T3 levels when compared to control fed chickens. However, the molecular mechanisms producing these changes remain unknown.

1.5 | Thyroid hormones in diabetes mellitus

1.5.1 | The implications of thyroid hormones in glucose and lipid metabolism

As previously mentioned, THs enhance oxygen consumption, inducing the catabolism of all types of energy sources (Johannsen et al., 2012; Weinstein et al., 1991). THs are efficient modulators of lipid and glucose metabolism. In particular, THs reduce circulating triglycerides and cholesterol-containing lipoproteins. THs stimulate the expression of the Sterol response element-binding protein 2 (Srebp-2) (Mullur et al., 2014). Increased levels of Srebp-2 contribute to enhance LDL receptor expression, which potentiates hepatic cholesterol uptake. Moreover, THs are known to increase simultaneously lipolysis and liponeogenesis. Actually, THs are known to increase the expression of carnitine palmitoyltransferase Iα (mitochondrial fatty acid uptake) and the acetyl-coenzyme A carboxylase (lipogenic) (Mullur et al., 2014). A comprehensive analysis of these processes has indicated that liponeogenesis is enhanced to maintain lipid levels under conditions of high lipolysis (Oppenheimer et al., 1991). Under these circumstances, lipolysis is enhanced to provide substrates for thermogenesis. Carbohydrate metabolism is also influenced by TH. Gluconeogenesis and glycogenolysis are known to be enhanced by THs in a process that supports tissues with fuel to maintain their energy requirements. In this sense, hepatic insulin resistance in hyperthyroid individuals has been shown to increase gluconeogenesis and subsequent hepatic glucose output (Figure 3) (Klieverik et al., 2008; Potenza et al., 2009). Increased rates of gluconeogenesis are supported by increased Cory cycle activity, which implicates muscle tissue in the provision of substrates for hepatic gluconeogenesis (lactate and certain amino acids such as alanine and glutamine). This process represents a dynamic buffer of glucose that allows its use by other tissues under glucose requirements when needed. Within the liver, THs are known to enhance the expression of the phosphoenolpyruvate carboxykinase, the rate-limiting step in gluconeogenesis, supporting a direct role of THs in the regulation of these processes (Park et al., 1999). Studies in mice exposed to T4 mimicking hyperthyroidism have also indicated that insulin signaling is active in insulin-target tissues even under fasting conditions, due to a deregulated function of the endocrine pancreas (e.g., increased insulin secretion and subsequent levels in circulation) (Lopez-Noriega et al., 2017). Overall, compelling data in the literature indicate that THs produce effects in several, if not all, tissues involved in glucose and lipid homeostasis (Figure 3).

1.5.2 | Alterations of thyroid hormones in diabetes mellitus

The relationship between alterations on thyroid function and the development of different types of DM has been the focus of intense research. The prevalence of hyperthyroidism in subjects suffering DM

TABLE 1 Genetic alterations causing thyroid dysfunction associated with aging, DM, or cancer in mice and humans. ND: not determined

Gene	Function	Alteration	Phenotype			References
			Aging	DM	Cancer	
DIO2	TH activation/ inactivation	Homozygous knockout mouse	ND	Several hallmarks of T2DM	ND	Marsili et al. (2011)
		SNPs in humans	ND	Several hallmarks of T2DM	ND	Canani et al. (2005); Dora et al. (2010); Mentuccia et al. (2002)
DUOX2	TH production	SNPs in humans	ND	ND	Predisposes to thyroid cancer	Bann et al. (2019)
TG	TH transport	SNPs in humans	ND	ND	Found in thyroid cancer	Hishinuma et al., 2005)
THRα	TH signaling	Homozygous knockout mouse	ND	Protected from hallmarks of T2DM	ND	Jornayvaz et al. (2012)
		Truncations and SNPs in cancer tissue in humans	ND	ND	Found in several types of cancer	Kim and Cheng (1830); Lin et al. (1999); Kamiya et al. (2002); Puzianowska-Kuznicka et al. (2002); Chan and Privalsky (2006); Rosen and Privalsky (2011) McCabe et al. (1999); Cheng (2003)
THRβ	TH signaling	Truncations and SNPs in cancer tissue in humans	ND	ND	Found in several types of cancer	Kim and Cheng (1830); Lin et al. (1999); Kamiya et al. (2002); Puzianowska-Kuznicka et al. (2002); Chan and Privalsky (2006); Rosen and Privalsky (2011); Cheng (2003)
TSHR	TSH signaling	Homozygous knockout mouse	Premature death	Glucose intolerance	ND	Abe et al. (2003); Yang et al. (2019)
		Truncations and SNPs in cancer tissue in humans	ND	ND	Mutations found in HCC and thyroid cancer	Shih et al. (2018); Russo et al. (1995); Camacho et al. (2000)
PAX8	Thyroid development and function.	Homozygous knockout mouse	Premature death	No	No	Lopez-Noriega et al. (2019); Mansouri et al. (1998)
		Heterozygous knockout mouse	Unhealthy aging; normal life span	Several hallmarks of T2DM	Liver cancer	Lopez-Noriega et al. (2019)
		Human SNPs	ND	GDM	Propensity to HCC	Martin-Montalvo et al. (2019); Ma et al. (2017)

TABLE 1 (Continued)

| Gene | Function | Alteration | Phenotype | | | References |
			Aging	DM	Cancer	
PIT-1	TRH/TSH production	Homozygous loss-of-function point mutation in mouse	Delayed aging	Increased insulin sensitivity	Reduced occurrence of spontaneous cancer	Brown-Borg (2007); Flurkey et al. (2001); Alderman et al. (2009)
PROP-1	TRH/TSH production	Homozygous loss-of-function point mutation in mouse	Delayed aging	Increased insulin sensitivity	Delayed spontaneous occurrence of cancer	Brown-Borg (2007) Brown-Borg et al. (1996); Ikeno et al. (2003)

is greater than in non-diabetic subjects (Biondi et al., 2019), and a nationwide Danish study has determined that patients suffering hyperthyroidism have greater risk to develop DM (Brandt et al., 2013). Among adult patients with T2DM, ~4.4% have overt hyperthyroidism and 2%–4% have subclinical hyperthyroidism (Biondi et al., 2019). Interestingly, improved diabetic control in T2DM patients normalizes TSH levels in patients with subclinical hyperthyroidism, suggesting that treatments improving T2DM might contribute to normalize thyroid function (Celani et al., 1994). However, a recent report has indicated that non-diabetic patients diagnosed with hyperthyroidism have increased risk to develop T2DM later in life, suggesting that thyroid dysfunction might precede diabetogenic processes (Chen et al., 2019). In this line, while hyperthyroid patients exhibit increased basal hepatic glucose production and increased fasting insulin levels when compared to healthy individuals, hyperthyroid patients treated with methimazole rendered euthyroid, exhibited significantly reduced levels on the same parameters, reaching the levels of the healthy control group (Cavallo-Perin et al., 1988). An independent report has also indicated that patients with overt or subclinical hyperthyroidism exposed to a glucose tolerance test have higher circulating levels of glucose and insulin (Maratou et al., 2010). Glucose intolerance in these patients is due to potentiated hepatic gluconeogenesis (Maratou et al., 2010). These effects might be related to the control that exerts THs in the expression of genes involved in glucose and lipid metabolism and suggests that several physiological aberrations are common to hyperthyroidism and T2DM, which contribute to the loss of metabolic homeostasis. Longitudinal studies have also investigated the association of alterations in thyroid function and the prevalence of DM and metabolic syndrome in older adults (Heima et al., 2013; Waring, et al., 2012). At baseline, individuals in the metabolic syndrome group exhibited significantly higher TSH values than individuals not included in the metabolic syndrome group. The authors indicated that increased circulating levels of TSH were associated with greater prevalence of metabolic syndrome, even in participants within the normal range (Waring et al., 2012). Another longitudinal study performed in Amsterdam also associated higher prevalence of metabolic syndrome and obesity with individuals exhibiting higher circulating levels of TSH (Heima et al., 2013). Separated research as also indicated that hypothyroidism is associated with insulin resistance and

dyslipidemia (Dimitriadis et al., 2006; Gierach & Junik, 2015; Wang, 2013). Further evidence also indicates an increased risk of DM in patients with hypothyroidism and a systematic review reported the increased prevalence of even subclinical hypothyroidism in patients with T2DM (Gronich et al., 2015; Han et al., 2015). As opposed to compelling research indicating the association of DM and thyroid dysfunction, which is supported by the well-described role of THs on glucose metabolism and insulin secretion, other studies have failed to link hypothyroidism to the development of T2DM (Ishay et al., 2009; Radaideh et al., 2004).

A growing evidence is associating alterations in thyroid function with other types of DM such as type 1 DM (T1DM) and gestational DM (GDM). Several studies have shown that patients with T1DM, an autoimmune disease, are prone to exhibit autoimmune thyroid diseases such as Hashimoto's thyroiditis and Graves' disease. Current data indicate that up to 30% of adults with T1DM have thyroid diseases of autoimmune origin (Araujo et al., 2008; Shun et al., 2014). Genetic studies have revealed susceptibility genes for this syndrome, which include the human leukocyte antigen, cytotoxic T-lymphocyte-associated antigen 4, protein tyrosine phosphatase non-receptor type 22, forkhead box P3, and the interleukin-2 receptor alpha/CD25 gene region (Dittmar & Kahaly, 2010). These genes are involved in immunological synapse and T-cell activation, suggesting that similar pathogenic processes occur in T1DM and thyroid diseases of autoimmune origin (Dittmar & Kahaly, 2010).

Gestational DM is a common complication that affects ~10% of all pregnancies associated with adverse pregnancy outcomes, such as preeclampsia, macrosomia, and caesarean delivery (International Association of Diabetes, 2010; Petra et al., 2019). Upon delivery, GDM disappears but in many cases different types of DM (GDM in a subsequent pregnancy or T2DM) can spur later in life (Martin et al., 1999; Seely & Solomon, 2003). Among the changes that occur during pregnancy, it is known that the placenta increases the secretion of pro-inflammatory cytokines that induce insulin resistance to favor nutrient availability to the fetus (Kim et al., 2010). Under these circumstances (e.g., transient insulin resistance during pregnancy), GDM is the result of compromised capacity of pancreatic β-cells to increase insulin secretion to compensate insulin resistance in insulin-target tissues (Kuhl, 1991). Several reports have determined that maternal hypothyroidism predisposes the offspring to exhibit limited
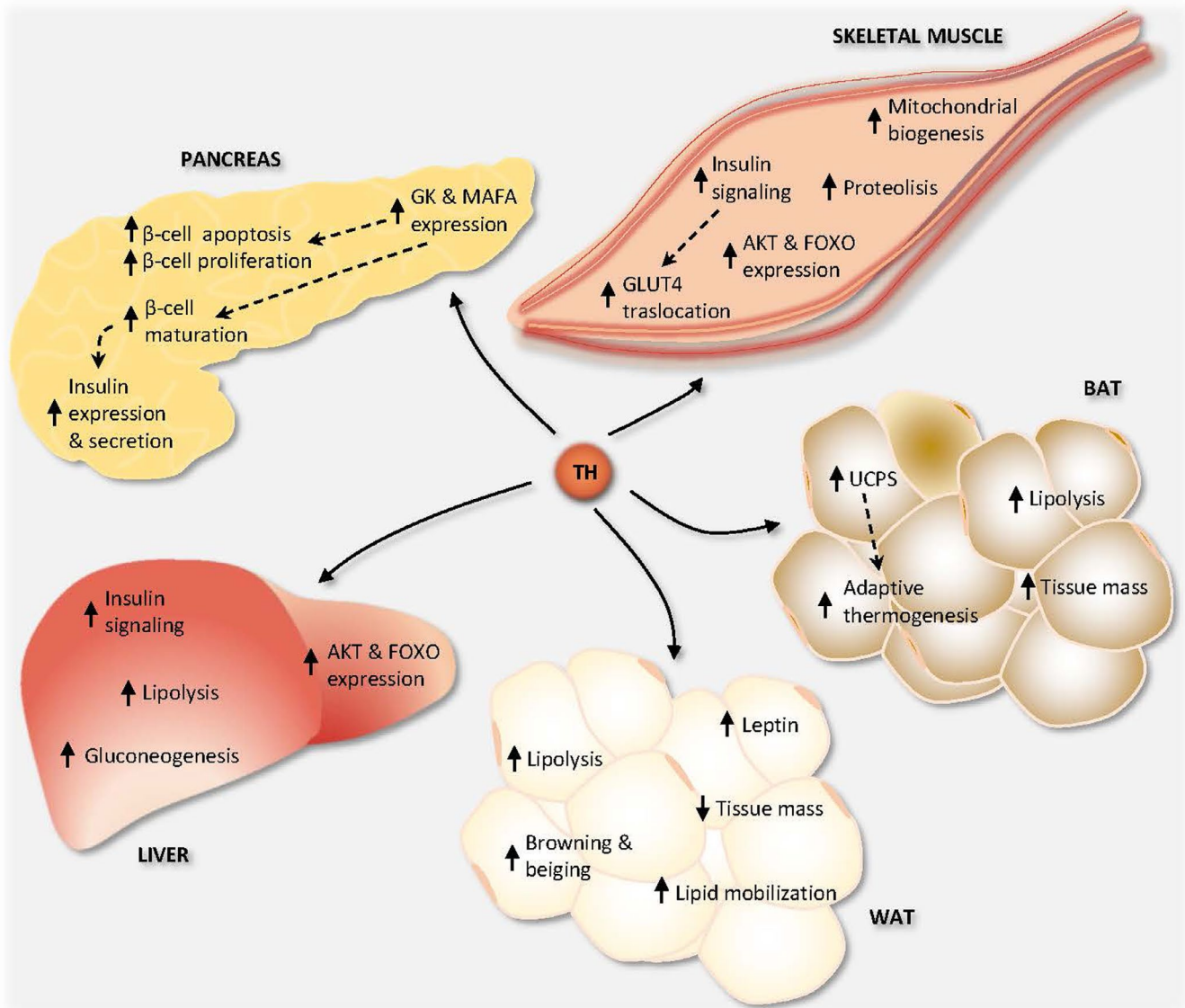
FIGURE 3 Scheme summarizing the processes regulated by THs in the main metabolic tissues. THs exert profound effects in metabolic tissues. THs enhance GK and MAFA expression in the pancreas favoring a rapid maturation and turnover of β cells. THs also potentiate insulin expression and secretion in the endocrine pancreas. Insulin-target tissues respond increasing the activity of insulin signaling, which produces increased rates of lipolysis and gluconeogenesis in the liver and proteolysis and mitochondrial biogenesis in the skeletal muscle. Adipose tissues respond to THs increasing lipolysis and lipid mobilization. Browning/beiging of adipocytes occurs in the WAT and increasing thermogenesis via increased UCP expression and subsequent lipolysis occurs in the BAT. AKT, protein kinase B. FOXO: forkhead box O 1. GK: glucokinase. GLUT4: glucose transporter 4. MAFA: MAF bZIP transcription factor A

insulin secretion and to develop glucose intolerance, increasing the risk of T2DM in the offspring (Karbalaei et al., 2013). Moreover, separated reports have also determined that hypothyroidism is associated with GDM (Martin-Montalvo et al., 2019; Sell et al., 2008). In this regard, we found several mutations in *PAX8* leading to hypothyroidism associated with the development of GDM, indicating that human GDM could have a genetic component (Martin-Montalvo et al., 2019). Remarkably, this work has revealed that PAX8 expression in pancreatic islets modulates cellular pathways involved in cellular survival (Martin-Montalvo et al., 2019).

1.5.3 | The physiological and pathophysiological role of thyroid hormones in the endocrine pancreas

One of the main organs involved in the control of circulating glucose levels is the endocrine pancreas. Extensive research has demonstrated the role of THs in the differentiation, maturation, and functionality of metabolic tissues (Figure 3) (Mastracci & Evans-Molina, 2014). *In vivo* research has determined that during postnatal development circulating levels of T3 increase and induce the expression of the MAF bZIP transcription factor A (MAFA) and THRs in pancreatic

β-cells to facilitate their maturation (Aguayo-Mazzucato et al., 2011, 2013, 2015). Experiments performed in adult wild-type mice have also indicated severe effects of TH supplementation in β-cells, enhancing concomitantly β-cell proliferation and apoptosis (Lopez-Noriega et al., 2017). Remarkably, β-cells of mice treated with T4 exhibit increased glucokinase (GK) expression (Figure 3). Enhanced GK activity is associated with increased β-cell proliferation and apoptosis, which might facilitate a rapid β-cell turnover (Kassem et al., 2000, 2010; Lopez-Noriega et al., 2017). THs are involved in β-cell aging since they induce the expression of the senescence marker p16INK4A (also known as CDKN2A). The effects of THs via binding to the different THR produce the maturation (MAFA) and the senescence (p16INK4A) of β-cells. THRβ1 binds to the TRE site 2 of *MAFA* promoter, and THRα binds to the TRE site 5 of the *CDKN2A* promoter (Aguayo-Mazzucato et al., 2018). At the organismic level, mice treated with T4 exhibit greater insulin expression and secretion in pancreatic islets under fasting conditions, indicating that the insulin secretion machinery is constitutively active to facilitate nutrient uptake by insulin-target tissues (Figure 3) (Lopez-Noriega et al., 2017).

Separated research in mild hypothyroid PAX8 heterozygous knockout mice, which exhibit several hallmarks of T2DM, has indicated that pancreatic islets exhibit a transcriptional profile associated with increased metabolic activity and impaired antioxidant capacity (Lopez-Noriega et al., 2019). Pancreatic β-cells are particularly vulnerable to oxidative stress due to a very limited expression of antioxidant genes, such as catalase and glutathione peroxidase (e.g. less than 5% of hepatic levels) (Tiedge et al., 1997). More importantly, under typical situations of cellular stress such as high glucose, high oxygen, or heat shock, pancreatic islets have a virtually absent capacity to increase the expression of antioxidant enzymes (Tiedge et al., 1997). Situations of enhanced metabolic activity concomitant with restricted antioxidant defenses can generate oxidative stress, which may lead to the accumulation of oxidative damage. Under these situations, if cellular stress is not resolved pancreatic endocrine function might be compromised and apoptotic processes might be initiated (Supale et al., 2012; Tiedge et al., 1997).

1.5.4 | Thyroid hormone-related alterations in insulin-target tissues

Alterations in TH function have tremendous effects in liver tissue (Figure 3). THs induce increases in intracellular glucose production and insulin resistance (Klieverik et al., 2008). TH-mediated insulin resistance might be produced by increased levels of cytokines generated in peripheral tissues, such as the adipose tissue (Gierach et al., 2014; Mitrou et al., 2010). Compromised insulin sensitivity produced by THs can per se have important consequences for glucose homeostasis given the central role of insulin action on the regulation of hepatic gluconeogenesis and glycogenolysis (Hatting et al., 2018). Interestingly, the effects on endogenous glucose production in the liver have been shown to be mediated, in some part, by the effects of THs in the paraventricular nucleus of the hypothalamus that mediate effects via sympathetic projections to the liver (Klieverik et al., 2008, 2009). In this regard, elegant studies conducted by Klieverik et al. have shown that the increases in endogenous glucose production mediated by the paraventricular nucleus are independent of circulating levels of glucoregulatory hormones (Klieverik et al., 2009; Martin et al., 1999). Moreover, these studies have demonstrated that hepatic sympathetic denervation entirely blunts the paraventricular TH-induced increase in endogenous glucose production.

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome. Several alterations have been found in the pathogenesis of NAFLD in hypothyroid patients, which include the development of insulin resistance, dyslipidemia, and increased adiposity (Dimitriadis et al., 2006; Pagadala et al., 2012; Pucci et al., 2000; Waring, et al., 2012). Epidemiological studies have determined the existence of an inverse correlation between circulating TH levels and the incidence of NAFLD (Ludwig et al., 2015). Separated evidence has also indicated that patients with NAFLD exhibit higher serum TSH levels and lower free T4 levels (Xu et al., 2011). In this line, hypothyroidism is more frequent in patients with NAFLD when compared to healthy individuals matched for ethnicity, age, sex, and body mass index. Hypothyroidism was also higher in patients with non-alcoholic steatohepatitis (NASH), a more serious form of fatty liver disease, when compared to patients suffering NAFLD without NASH. Individuals diagnosed with hypothyroidism were 2.1 (95% confidence interval: 1.1–3.9, $p = 0.02$) and 3.8 (95% confidence interval: 2–6.9, $p < 0.001$) times more likely to suffer NAFLD and NASH, respectively (Pagadala et al., 2012). Moreover, NASH and advanced fibrosis are more prevalent in patients with overt and subclinical hypothyroidism (Kim et al., 2018). Interestingly, besides overt and subclinical hypothyroidism, even upper TSH levels within the euthyroid range have also been associated with NAFLD, irrespective of well-established metabolic risk factors (Bano et al., 2016; Chung et al., 2012; Pagadala et al., 2012). Moreover, hypothyroid patients exhibit increased esterification of hepatic fatty acids with restricted lipoprotein lipase activity and decreased hepatic uptake of HDL, indicating an improper cholesterol metabolism (Pearce, 2004; Pucci et al., 2000). Mild hypothyroid PAX8 heterozygous knockout mice exhibit increased hepatic levels of *CD36* expression (Lopez-Noriega et al., 2019), a long-chain fatty acid translocase that participates in fatty acid uptake (Greco et al., 2008; Pepino et al., 2014). Increased fatty acid uptake mediated by *CD36* might contribute to potentiate hepatic lipid accumulation in mild hypothyroid mice (Lopez-Noriega et al., 2019).

THs play also a significant role in other insulin-target tissues such as the adipose tissue and the skeletal muscle (Figure 3). The association of hypothyroidism and compromised insulin-stimulated glucose uptake in muscle and adipose tissue has been documented on animals and humans (Dimitriadis et al., 2006; Pagadala et al., 2012; Rochon et al., 2003). Nonetheless, conflicting results have been obtained when hyperthyroid patients were analyzed for positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (^{18}F-FDG PET/CT). One report indicated that hyperthyroid patients exhibit increased

radioactive glucose uptake in brown adipose tissue (BAT) when compared to euthyroid patients (Lahesmaa et al., 2014). A second study obtained similar results (e.g., increased radioactive glucose uptake) in hypothyroid patients suffering thyroid carcinomas when these patients became mildly hyperthyroid upon TSH suppression (Broeders et al., 2016). However, other studies have shown no differences in glucose uptake in patients with hyperthyroidism (Zhang et al., 2014) and in hypothyroid patients with thyroid cancer rendered thyrotoxic (Gavrila et al., 2017).

Interestingly, the effects of THs on WAT browning have been described, indicating that T4 supplementation for 14 days produces a marked increase in radioactive glucose uptake in suprascapular subcutaneous WAT regions (Figure 3). Transcriptional analyses indicated a marked induction of UCP1 and DIO2 expression, which suggests increased energy expenditure via thermogenesis (Skarulis et al., 2010). Given the inconsistent results on BAT function in hyperthyroid subjects, it is plausible that the TH effects on WAT are more physiologically relevant than the effects on BAT. Supporting this hypothesis, research carried out in rats has indicated that triiodothyroacetic acid induces the expression of UCP1 in abdominal WAT (Medina-Gomez et al., 2008) and long-term administration of the THRβ analog sobetirome produced the browning of subcutaneous WAT in obese rodents (Lin et al., 2015; Villicev et al., 2007). Remarkably, sobetirome administration to ob/ob mice produced a decrease in BAT thermogenic function, further suggesting that metabolic effects of sobetirome are mediated by WAT browning. Interestingly, hypothyroidism is also associated with increased WAT browning (Weiner et al., 2016). Weiner et al. determined that WATs at different locations of hypothyroid mice exhibit markers of WAT browning, such as multilocular UCP1 expression and reduced BAT activity using (Nunez et al., 2008) F-FDG PET/CT determinations (Weiner et al., 2016). These data indicate that under conditions of compromised BAT functionality compensatory WAT browning occurs.

THs exert important influences in energy metabolism, which predisposes tissues and organs with a high metabolic demand, such as skeletal muscle, to severe effects in patients suffering hypothyroidism and hyperthyroidism (Figure 3). In skeletal muscle, glucose uptake represents the limiting step in glucose metabolism and it is mediated by the plasma membrane glucose transporter 4 (Glut4). THs stimulate Glut4 expression through a positive TRE (DR+4) site in its promoter, which represents a direct link with carbohydrate metabolism (Torrance et al., 1997). Studies focused to determine the physiological and pathophysiological role of THs in skeletal muscle have indicated that up to 57% of patients with hypothyroidism exhibit muscle damage, revealed by high levels of creatine kinase (Hekimsoy & Oktem, 2005). Remarkably, TH treatment on hypothyroid patients reduced creatine kinase levels and improved muscle complications (Hekimsoy & Oktem, 2005; Rodolico et al., 1998). Individuals suffering hyperthyroidism also display muscle weakness, and the normalization of TH function in these patients increases muscle strength and muscle cross-sectional area (Brennan et al., 2006). Insulin responsiveness is improved upon TH administration in patients and experimental models of hypothyroidism (Lopez-Noriega et al., 2019; Rochon et al., 2003). At the tissue level, THs promote insulin sensitivity in skeletal muscle, an effect that depends on the proper conversion of T4 to T3 by DIO2. Accordingly, cell cultures of myotubes developed from DIO2 knockout mice and DIO2 knockout mice exhibit insulin resistance (Table 1) (Grozovsky et al., 2009; Marsili et al., 2011). *In vivo* research mice treated with T4 rendered hyperthyroid has shown that insulin signaling is chronically activated in skeletal muscle lysates, which might be detrimental at long term (Figure 3) (Lopez-Noriega et al., 2017).

1.5.5 | Therapeutic approaches based on thyroid hormones or thyromimetics for diabetes mellitus

As previously mentioned hypothyroidism is associated with metabolic deregulations that increase the propensity to develop T2DM. TH supplementation normalizes parameters associated with DM, such as lipid and lipoprotein levels, diminishing the risk of developing this disease (Tzotzas et al., 2000). Studies in mice have also supported the potential of THs to improve metabolic health. TH supplementation has been shown to enhance glucose tolerance in wild-type mice (Lopez-Noriega et al., 2017) and to attenuate hyperglycemia in leptin receptor-deficient mice (Lin & Sun, 2011). Remarkably, research in mice has also determined the potential of THs to improve metabolic health and survival in experimental models of T1DM (Lopez-Noriega et al., 2017; Verga Falzacappa et al., 2009). Our results indicated that levothyroxine supplementation blunted the onset of experimental T1DM using the RIP-B7.1 model, which recapitulates the β-cell-specific autoimmune attack that suffer patients with T1DM (Lopez-Noriega et al., 2017). Interventional studies in humans using levothyroxine and the thyroxine enantiomer dextrothyroxine indicated that serum levels of LDL cholesterol were improved upon treatment. However, treatments were discontinued because participants developed serious adverse effects, substantiating the narrow therapeutic window of interventions based on the use of THs (Ochs et al., 2008; Sherman et al., 1997). Notwithstanding, the beneficial effects of interventions based on the use of THs in certain metabolic parameters have prompted the development of thyromimetics as promising agents to improve metabolic health. Newly generated thyromimetics could in principle bestow therapeutic benefits in specific cell types or organs producing an improvement of metabolic homeostasis, while avoiding side effects (Finan et al., 2016; Shoemaker et al., 2012). As such, fatty liver might be treated with thyromimetics designed to target specifically hepatic tissue (Taylor et al., 1997). An elegant work from Finan et al. (2016) has determined that the liver could be directly targeted using a glucagon-T3 mixed agonist, which mediates the selective delivery of T3 to the liver. In principle, similar approaches could potentially be effective to target the WAT, BAT, or pancreatic islets, since THs are known to play an important role in these tissues (Gavrila et al., 2017; Lopez-Noriega et al., 2017). Separated research has also investigated interventions targeting THRα1 or THRβ1 to obtain beneficial effects in target tissues while

avoiding undesirable effects on other target organs (Mishra et al., 2010). The THRβ agonists sobetirome and eprotirome have proved effectiveness in several experimental models reducing circulating LDL levels without altering heart rate (Martagon et al., 2015; Perra et al., 2008; Sharma et al., 2014). Separated research has also shown beneficial effects in hepatic steatosis, cholesterol, and triglyceride levels in rodents (Cable et al., 2009; Erion et al., 2007; Grover et al., 2003). However, in several cases, thyromimetics (e.g., eprotirome and DIPTA) have failed due to inefficacy or toxicity in human or pre-clinical research (Ladenson et al., 2010; Sjouke et al., 2014; van der Valk. et al., 2014). Remarkably, the selective THRβ agonists MGL-3196 and VK2809 have recently been investigated as lipid-lowering agents and in phase 2 clinical trials to treat NASH (Lonardo et al., 2017; Sinha et al., 2019; Taub et al., 2013). The latest results using MGL-3196 in humans indicate a significant reduction in hepatosteatosis after 12 and 36 weeks of treatment (Harrison et al., 2019; Sinha et al., 2019). Moreover, VK2809 has been shown to reduce hepatic lipid content and circulating LDL levels (Sinha et al., 2019). However, given the potential side effects of thyromimetics, a better understanding of their selective metabolic actions and experimental and clinical studies evaluating the long-term effects of these interventions is needed. Altogether, we believe that the proof of concept of the efficacy of thyromimetics has been established in several pathophysiological contexts. Sufficient arguments are available to foster research to generate site-specific modulators of TH function for DM and other diseases.

1.6 | Thyroid hormones in cancer

1.6.1 | The alterations of thyroid hormone function and cancer

In the scientific literature, there are enough evidences to clearly state that TH dysfunction increases the risk to develop different types of cancers, as elegantly reviewed by Liu et al. (2019). Recent reports have indicated that hyperthyroidism is associated with higher risks to develop thyroid cancer, breast cancer, and prostate cancer, while hypothyroidism is associated with a higher risk to develop thyroid cancer specifically within the first 10 years of follow-up (Hellevik et al., 2009; Kim et al., 2019; Tran et al., 2020). Another report has indicated that subclinical hypothyroid women without a previous history of thyroid disease have higher risk of breast cancer, bone cancer, or skin cancer (Tseng et al., 2015), whereas a different investigation indicates that breast cancer in hypothyroid women was associated with lower risk and better prognostic markers such as smaller tumor size or fewer metastases (Cristofanilli et al., 2005). Pertinent questions arise from epidemiological studies that in the majority of the cases have not been addressed. In this regard, information related to treatments used to normalize thyroid function, which might influence the risk, progression, and mortality of cancer, is not described (Hellevik et al., 2009; Kim et al., 2019; Pinter et al., 2017; Tseng et al., 2015). Limitations on clinical studies and conflicting results in the literature indicate that further studies are required to define the exact contribution of TH deregulations in carcinogenesis and cancer progression.

Of particular interest is the association of hepatocellular carcinoma (HCC) and hypothyroidism. Historically, the main known causes of HCC are viral hepatitis viruses, tobacco smoking, alcohol abuse, non-alcoholic steatohepatitis, T1DM, T2DM, autoimmune hepatitis, aflatoxin, and cirrhosis (Adami et al., 1996; Bosetti et al., 2014; Dragani, 2010; Hassan et al., 2002). However, genetic predisposition might play a role in the risk of HCC since it has been estimated that ~1/5 of diagnosed HCCs in the United States of America are not associated with known predisposing risk factors (El-Serag & Mason, 2000). Clinical findings have supported that hypothyroidism predisposes to HCC development, suggesting that improper TH function might represent a risk factor for this type of cancer (Hassan et al., 2009; Reddy et al., 2007). Reddy et al. reported a significantly increased odds ratio of 6.8 (95% confidence interval, 1.1–42.1) of hypothyroidism in patients with HCC with unknown cancer etiology when compared to patients with HCC with alcoholic liver disease or hepatitis C after adjusting for confounding factors. In this report, a twofold higher risk of HCC was determined for subjects with hypothyroidism when compared to patients without thyroid disorders. This association was specifically significant in female patients, even when analyses were adjusted to gender as a covariate. In this line, supportive research further analyzed the association of hypothyroidism and HCC risk in men and women (Hassan et al., 2009). In this work, authors determined that long-term (10 years or more) hypothyroidism was associated with greater risk of HCC specifically in women. Remarkably, the association between hypothyroidism and HCC in women was independent of other established risk factors for HCC. Supporting the role of thyroid dysfunction in HCC progression, TSH levels greater than 3.77 mIU/L have been associated with larger HCCs and increased levels of free T4 at the time of diagnosis have been associated with reduced survival (Pinter et al., 2017). Separated research in mammals indicates that hypothyroidism can directly cause liver cell damage, representing a risk factor for spontaneous liver cancer. Indeed, PAX8 heterozygous knockout mice, which have a direct disorder in thyroid tissue leading to a mild hypothyroidism, have a ~ threefold increased incidence of liver cancers (Lopez-Noriega et al., 2019). In principle, since hepatocarcinogenesis is a multistep process that originates from premalignant lesions, the severity of hypothyroidism and the effectiveness of treatments to normalize TH function might affect the risk to develop HCC.

1.6.2 | Molecular mechanisms of cancer in thyroid hormone dysfunction

The role of TH signaling in cancer has also been investigated, and growing evidences indicate that THRs play a significant role in inhibiting the proliferation, transformation, progression, invasion, and metastatic processes in tumors (Garcia-Silva & Aranda, 2004; Garcia-Silva et al., 2011; Liu et al., 2019). Supporting the role of THRs in

cancer, the lack of expression or mutations on THRs has been identified in several tumors, such as HCC, renal cell carcinomas, and papillary thyroid carcinomas (Table 1) (Chan & Privalsky, 2006; Kamiya et al., 2002; Kim & Cheng, 1830; Lin et al., 1999; Puzianowska-Kuznicka et al., 2002). Remarkably, several reports have described that ~70% of HCC harbor mutations in THRα or THRβ and several tumors exhibit mutation in both loci (Chan & Privalsky, 2006; Kim & Cheng, 1830; Lin et al., 1999). However, despite compelling evidence linking THR gene mutations to several cancers, other reports have not identified THR mutations in deep sequencing analysis of HCCs (Ahn et al., 2014; Cleary et al., 2013; Guichard et al., 2012; Schulze et al., 2015; Totoki et al., 2014), indicating that further research must be performed to fully determine the role of THR mutations in HCC. Notwithstanding, researchers have proposed that THRs act as tumor suppressors via inhibition of WNT signaling, inhibition of the expression of CDK2 and cyclin E, and stimulation of TGFβ signaling. These alterations lead to cell cycle arrest at the G1 phase of cell cycle (Yen et al., 2006). Mutant variants of TRHs, such as THRα-V390A and THRα-E350 K/P398S, act as dominant negative of the wild-type THRs and might escape from these regulatory mechanisms, promoting cancer progression (Chan & Privalsky, 2006; Lin et al., 1997; Sinha et al., 2018). The main effects of these mutations are the impairment of T3 binding and altered recognition of TRE, leading to deregulation of the expression of THR targets (Rosen & Privalsky, 2011). In this regard, whereas wild-type THRs modulate c-Jun/AP-1 function and suppress anchorage-independent growth, THR mutants are ineffective (Chan & Privalsky, 2006). Research in animals has indicated that mice transgenic for *v-erbA*, an avian retroviral gag gene fused to a mutated THR that produces a dominant negative of the THRα, exhibited hypothyroidism and increased incidence of HCCs in male mice (58% in transgenic mice vs. 8% in control mice) (Barlow et al., 1994). These data further indicate that inadequate TH signaling predisposes to liver cancer in male mice (Barlow et al., 1994). Reports have indicated that early in the tumorigenic process, there is a restriction on THRα1 and THRβ1 expression, which favors the progression to HCC (Frau et al., 2015). Interference of THRβ1 expression promoted cell growth and migration in HCC cells. Moreover, down-regulation of THRβ1 induced the proliferative capacity, indicating that this receptor is a negative regulator of cell replication and that hypothyroidism favors the progression of HCC (Frau et al., 2015). These data suggest that THR agonists could be studied as therapeutic targets to block HCC development and progression.

Additional research has also pointed that other components of TH signaling might affect different aspects of carcinogenesis and cancer progression. In particular, the interaction of T4 with integrin αvβ3 has been shown to play a significant role in cancer progression and invasion. Integrin αvβ3 is a cell adhesion molecule that connects the cytoskeleton with the extracellular matrix or other cells. Interaction of T4 with integrin αvβ3 is a non-genomic action of THs that supports angiogenesis. This process facilitates the generation of new blood vessels during development and wound healing (Al Husseini et al., 2013; Liu et al., 2014; Zhang et al., 2019). However, the same process favors cancer progression (Davis et al., 2016; Schmohl et al., 2019).

At mechanistic level, T4-activated integrin αvβ3 enhances signaling non-genomic action of THs via activation of MAPK/ERK1/2 and/or PI3 K signaling. Activation of these signaling pathways produces cellular proliferation, which might favor cancer progression, and blockade of apoptotic processes and metastasis (Davis et al., 2016; Mousa et al., 2012, 2018; Weingarten et al., 2018). Moreover, separated evidences indicate that differences in deiodinase expression and differential splicing have been found in several cancers (Meyer et al., 2008) and increased TSHR expression have been detected in liver, ovarian, lung, and breast cancers (Table 1) (Govindaraj et al., 2012; Gyftaki et al., 2014; Kim et al., 2012; Shih et al., 2018; Tian et al., 2010). Moreover, it is known that TSHR is functional in the majority of human HCCs and that high TSHR expression is correlated with unfavorable postoperative outcome in patients with HCC receiving surgical treatment (Shih et al., 2018). These results suggest that high TSH levels might confer pathophysiological advantage to HCCs. Therefore, it is tempting to speculate that alterations in TH signaling due to changes in deiodinase or TSHR expression and/or activity could also play a role in tumor progression. Therefore, deiodinase or TSHR expression or activation could be studied as markers for cancer diagnosis (Piekielko-Witkowska et al., 2009).

Alterations in thyroid function have been associated with mitochondrial dysfunction, leading to increased generation of mitochondrial reactive oxygen species (ROS) and altered antioxidant defenses such as superoxide dismutase, catalase, and glutathione (Grattagliano et al., 2003; Lopez-Noriega et al., 2019; Venditti et al., 2003; Videla et al., 2015; Zhao et al., 2020). In this regard, an elegant study has recently shown that mitochondria isolated from the liver of hyperthyroid rats display an increase on oxygen consumption, the generation of hydrogen peroxide production, and the accumulation of lipid peroxidation, while present a reduced efficiency of oxidative phosphorylation (Venediktova et al., 2020). Remarkably, experiments using a model of hypothyroidism in rats have also shown that, in liver mitochondrial isolations, mitochondrial respiration is decreased and the capacity of mitochondria to remove hydrogen peroxide is compromised (Venditti et al., 2003). If antioxidant responses are not capable of restoring cellular homeostasis, increased ROS generation results in the accumulation of oxidative damage to macromolecules including lipids, proteins, and DNA (Mancini et al., 2016). ROS induce nicks in DNA that, if not repaired, contribute to premature senescence and carcinogenic processes on susceptible cells. T3 is known to increase the levels of 8-oxo-2'-deoxyguanosine (8-OH-dG), a biomarker of oxidative DNA damage. Moreover, a strong cofocalization of 8-OH-dG with TP53BP1 has supported the presence of oxidized DNA at double-strand break sites. Supporting the role of TH-induced oxidative stress leading to DNA damage, antioxidant treatment using N-acetyl-l-cysteine in TH-treated samples blunted formation of 8-OH-dG/TP53BP1 foci (Zambrano et al., 2014). Several studies have pinpointed that the accumulation of liver damage in hypothyroidism and the increased propensity to develop HCC could be mediated by the accumulation of oxidative damage (Baskol et al., 2007; Lopez-Noriega et al., 2019; Nanda et al., 2007). Mild hypothyroid PAX8 heterozygous knockout mice exhibit

an ~threefold increase in the prevalence of liver cancers (Table 1). Analyses in liver tissues isolated before the initiation of cancer occurrence indicated the existence of increased ROS production and accumulation of oxidative damage, suggesting a causal link with carcinogenesis. Data generated in the murine model of PAX8 deficiency suggest that humans bearing *PAX8* mutations might have greater propensity to develop metabolic complications and liver cancer. In this line, a study investigated the associations of two single nucleotide polymorphisms (SNPs) on *PAX8* with HCC survival (Table 1) (Ma et al., 2017). In this report, patients harboring the rs1110839 GT/GG genotypes and rs4848320 CT/TT genotypes exhibited longer survival time than patients harboring the rs1110839 TT and rs4848320 CC genotypes. Moreover, multivariable Cox regression analysis showed that these SNPs had a significant prognostic value for HCC, suggesting that *PAX8* gene might be considered a biomarker to predict HCC survival.

Interestingly, the scientific literature indicates that, despite the known pro-proliferative actions of THs, potentiated cellular proliferation driven by THs is not sufficient *per se* to enhance HCC progression (Columbano et al., 2006, 2008; Ledda-Columbano et al., 2000; Perra et al., 2009). An elegant report investigating THR knockout mice has supported that TH function has a dual role in tumor development (Martinez-Iglesias, Garcia-Silva, Tenbaum, et al., 2009). Research performed in THRα-THRβ double homozygous knockout mice showed that the lack of THR results in the restriction of benign tumor formation at early stages of skin carcinogenesis, but enhanced malignant transformation at the later stages of the disease. These mice developed fewer number of tumors than wild-type mice (Martinez-Iglesias, Garcia-Silva, Tenbaum, et al., 2009). Subsequent work on experimental models of cancer using nude mice indicated that systemic hypothyroidism slows tumor growth but potentiates metastatic processes in a process that is independent of THRβ1 expression (Martinez-Iglesias, Garcia-Siva, Regadera, et al., 2009). Hypothyroid mice exhibited greater number of spontaneous metastasis in tissues such as lung, liver, or bone, when compared to euthyroid hosts. These effects were determined in hepatoma and breast cancer cells that stably express THRβ1, indicating that systemic TH function is more relevant than direct effects of THRβ1 on tumorigenesis (Martinez-Iglesias, Garcia-Siva, Regadera, et al., 2009). These results support the notion that restricted thyroid function favors cancer metastasis.

1.6.3 | Therapeutic approaches based on thyroid hormones or thyromimetics for cancer

In the late nineteenth century, Beatson proposed the use of thyroid extract in conjunction with oophorectomy as a therapy for breast cancer (Beatson, 1896). In this line, TH treatment has been shown to reduce HCC progression, development of lung metastases, and the risk of colorectal cancer (Frau et al., 2015; Kowalik et al., 2020; Ledda-Columbano et al., 2000; Rennert et al., 2010). Despite the fact that THs are known to induce hepatocyte proliferation, TH administration

or treatments with the THRβ agonist sobetirome induces regression of carcinogen-induced hepatic nodules in xenobiotic-based research models (Perra et al., 2009). These findings support the exploration of treatments based on the use of THs or thyromimetics for cancer treatment. However, it is unlikely that current thyromimetics, such as sobetirome, could be used in the clinical practice for cancer treatment given their potential severe side effects (Lammel Lindemann & Webb, 2016). Moreover, separated evidences indicate that TH treatments for hypothyroidism are associated with increased risk of renal carcinomas and breast cancer (Kapdi & Wolfe, 1976; Rosenberg et al., 1990), suggesting that TH supplementation might accelerate tumor growth or recurrence (Hercbergs, 1996, 1999). Notwithstanding, the use of tissue-specific thyromimetics devoid of toxicity might be realistic in the future for cancer treatment, but further studies are required to determine their safety and efficacy.

1.7 | Concluding remarks

THs are essential hormones that orchestrate whole-body metabolism acting on every single cell of the body. Alterations in TH function have been associated with both disease and health, ranging from exceptional long longevity in individuals with a low thyroid function to the lack of viability in individuals devoid of THs. Studies in humans have demonstrated that the oldest old exhibit restricted TH function. However, studies directly targeting TH production do not extend life span, indicating that a genetic or epigenetic signature is required to achieve the longest life expectancy. Alterations in THs leading to different forms of hyperthyroidism and hypothyroidism have been associated with several age-related diseases, such as DM and cancer. In this regard, different types of DM have been determined as risk factors to develop certain types of cancer. The association of TH alterations with different aspects of the pathogenesis of DM and cancer and overall life expectancy suggests that aging, DM, and cancer share certain mechanisms of pathogenesis in which THs contribute. Therefore, it is tempting to speculate that treatments or interventions designed to treat DM might have positive effects on cancer and *vice versa*, which might also have beneficial consequences on aging and life expectancy. Further research is required to increase knowledge on the alterations that occur in early stages of DM and cancer related to THs, which currently limits the identification of potential biomarkers and targets to facilitate the diagnosis, the prognosis, and the development of novel therapies for DM and cancer. The pleiotropic effects of TH alterations in different tissues indicate that personalized and precision medicine must be applied to provide the optimal treatment for each patient. The narrow therapeutic window of interventions based on the use of natural THs has prompted the development of thyromimetics. However, the majority of thyromimetics tested to date have failed due to inefficacy or toxicity. Notwithstanding, the latest research indicates that there is hope in the development of safe and effective thyromimetics that might provide therapeutic benefit for different diseases including cancer and DM.

AUTHOR CONTRIBUTIONS

A.M-M conceived the manuscript. All authors contributed to the manuscript revision and approved the submitted version.

ORCID

Alejandro Martin-Montalvo 🔟 https://orcid.org/0000-0002-3886-5355

REFERENCES

Abe, E., Marians, R. C., Yu, W., Wu, X.-B., Ando, T., Li, Y., Iqbal, J., Eldeiry, L., Rajendren, G., Blair, H. C., Davies, T. F., & Zaidi, M. (2003). TSH is a negative regulator of skeletal remodeling. *Cell*, 115, 151–162. https://doi.org/10.1016/s0092-8674(03)00771-2

Adami, H.-O., Chow, W.-H., Nyren, O., Berne, C., Linet, M. S., Ekbom, A., Wolk, A., McLaughlin, J. K., & Fraumeni, J. F. (1996). Excess risk of primary liver cancer in patients with diabetes mellitus. *Journal of the National Cancer Institute*, 88, 1472–1477. https://doi.org/10.1093/jnci/88.20.1472

Aguayo-Mazzucato, C., Zavacki, A. M., Marinelarena, A., Hollister-Lock, J., El Khattabi, I., Marsili, A., Weir, G. C., Sharma, A., Larsen, P. R., & Bonner-Weir, S. (2013). Thyroid hormone promotes postnatal rat pancreatic beta-cell development and glucose-responsive insulin secretion through MAFA. *Diabetes*, 62, 1569–1580. https://doi.org/10.2337/db12-0849

Aguayo-Mazzucato, C., Lee Jr, T. B., Matzko, M., Dilenno, A., Rezanejad, H., Ramadoss, P., Scanlan, T., Zavacki, A. M., Larsen, P. R., Hollenberg, A., Colton, C., Sharma, A., & Bonner-Weir, S. (2018). T3 induces both markers of maturation and aging in pancreatic beta-cells. *Diabetes*, 67, 1322–1331. https://doi.org/10.2337/db18-0030

Aguayo-Mazzucato, C., DiIenno, A., Hollister-Lock, J., Cahill, C., Sharma, A., Weir, G., Colton, C., & Bonner-Weir, S. (2015). MAFA and T3 drive maturation of both fetal human islets and insulin-producing cells differentiated from hESC. *The Journal of Clinical Endocrinology & Metabolism*, 100(10), 3651–3659. https://doi.org/10.1210/jc.2015-2632

Aguayo-Mazzucato, C., Koh, A., El Khattabi, I., Li, W.-C., Toschi, E., Jermendy, A., Juhl, K., Mao, K., Weir, G. C., Sharma, A., & Bonner-Weir, S. (2011). Mafa expression enhances glucose-responsive insulin secretion in neonatal rat beta cells. *Diabetologia*, 54(3), 583–593. https://doi.org/10.1007/s00125-010-2026-z

Ahn, S. M., Jang, S. J., Shim, J. H., Kim, D., Hong, S., Sung, C. O., Baek, D., Haq, F., Ansari, A. A., Lee, S. Y., Chun, S., Choi, S., Choi, H., Kim, J., Kim, S., Hwang, S., Lee, Y., Lee, J., Jung, J., ... Kong, G. (2014). Genomic portrait of resectable hepatocellular carcinomas: implications of RB1 and FGF19 aberrations for patient stratification. *Hepatology*, 60, 1972–1982. https://doi.org/10.1002/hep.27198

Al Husseini, A., Bagnato, G., Farkas, L., Gomez-Arroyo, J., Farkas, D., Mizuno, S., Kraskauskas, D., Abbate, A., Van Tassel, B., Voelkel, N. F., & Bogaard, H. J. (2013). Thyroid hormone is highly permissive in angioproliferative pulmonary hypertension in rats. *The European Respiratory Journal*, 41, 104–114. https://doi.org/10.1183/09031936.00196511

Alderman, J. M. K., Flurkey, K., Brooks, N. L., Naik, S. B., Gutierrez, J. M., Srinivas, U., Ziara, K. B., Jing, L., Boysen, G., Bronson, R., Klebanov, S., Chen, X., Swenberg, J. A., Stridsberg, M., Parker, C. E., Harrison, D. E., & Combs, T. P. (2009). Neuroendocrine inhibition of glucose production and resistance to cancer in dwarf mice. *Experimental Gerontology*, 44, 26–33. https://doi.org/10.1016/j.exger.2008.05.014

Arantes-Oliveira, N., Berman, J. R., & Kenyon, C. (2003). Healthy animals with extreme longevity. *Science*, 302, 611. https://doi.org/10.1126/science.1089169

Araujo, J., Brandão, L. A. C., Guimarães, R. L., Santos, S., Falcão, E. A., Milanese, M., Segat, L., Souza, P. R., de Lima-Filho, J. L., & Crovella, S. (2008). Prevalence of autoimmune thyroid disease and thyroid dysfunction in young Brazilian patients with type 1 diabetes. *Pediatric Diabetes*, 9, 272–276. https://doi.org/10.1111/j.1399-5448.2008.00394.x

Atzmon, G., Barzilai, N., Hollowell, J. G., Surks, M. I., & Gabriely, I. (2009). Extreme longevity is associated with increased serum thyrotropin. *The Journal of Clinical Endocrinology and Metabolism*, 94, 1251–1254. https://doi.org/10.1210/jc.2008-2325

Atzmon, G., Barzilai, N., Surks, M. I., & Gabriely, I. (2009). Genetic predisposition to elevated serum thyrotropin is associated with exceptional longevity. *The Journal of Clinical Endocrinology and Metabolism*, 94, 4768–4775. https://doi.org/10.1210/jc.2009-0808

Aubert, C. E., Bauer, D. C., da Costa, B. R., Feller, M., Rieben, C., Simonsick, E. M., Yaffe, K., & Rodondi, N. (2017). The association between subclinical thyroid dysfunction and dementia: The Health, Aging and Body Composition (Health ABC) Study. *Clinical Endocrinology*, 87(5), 617–626. https://doi.org/10.1111/cen.13458

Auer, J., Scheibner, P., Mische, T., Langsteger, W., Eber, O., & Eber, B. (2001). Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *American Heart Journal*, 142, 838–842. https://doi.org/10.1067/mhj.2001.119370

Bann, D. V., Jin, Q., Sheldon, K. E., Houser, K. R., Nguyen, L., Warrick, J. I., Baker, M. J., Broach, J. R., Gerhard, G. S., & Goldenberg, D. (2019). Genetic variants implicate dual oxidase-2 in familial and sporadic nonmedullary thyroid cancer. *Cancer Research*, 79, 5490–5499. https://doi.org/10.1158/0008-5472.CAN-19-0721

Bannister, P., & Barnes, I. (1989). Use of sensitive thyrotrophin measurements in an elderly population. *Gerontology*, 35, 225–229. https://doi.org/10.1159/000213027

Bano, A., Chaker, L., Mattace-Raso, F. U. S., Terzikhan, N., Kavousi, M., Peeters, R. P., & Franco, O. H. (2019). Thyroid function and life expectancy with and without noncommunicable diseases: A population-based study. *PLoS Med*, 16, e1002957. https://doi.org/10.1371/journal.pmed.1002957

Bano, A., Chaker, L., Darweesh, S. K. L., Korevaar, T. I. M., Mattace-Raso, F. U. S., Dehghan, A., Franco, O. H., van der Geest, J. N., Ikram, M. A., & Peeters, R. P. (2016). Gait patterns associated with thyroid function: The Rotterdam Study. *Scientific Reports*, 6, 38912. https://doi.org/10.1038/srep38912

Bano, A., Chaker, L., Plompen, E. P. C., Hofman, A., Dehghan, A., Franco, O. H., Janssen, H. L. A., Murad, S. D., & Peeters, R. P. (2016). Thyroid function and the risk of nonalcoholic fatty liver disease: The Rotterdam Study. *The Journal of Clinical Endocrinology and Metabolism*, 101, 3204–3211. https://doi.org/10.1210/jc.2016-1300

Barlow, C., Meister, B., Lardelli, M., Lendahl, U., & Vennstrom, B. (1994). Thyroid abnormalities and hepatocellular carcinoma in mice transgenic for v-erbA. *The EMBO Journal*, 13, 4241–4250.

Baskol, G., Atmaca, H., Tanrıverdi, F., Baskol, M., Kocer, D., & Bayram, F. (2007). Oxidative stress and enzymatic antioxidant status in patients with hypothyroidism before and after treatment. *Experimental and Clinical Endocrinology & Diabetes*, 115(08), 522–526. https://doi.org/10.1055/s-2007-981457

Beatson, G. T. (1896). On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Transactions. Medico-chirurgical Society of Edinburgh*, 15, 153–179.

Bensenor, I. M., Lotufo, P. A., Menezes, P. R., & Scazufca, M. (2010). Subclinical hyperthyroidism and dementia: The Sao Paulo Ageing & Health Study (SPAH). *BMC Public Health*, 10, 298. https://doi.org/10.1186/1471-2458-10-298

Biondi, B., & Cooper, D. S. (2008). The clinical significance of subclinical thyroid dysfunction. *Endocrine Reviews*, 29, 76–131. https://doi.org/10.1210/er.2006-0043

Biondi, B., Kahaly, G. J., & Robertson, R. P. (2019). Thyroid dysfunction and diabetes mellitus: Two closely associated disorders. *Endocrine Reviews*, 40, 789–824. https://doi.org/10.1210/er.2018-00163

Biondi, B., Palmieri, E. A., Lombardi, G., & Fazio, S. (2002). Effects of subclinical thyroid dysfunction on the heart. *Annals of Internal Medicine*, 137, 904–914. https://doi.org/10.7326/0003-4819-137-11-200212030-00011

Blum, M. R., Bauer, D. C., Collet, T.-H., Fink, H. A., Cappola, A. R., da Costa, B. R., Wirth, C. D., Peeters, R. P., Åsvold, B. O., den Elzen, W. P. J., Luben, R. N., Imaizumi, M., Bremner, A. P., Gogakos, A., Eastell, R., Kearney, P. M., Strotme, E. S., Wallace, E. R., Hoff, M., … Rodondi, N. (2015). Subclinical thyroid dysfunction and fracture risk. *JAMA*, 313(20), 2055–2065. https://doi.org/10.1001/jama.2015.5161

Boelaert, K. (2013). Thyroid dysfunction in the elderly. *Nature Reviews Endocrinology*, 9, 194–204. https://doi.org/10.1038/nrendo.2013.30

Boelen, A., Wiersinga, W. M., & Fliers, E. (2008). Fasting-induced changes in the hypothalamus-pituitary-thyroid axis. *Thyroid*, 18, 123–129. https://doi.org/10.1089/thy.2007.0253

Bosetti, C., Turati, F., & La Vecchia, C. (2014). Hepatocellular carcinoma epidemiology. *Best Practice & Research Clinical Gastroenterology*, 28, 753–770. https://doi.org/10.1016/j.bpg.2014.08.007

Bowers, J., Terrien, J., Clerget-Froidevaux, M. S., Gothié, J. D., Rozing, M. P., Westendorp, R. G. J., Van Heemst, D., & Demeneix, B. A. (2013). Thyroid hormone signaling and homeostasis during aging. *Endocrine Reviews*, 34, 556–589. https://doi.org/10.1210/er.2012-1056

Brandt, F., Green, A., Hegedus, L., & Brix, T. H. (2011). A critical review and meta-analysis of the association between overt hyperthyroidism and mortality. *European Journal of Endocrinology*, 165, 491–497. https://doi.org/10.1530/EJE-11-0299

Brandt, F., Thvilum, M., Almind, D., Christensen, K., Green, A., Hegedüs, L., & Brix, T. H. (2013). Morbidity before and after the diagnosis of hyperthyroidism: A nationwide register-based study. *PLoS One*, 8, e66711. https://doi.org/10.1371/journal.pone.0066711

Brennan, M. D., Powell, C., Kaufman, K. R., Sun, P. C., Bahn, R. S., & Nair, K. S. (2006). The impact of overt and subclinical hyperthyroidism on skeletal muscle. *Thyroid*, 16, 375–380. https://doi.org/10.1089/thy.2006.16.375

Brent, G. A. (2012). Mechanisms of thyroid hormone action. *The Journal of Clinical Investigation*, 122, 3035–3043. https://doi.org/10.1172/JCI60047

Broeders, E. P. M., Vijgen, G. H. E. J., Havekes, B., Bouvy, N. D., Mottaghy, F. M., Kars, M., Schaper, N. C., Schrauwen, P., Brans, B., & van Marken Lichtenbelt, W. D. (2016). Thyroid hormone activates brown adipose tissue and increases non-shivering thermogenesis–A cohort study in a group of thyroid carcinoma patients. *PLoS One*, 11, e0145049. https://doi.org/10.1371/journal.pone.0145049

Brown-Borg, H. M. (2007). Hormonal regulation of longevity in mammals. *Ageing Research Reviews*, 6, 28–45. https://doi.org/10.1016/j.arr.2007.02.005

Brown-Borg, H. M. (2009). Hormonal control of aging in rodents: The somatotropic axis. *Molecular and Cellular Endocrinology*, 299, 64–71. https://doi.org/10.1016/j.mce.2008.07.001

Brown-Borg, H. M., Borg, K. E., Meliska, C. J., & Bartke, A. (1996). Dwarf mice and the ageing process. *Nature*, 384, 33. https://doi.org/10.1038/384033a0

Buffenstein, R., & Pinto, M. (2009). Endocrine function in naturally long-living small mammals. *Molecular and Cellular Endocrinology*, 299, 101–111. https://doi.org/10.1016/j.mce.2008.04.021

Cable, E. E., Finn, P. D., Stebbins, J. W., Hou, J., Ito, B. R., van Poelje, P. D., Linemeyer, D. L., & Erion, M. D. (2009). Reduction of hepatic steatosis in rats and mice after treatment with a liver-targeted thyroid hormone receptor agonist. *Hepatology*, 49, 407–417. https://doi.org/10.1002/hep.22572

Camacho, P., Gordon, D., Chiefari, E., Yong, S., DeJong, S., Pitale, S., Russo, D., & Filetti, S. (2000). A Phe 486 thyrotropin receptor mutation in an autonomously functioning follicular carcinoma that was causing hyperthyroidism. *Thyroid*, 10, 1009–1012. https://doi.org/10.1089/thy.2000.10.1009

Canani, L. H., Capp, C., Dora, J. M., Meyer, E. L. S., Wagner, M. S., Harney, J. W., Larsen, P. R., Gross, J. L., Bianco, A. C., & Maia, A. L. (2005). The type 2 deiodinase A/G (Thr92Ala) polymorphism is associated with decreased enzyme velocity and increased insulin resistance in patients with type 2 diabetes mellitus. *The Journal of Clinical Endocrinology and Metabolism*, 90, 3472–3478. https://doi.org/10.1210/jc.2004-1977

Cao, X., Kambe, F., Moeller, L. C., Refetoff, S., & Seo, H. (2005). Thyroid hormone induces rapid activation of Akt/protein kinase B-mammalian target of rapamycin-p70S6K cascade through phosphatidylinositol 3-kinase in human fibroblasts. *Molecular Endocrinology*, 19, 102–112. https://doi.org/10.1210/me.2004-0093

Cappola, A. R., & Ladenson, P. W. (2003). Hypothyroidism and atherosclerosis. *The Journal of Clinical Endocrinology and Metabolism*, 88, 2438–2444. https://doi.org/10.1210/jc.2003-030398

Carew, L. B., Evarts, K. G., & Alster, F. A. (1997). Growth and plasma thyroid hormone concentrations of chicks fed diets deficient in essential amino acids. *Poultry Science*, 76, 1398–1404. https://doi.org/10.1093/ps/76.10.1398

Cavallo-perin, P., Bruno, A., Boine, L., Cassader, M., Lenti, G., & Pagano, G. (1988). Insulin resistance in Graves' disease: A quantitative in-vivo evaluation. *European Journal of Clinical Investigation*, 18, 607–613. https://doi.org/10.1111/j.1365-2362.1988.tb01275.x

Celani, M. F., Bonati, M. E., & Stucci, N. (1994). Prevalence of abnormal thyrotropin concentrations measured by a sensitive assay in patients with type 2 diabetes mellitus. *Diabetes Research*, 27, 15–25.

Ceresini, G., Ceda, G. P., Lauretani, F., Maggio, M., Bandinelli, S., Guralnik, J. M., Cappola, A. R., Usberti, E., Morganti, S., Valenti, G., & Ferrucci, L. (2011). Mild thyroid hormone excess is associated with a decreased physical function in elderly men. *The Aging Male*, 14, 213–219. https://doi.org/10.3109/13685538.2011.606514

Ceresini, G., Ceda, G. P., Lauretani, F., Maggio, M., Usberti, E., Marina, M., Bandinelli, S., Guralnik, J. M., Valenti, G., & Ferrucci, L. (2013). Thyroid status and 6-year mortality in elderly people living in a mildly iodine-deficient area: the aging in the Chianti Area Study. *Journal of the American Geriatrics Society*, 61, 868–874. https://doi.org/10.1111/jgs.12267

Chaker, L., Cappola, A. R., Mooijaart, S. P., & Peeters, R. P. (2018). Clinical aspects of thyroid function during ageing. *The Lancet Diabetes & Endocrinology*, 6, 733–742. https://doi.org/10.1016/S2213-8587(18)30028-7

Chan, I. H., & Privalsky, M. L. (2006). Thyroid hormone receptors mutated in liver cancer function as distorted antimorphs. *Oncogene*, 25, 3576–3588. https://doi.org/10.1038/sj.onc.1209389

Chen, R.-H., Chen, H.-Y., Man, K.-M., Chen, S.-J., Chen, W., Liu, P.-L., Chen, Y.-H., & Chen, W.-C. (2019). Thyroid diseases increased the risk of type 2 diabetes mellitus: A nation-wide cohort study. *Medicine*, 98, e15631. https://doi.org/10.1097/MD.0000000000015631

Cheng, S. Y. (2003). Thyroid hormone receptor mutations in cancer. *Molecular and Cellular Endocrinology*, 213, 23–30. https://doi.org/10.1016/j.mce.2003.10.051

Chiofalo, B., Fazio, E., Cucinotta, S., & Cravana, C. (2019). Thyroid and lipid status in guide dogs during training: Effects of dietary protein and fat content. *Animals*, 9, https://doi.org/10.3390/ani9090597

Chiovato, L., Mariotti, S., & Pinchera, A. (1997). Thyroid diseases in the elderly. *Bailliere's Clinical Endocrinology and Metabolism*, 11, 251–270. https://doi.org/10.1016/s0950-351x(97)80272-8

Chung, G. E., Kim, D., Kim, W., Yim, J. Y., Park, M. J., Kim, Y. J., Yoon, J.-H., & Lee, H.-S. (2012). Non-alcoholic fatty liver disease across the spectrum of hypothyroidism. *Journal of Hepatology*, 57, 150–156. https://doi.org/10.1016/j.jhep.2012.02.027

Cleary, S. P., Jeck, W. R., Zhao, X., Chen, K., Selitsky, S. R., Savich, G. L., Tan, T.-X., Wu, M. C., Getz, G., Lawrence, M. S., Parker, J. S., Li, J., Powers, S., Kim, H., Fischer, S., Guindi, M., Ghanekar, A., & Chiang, D. Y. (2013). Identification of driver genes in hepatocellular carcinoma by exome sequencing. *Hepatology*, 58, 1693–1702. https://doi.org/10.1002/hep.26540

Columbano, A., Pibiri, M., Deidda, M., Cossu, C., Scanlan, T. S., Chiellini, G., Muntoni, S., & Ledda-Columbano, G. M. (2006). The thyroid hormone receptor-beta agonist GC-1 induces cell proliferation in rat liver and pancreas. *Endocrinology*, 147, 3211–3218. https://doi.org/10.1210/en.2005-1561

Columbano, A., Simbula, M., Pibiri, M., Perra, A., Deidda, M., Locker, J., Pisanu, A., Uccheddu, A., & Ledda-Columbano, G. M. (2008). Triiodothyronine stimulates hepatocyte proliferation in two models of impaired liver regeneration. *Cell Proliferation*, 41, 521–531. https://doi.org/10.1111/j.1365-2184.2008.00532.x

Cristofanilli, M., Yamamura, Y., Kau, S.-W., Bevers, T., Strom, S., Patangan, M., Hsu, L., Krishnamurthy, S., Theriault, R. L., & Hortobagyi, G. N. (2005). Thyroid hormone and breast carcinoma. Primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma. *Cancer*, 103, 1122–1128. https://doi.org/10.1002/cncr.20881

Davis, P. J., Goglia, F., & Leonard, J. L. (2016). Nongenomic actions of thyroid hormone. *Nature Reviews Endocrinology*, 12, 111–121. https://doi.org/10.1038/nrendo.2015.205

De Andrade, P. B. M., Neff, L. A., Strosova, M. K., Arsenijevic, D., Patthey-Vuadens, O., Scapozza, L., Montani, J.-P., Ruegg, U. T., Dulloo, A. G., & Dorchies, O. M. (2015). Caloric restriction induces energy-sparing alterations in skeletal muscle contraction, fiber composition and local thyroid hormone metabolism that persist during catch-up fat upon refeeding. *Frontiers in Physiology*, 6, 254. https://doi.org/10.3389/fphys.2015.00254

Dimitriadis, G., Mitrou, P., Lambadiari, V., Boutati, E., Maratou, E., Panagiotakos, D. B., Koukkou, E., Tzanela, M., Thalassinos, N., & Raptis, S. A. (2006). Insulin action in adipose tissue and muscle in hypothyroidism. *The Journal of Clinical Endocrinology and Metabolism*, 91, 4930–4937. https://doi.org/10.1210/jc.2006-0478

Dittmar, M., & Kahaly, G. J. (2010). Genetics of the autoimmune polyglandular syndrome type 3 variant. *Thyroid*, 20, 737–743. https://doi.org/10.1089/thy.2010.1639

Donda, A., & Lemarchand-Beraud, T. (1989). Aging alters the activity of 5'-deiodinase in the adenohypophysis, thyroid gland, and liver of the male rat. *Endocrinology*, 124, 1305–1309. https://doi.org/10.1210/endo-124-3-1305

Dora, J. M., Machado, W. E., Rheinheimer, J., Crispim, D., & Maia, A. L. (2010). Association of the type 2 deiodinase Thr92Ala polymorphism with type 2 diabetes: case-control study and meta-analysis. *European Journal of Endocrinology*, 163, 427–434. https://doi.org/10.1530/EJE-10-0419

Dragani, T. A. (2010). Risk of HCC: genetic heterogeneity and complex genetics. *Journal of Hepatology*, 52, 252–257. https://doi.org/10.1016/j.jhep.2009.11.015

Duntas, L. H. (2002). Thyroid disease and lipids. *Thyroid : Official Journal of the American Thyroid Association*, 12, 287–293. https://doi.org/10.1089/10507250252949405

Duntas, L. H. (2018). Thyroid function in aging: A discerning approach. *Rejuvenation Research*, 21, 22–28. https://doi.org/10.1089/rej.2017.1991

El-Serag, H. B., & Mason, A. C. (2000). Risk factors for the rising rates of primary liver cancer in the United States. *Archives of Internal Medicine*, 160, 3227–3230. https://doi.org/10.1001/archinte.160.21.3227

Erion, M. D., Cable, E. E., Ito, B. R., Jiang, H., Fujitaki, J. M., Finn, P. D., Zhang, B.-H., Hou, J., Boyer, S. H., van Poelje, P. D., & Linemeyer, D. L. (2007). Targeting thyroid hormone receptor-beta agonists to the liver reduces cholesterol and triglycerides and improves the therapeutic index. *Proceedings of the National Academy of Sciences of the United States of America*, 104, 15490–15495. https://doi.org/10.1073/pnas.0702759104

Finan, B., Clemmensen, C., Zhu, Z., Stemmer, K., Gauthier, K., Müller, L., De Angelis, M., Moreth, K., Neff, F., Perez-Tilve, D., Fischer, K., Lutter, D., Sánchez-Garrido, M. A., Liu, P., Tuckermann, J., Malehmir, M., Healy, M. E., Weber, A., Heikenwalder, M., ... Müller, T. D. (2016). Chemical hybridization of glucagon and thyroid hormone optimizes therapeutic impact for metabolic disease. *Cell*, 167(3), 843–857. e14. https://doi.org/10.1016/j.cell.2016.09.014

Flamant, F., Cheng, S.-Y., Hollenberg, A. N., Moeller, L. C., Samarut, J., Wondisford, F. E., Yen, P. M., & Refetoff, S. (2017). Thyroid hormone signaling pathways: time for a more precise nomenclature. *Endocrinology*, 158, 2052–2057. https://doi.org/10.1210/en.2017-00250

Flores-Morales, A., Gullberg, H., Fernandez, L., Stahlberg, N., Lee, N. H., Vennström, B, & Norstedt, G. (2002). Patterns of liver gene expression governed by TRbeta. *Molecular Endocrinology*, 16, 1257–1268. https://doi.org/10.1210/mend.16.6.0846

Flurkey, K., Papaconstantinou, J., Miller, R. A., & Harrison, D. E. (2001). Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. *Proceedings of the National Academy of Sciences of the United States of America*, 98, 6736–6741. https://doi.org/10.1073/pnas.111158898

Fontana, L., Klein, S., Holloszy, J. O., & Premachandra, B. N. (2006). Effect of long-term calorie restriction with adequate protein and micronutrients on thyroid hormones. *The Journal of Clinical Endocrinology and Metabolism*, 91, 3232–3235. https://doi.org/10.1210/jc.2006-0328

Franklyn, J. A., Sheppard, M. C., & Maisonneuve, P. (2005). Thyroid function and mortality in patients treated for hyperthyroidism. *JAMA*, 294, 71–80. https://doi.org/10.1001/jama.294.1.71

Frau, C., Loi, R., Petrelli, A., Perra, A., Menegon, S., Kowalik, M. A., Pinna, S., Leoni, V. P., Fornari, F., Gramantieri, L., Ledda-Columbano, G. M., Giordano, S., & Columbano, A. (2015). Local hypothyroidism favors the progression of preneoplastic lesions to hepatocellular carcinoma in rats. *Hepatology*, 61, 249–259. https://doi.org/10.1002/hep.27399

Gao, N., Zhang, W., Zhang, Y. Z., Yang, Q., & Chen, S. H. (2013). Carotid intima-media thickness in patients with subclinical hypothyroidism: A meta-analysis. *Atherosclerosis*, 227, 18–25. https://doi.org/10.1016/j.atherosclerosis.2012.10.070

Garcia-Silva, S., & Aranda, A. (2004). The thyroid hormone receptor is a suppressor of ras-mediated transcription, proliferation, and transformation. *Molecular and Cellular Biology*, 24, 7514–7523. https://doi.org/10.1128/MCB.24.17.7514-7523.2004

Garcia-Silva, S., Martinez-Iglesias, O., Ruiz-Llorente, L., & Aranda, A. (2011). Thyroid hormone receptor beta1 domains responsible for the antagonism with the ras oncogene: Role of corepressors. *Oncogene*, 30, 854–864. https://doi.org/10.1038/onc.2010.464

Gavrila, A., Hasselgren, P.-O., Glasgow, A., Doyle, A. N., Lee, A. J., Fox, P., Gautam, S., Hennessey, J. V., Kolodny, G. M., & Cypess, A. M. (2017). Variable cold-induced brown adipose tissue response to thyroid hormone status. *Thyroid*, 27(1), 1–10. https://doi.org/10.1089/thy.2015.0646

Gereben, B., Zavacki, A. M., Ribich, S., Kim, B. W., Huang, S. A., Simonides, W. S., Zeöld, A., & Bianco, A. C. (2008). Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocrine Reviews*, 29, 898–938. https://doi.org/10.1210/er.2008-0019

Gesing, A., Lewinski, A., & Karbownik-Lewinska, M. (2012). The thyroid gland and the process of aging; what is new? *Thyroid Research*, 5, 16. https://doi.org/10.1186/1756-6614-5-16

Gierach, M., Gierach, J., & Junik, R. (2014). Insulin resistance and thyroid disorders. *Endokrynologia Polska*, 65, 70–76. https://doi.org/10.5603/EP.2014.0010

Gierach, M., & Junik, R. (2015). The effect of hypothyroidism occurring in patients with metabolic syndrome. *Endokrynologia Polska*, 66, 288–294. https://doi.org/10.5603/EP.2015.0036

Giuliani, C., Iezzi, M., Ciolli, L., Hysi, A., Bucci, I., Di Santo, S., Zucchelli, M., & Napolitano, G. (2017). Resveratrol has anti-thyroid effects both in vitro and in vivo. *Food and Chemical Toxicology*, 107, 237–247. https://doi.org/10.1016/j.fct.2017.06.044

Govindaraj, V., Yaduvanshi, N. S., Krishnamachar, H., & Rao, A. J. (2012). Expression of thyroid-stimulating hormone receptor, octamer-binding transcription factor 4, and intracisternal A particle-promoted polypeptide in human breast cancer tissues. *Hormone Molecular Biology and Clinical Investigation*, 9, 173–178. https://doi.org/10.1515/hmbci-2011-0130

Grattagliano, I., Lauterburg, B. H., Portincasa, P., Caruso, M. L., Vendemiale, G., Valentini, A. M., Palmieri, V. O., & Palasciano, G. (2003). Mitochondrial glutathione content determines the rate of liver regeneration after partial hepatectomy in eu- and hypothyroid rats. *Journal of Hepatology*, 39, 571–579. https://doi.org/10.1016/s0168-8278(03)00317-9

Greco, D., Kotronen, A., Westerbacka, J., Puig, O., Arkkila, P., Kiviluoto, T., Laitinen, S., Kolak, M., Fisher, R. M., Hamsten, A., Auvinen, P., & Yki-Järvinen, H. (2008). Gene expression in human NAFLD. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, 294, G1281–1287. https://doi.org/10.1152/ajpgi.00074.2008

Gronich, N., Deftereos, S. N., Lavi, I., Persidis, A. S., Abernethy, D. R., & Rennert, G. (2015). Hypothyroidism is a risk factor for new-onset diabetes: A cohort study. *Diabetes Care*, 38, 1657–1664. https://doi.org/10.2337/dc14-2515

Grover, G. J., Mellström, K., Ye, L., Malm, J., Li, Y., Bladh, L., Sleph, P. G., Smith, M. A., George, R., Vennström, B., Mookhtiar, K., Horvath, R., Speelman, J., Egan, D., & Baxter, J. D. (2003). Selective thyroid hormone receptor-beta activation: a strategy for reduction of weight, cholesterol, and lipoprotein (a) with reduced cardiovascular liability. *Proceedings of the National Academy of Sciences of the United States of America*, 100, 10067–10072. https://doi.org/10.1073/pnas.1633737100

Grozovsky, R., Ribich, S., Rosene, M. L., Mulcahey, M. A., Huang, S. A., Patti, M. E., Bianco, A. C., & Kim, B. W. (2009). Type 2 deiodinase expression is induced by peroxisomal proliferator-activated receptor-gamma agonists in skeletal myocytes. *Endocrinology*, 150, 1976–1983. https://doi.org/10.1210/en.2008-0938

Gudmundsson, H., Gudbjartsson, D. F., Frigge, M., Gulcher, J. R., & Stefansson, K. (2000). Inheritance of human longevity in Iceland. *European Journal of Human Genetics*, 8, 743–749. https://doi.org/10.1038/sj.ejhg.5200527

Guichard, C., Amaddeo, G., Imbeaud, S., Ladeiro, Y., Pelletier, L., Maad, I. B., Calderaro, J., Bioulac-Sage, P., Letexier, M., Degos, F., Clément, B., Balabaud, C., Chevet, E., Laurent, A., Couchy, G., Letouzé, E., Calvo, F., & Zucman-Rossi, J. (2012). Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma. *Nature Genetics*, 44, 694–698. https://doi.org/10.1038/ng.2256

Gussekloo, J. (2004). Thyroid status, disability and cognitive function, and survival in old age. *JAMA*, 292, 2591–2599. https://doi.org/10.1001/jama.292.21.2591

Gussekloo, J., Exel, E. V., Craen, J. M., Meinders, A. E., Frölich, M., & Westendorp, R. G. J. (2006). Thyroid function, activities of daily living and survival in extreme old age: the 'Leiden 85-plus Study'. *Nederlands Tijdschrift Voor Geneeskunde*, 150, 90–96.

Han, C., He, X., Xia, X., Li, Y., Shi, X., Shan, Z., & Teng, W. (2015). Subclinical hypothyroidism and type 2 diabetes: A systematic review and meta-analysis. *PLoS One*, 10, e0135233. https://doi.org/10.1371/journal.pone.0135233

Harrison, S. A., Bashir, M. R., Guy, C. D., Zhou, R., Moylan, C. A., Frias, J. P., Alkhouri, N., Bansal, M. B., Baum, S., Neuschwander-Tetri, B. A., Taub, R., & Moussa, S. E. (2019). Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*, 394, 2012–2024. https://doi.org/10.1016/S0140-6736(19)32517-6

Hassan, M. M. (2002). Risk factors for hepatocellular carcinoma: Synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology*, 36, 1206–1213. https://doi.org/10.1053/jhep.2002.36780

Hassan, M. M., Kaseb, A., Li, D., Patt, Y. Z., Vauthey, J.-N., Thomas, M. B., Curley, S. A., Spitz, M. R., Sherman, S. I., Abdalla, E. K., Davila, M., Lozano, R. D., Hassan, D. M., Chan, W., Brown, T. D., & Abbruzzese, J. L. (2009). Association between hypothyroidism and hepatocellular carcinoma: a case-control study in the United States. *Hepatology*, 49, 1563–1570. https://doi.org/10.1002/hep.22793

Hatting, M., Tavares, C. D. J., Sharabi, K., Rines, A. K., & Puigserver, P. (2018). Insulin regulation of gluconeogenesis. *Annals of the New York Academy of Sciences*, 1411, 21–35. https://doi.org/10.1111/nyas.13435

Heima, N. E., Eekhoff, E. M. W., Oosterwerff, M. M., Lips, P. T. A., van Schoor, N. M., & Simsek, S. (2013). Thyroid function and the metabolic syndrome in older persons: a population-based study. *European Journal of Endocrinology*, 168, 59–65. https://doi.org/10.1530/EJE-12-0375

Hekimsoy, Z., & Oktem, I. K. (2005). Serum creatine kinase levels in overt and subclinical hypothyroidism. *Endocrine Research*, 31, 171–175. https://doi.org/10.1080/07435800500371706

Hellevik, A. I., Asvold, B. O., Bjoro, T., Romundstad, P. R., Nilsen, T., & Vatten, L. J. (2009). Thyroid function and cancer risk: a prospective population study. *Cancer Epidemiology, Biomarkers & Prevention*, 18, 570–574. https://doi.org/10.1158/1055-9965.EPI-08-0911

Hercbergs, A. (1996). The thyroid gland as an intrinsic biologic response-modifier in advanced neoplasia–a novel paradigm. *Vivo*, 10, 245–247.

Hercbergs, A. (1999). Spontaneous remission of cancer–a thyroid hormone dependent phenomenon? *Anticancer Research*, 19, 4839–4844.

Hine, C., Kim, H., Zhu, Y., Harputlugil, E., Longchamp, A., Souza Matos, M., Ramadoss, P., Bauerle, K., Brace, L., Asara, J. M., Ozaki, C. K., Cheng, S., Singha, S., Ahn, K. H., Kimmelman, A., Fisher, F. M., Pissios, P., Whiters, D. J., Selman, C., ... Mitchell, J. R. (2017). Hypothalamic-pituitary axis regulates hydrogen sulfide production. *Cell Metabolism*, 25(6), 1320–1333.e5. https://doi.org/10.1016/j.cmet.2017.05.003

Hishinuma, A., Fukata, S., Kakudo, K., Murata, Y., & Ieiri, T. (2005). High incidence of thyroid cancer in long-standing goiters with thyroglobulin mutations. *Thyroid*, 15, 1079–1084. https://doi.org/10.1089/thy.2005.15.1079

Hogervorst, E., Huppert, F., Matthews, F. E., & Brayne, C. (2008). Thyroid function and cognitive decline in the MRC cognitive function and

ageing study. *Psychoneuroendocrinology*, *33*, 1013–1022. https://doi.org/10.1016/j.psyneuen.2008.05.008

Hollowell, J. G., Staehling, N. W., Flanders, W. D., Hannon, W. H., Gunter, E. W., Spencer, C. A., & Braverman, L. E. (2002). Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *The Journal of Clinical Endocrinology and Metabolism*, *87*, 489–499. https://doi.org/10.1210/jcem.87.2.8182

Ikeno, Y., Bronson, R. T., Hubbard, G. B., Lee, S., & Bartke, A. (2003). Delayed occurrence of fatal neoplastic diseases in ames dwarf mice: correlation to extended longevity. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *58*, 291–296. https://doi.org/10.1093/gerona/58.4.b291

International Association of Diabetes. (2010). International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care 33*, 676–682. https://doi.org/10.2337/dc09-1848

Ishay, A., Chertok-Shaham, I., Lavi, I., & Luboshitzky, R. (2009). Prevalence of subclinical hypothyroidism in women with type 2 diabetes. *Medical Science Monitor 15*, CR151-155.

Jackson-Hayes, L., Song, S., Lavrentyev, E. N., Jansen, M. S., Hillgartner, F. B., Tian, L., Wood, P. A., Cook, G. A., & Park, E. A. (2003). A thyroid hormone response unit formed between the promoter and first intron of the carnitine palmitoyltransferase-Ialpha gene mediates the liver-specific induction by thyroid hormone. *The Journal of Biological Chemistry*, *278*, 7964–7972. https://doi.org/10.1074/jbc.M211062200

Jansen, S. W., Akintola, A. A., Roelfsema, F., van der Spoel, E., Cobbaert, C. M., Ballieux, B. E., Egri, P., Kvarta-Papp, Z., Gereben, B., Fekete, C., Slagboom, P. E., van der Grond, J., Demeneix, B. A., Pijl, H., Westendorp, R. G. J., & van Heemst, D. (2015). Human longevity is characterised by high thyroid stimulating hormone secretion without altered energy metabolism. *Scientific Reports*, *5*, 11525. https://doi.org/10.1038/srep11525

Jansen, S. W., Roelfsema, F., van der Spoel, E., Akintola, A. A., Postmus, I., Ballieux, B. E., Slagboom, P. E., Cobbaert, C. M., van der Grond, J., Westendorp, R. G., Pijl, H., & van Heemst, D. (2015). Familial longevity is associated with higher TSH secretion and strong TSH-fT3 relationship. *The Journal of Clinical Endocrinology and Metabolism*, *100*, 3806–3813. https://doi.org/10.1210/jc.2015-2624

Johannsen, D. L., Galgani, J. E., Johannsen, N. M., Zhang, Z., Covington, J. D., & Ravussin, E. (2012). Effect of short-term thyroxine administration on energy metabolism and mitochondrial efficiency in humans. *PLoS One*, *7*, e40837. https://doi.org/10.1371/journal.pone.0040837

Jornayvaz, F. R., Lee, H., Jurczak, M. J., Alves, T. C., Gueebre-Egziabher, F., Guigni, B. A., Zhang, D., Samuel, V. T., Silva, J. E., & Shulman, G. I. (2012). Thyroid hormone receptor-alpha gene knockout mice are protected from diet-induced hepatic insulin resistance. *Endocrinology*, *153*, 583–591. https://doi.org/10.1210/en.2011-1793

Kamiya, Y. (2002). Expression of mutant thyroid hormone nuclear receptors is associated with human renal clear cell carcinoma. *Carcinogenesis*, *23*, 25–33. https://doi.org/10.1093/carcin/23.1.25

Kapdi, C. C., & Wolfe, J. N. (1976). Breast cancer. Relationship to thyroid supplements for hypothyroidism. *JAMA*, *236*, 1124–1127. https://doi.org/10.1001/jama.236.10.1124

Karbalaei, N., Ghasemi, A., Faraji, F., & Zahediasl, S. (2013). Comparison of the effect of maternal hypothyroidism on carbohydrate metabolism in young and aged male offspring in rats. *Scandinavian Journal of Clinical and Laboratory Investigation*, *73*, 87–94. https://doi.org/10.3109/00365513.2012.743164

Kassem, S. A., Ariel, I., Thornton, P. S., Scheimberg, I., & Glaser, B. (2000). Beta-cell proliferation and apoptosis in the developing normal human pancreas and in hyperinsulinism of infancy. *Diabetes*, *49*, 1325–1333. https://doi.org/10.2337/diabetes.49.8.1325

Kassem, S., Bhandari, S., Rodríguez-Bada, P., Motaghedi, R., Heyman, M., García-Gimeno, M. A., Cobo-Vuilleumier, N., Sanz, P., Maclaren, N. K., Rahier, J., Glaser, B., & Cuesta-Muñoz, A. L. (2010). Large islets, beta-cell proliferation, and a glucokinase mutation. *The New England Journal of Medicine*, *362*, 1348–1350. https://doi.org/10.1056/NEJMc0909845

Kerber, R. A., O'Brien, E., Smith, K. R., & Cawthon, R. M. (2001). Familial excess longevity in Utah genealogies. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *56*, B130–B139. https://doi.org/10.1093/gerona/56.3.b130

Kim, D., Kim, W., Joo, S. K., Bae, J. M., Kim, J. H., & Ahmed, A. (2018). Subclinical hypothyroidism and low-normal thyroid function are associated with nonalcoholic steatohepatitis and fibrosis. *Clinical Gastroenterology and Hepatology*, *16*(1), 123–131.e1. https://doi.org/10.1016/j.cgh.2017.08.014

Kim, E. Y., Chang, Y., Lee, K. H., Yun, J.-S., Park, Y. L., Park, C. H., Ahn, J., Shin, H., & Ryu, S. (2019). Serum concentration of thyroid hormones in abnormal and euthyroid ranges and breast cancer risk: A cohort study. *International Journal of Cancer*, *145*, 3257–3266. https://doi.org/10.1002/ijc.32283

Kim, H. J., Kang, T., Kang, M. J., Ahn, H. S., & Sohn, S. Y. (2020). Incidence and mortality of myocardial infarction and stroke in patients with hyperthyroidism: A Nationwide Cohort Study in Korea. *Thyroids*, *30*, 955–965. https://doi.org/10.1089/thy.2019.0543

Kim, H., Toyofuku, Y., Lynn, F. C., Chak, E., Uchida, T., Mizukami, H., Fujitani, Y., Kawamori, R., Miyatsuka, T., Kosaka, Y., Yang, K., Honig, G., van der Hart, M., Kishimoto, N., Wang, J., Yagihashi, S., Tecott, L. H., Watada, H., & German, M. S. (2010). Serotonin regulates pancreatic beta cell mass during pregnancy. *Nature Medicine*, *16*(7), 804–808. https://doi.org/10.1038/nm.2173

Kim, J. W. S., Lee, S., Lui, N., Choi, H., Mulvihill, M., Fang, L. T., Kang, H. C., Kwon, Y.-W., Jablons, D., & Kim, I.-J. (2012). A somatic TSHR mutation in a patient with lung adenocarcinoma with bronchioloalveolar carcinoma, coronary artery disease and severe chronic obstructive pulmonary disease. *Oncology Reports*, *28*, 1225–1230. https://doi.org/10.3892/or.2012.1938

Kim, W. G., & Cheng, S. Y. (1830). Thyroid hormone receptors and cancer. *Biochimica Et Biophysica Acta*, *3928–3936*, 2013. https://doi.org/10.1016/j.bbagen.2012.04.002

Klieverik, L. P., Janssen, S. F., Riel, A. V., Foppen, E., Bisschop, P. H., Serlie, M. J., Boelen, A., Ackermans, M. T., Sauerwein, H. P., Fliers, E., & Kalsbeek, A. (2009). Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 5966–5971. https://doi.org/10.1073/pnas.0805355106

Klieverik, L. P., Sauerwein, H. P., Ackermans, M. T., Boelen, A., Kalsbeek, A., & Fliers, E. (2008). Effects of thyrotoxicosis and selective hepatic autonomic denervation on hepatic glucose metabolism in rats. *American Journal of Physiology-Endocrinology and Metabolism*, *294*, E513–E520. https://doi.org/10.1152/ajpendo.00659.2007

Kouidhi, S., & Clerget-Froidevaux, M. S. (2018). Integrating thyroid hormone signaling in hypothalamic control of metabolism: Crosstalk between nuclear receptors. *International Journal of Molecular Sciences*, *19*, https://doi.org/10.3390/ijms19072017

Kovar, F. M., Fang, I.-F., Perkmann, T., Haslacher, H., Slavka, G., Födinger, M., Endler, G., & Wagner, O. F. (2015). Subclinical hypothyroidism and mortality in a large Austrian cohort: A possible impact on treatment? *Wiener Klinische Wochenschrift*, *127*, 924–930. https://doi.org/10.1007/s00508-015-0846-z

Kowalik, M. A., Puliga, E., Cabras, L., Sulas, P., Petrelli, A., Perra, A., Ledda-Columbano, G. M., Morandi, A., Merlin, S., Orrù, C., Sanchez-Martin, C., Fornari, F., Gramantieri, L., Parri, M., Rasola, A., Bellomo, S. E.,

Sebastian, C., Follenzi, A., Giordano, S., & Columbano, A. (2020). Thyroid hormone inhibits hepatocellular carcinoma progression via induction of differentiation and metabolic reprogramming. *Journal of Hepatology*, *72*(6), 1159–1169. https://doi.org/10.1016/j.jhep.2019.12.018

Kramer, C. K., von Muhlen, D., Kritz-Silverstein, D., & Barrett-Connor, E. (2009). Treated hypothyroidism, cognitive function, and depressed mood in old age: The Rancho Bernardo Study. *European Journal of Endocrinology*, *161*, 917–921. https://doi.org/10.1530/EJE-09-0606

Kuhl, C. (1991). Insulin secretion and insulin resistance in pregnancy and GDM. *Implications for Diagnosis and Management. Diabetes*, *40*(Suppl 2), 18–24. https://doi.org/10.2337/diab.40.2.s18

Ladenson, P. W., McCarren, M., Morkin, E., Edson, R. G., Shih, M.-C., Warren, S. R., Barnhill, J. G., Churby, L., Thai, H., O'Brien, T., Anand, I., Warner, A., Hattler, B., Dunlap, M., Erikson, J., & Goldman, S. (2010). Effects of the thyromimetic agent diiodothyropropionic acid on body weight, body mass index, and serum lipoproteins: a pilot prospective, randomized, controlled study. *The Journal of Clinical Endocrinology and Metabolism*, *95*, 1349–1354. https://doi.org/10.1210/jc.2009-1209

Lahesmaa, M., Orava, J., Schalin-Jäntti, C., Soinio, M., Hannukainen, J. C., Noponen, T., Kirjavainen, A., Iida, H., Kudomi, N., Enerbäck, S., Virtanen, K. A., & Nuutila, P. (2014). Hyperthyroidism increases brown fat metabolism in humans. *The Journal of Clinical Endocrinology & Metabolism*, *99*(1), E28–E35. https://doi.org/10.1210/jc.2013-2312

Lammel Lindemann, J., & Webb, P. S. (2016). Sobetirome: The past, present and questions about the future. *Expert Opinion on Therapeutic Targets*, *20*(2), 145–149. https://doi.org/10.1517/14728222.2016.1090429

Ledda-Columbano, G. M., Perra, A., Loi, R., Shinozuka, H., & Columbano, A. (2000). Cell proliferation induced by triiodothyronine in rat liver is associated with nodule regression and reduction of hepatocellular carcinomas. *Cancer Research*, *60*, 603–609.

Lin, J. Z., Martagón, A. J., Cimini, S. L., Gonzalez, D. D., Tinkey, D. W., Biter, A., Baxter, J. D., Webb, P., Gustafsson, J., Hartig, S. M., & Phillips, K. J. (2015). Pharmacological activation of thyroid hormone receptors elicits a functional conversion of white to brown fat. *Cell Reports*, *13*, 1528–1537. https://doi.org/10.1016/j.celrep.2015.10.022

Lin, K. H., Zhu, X. G., Hsu, H. C., Shieh, H. Y., Chen, S. T., McPhie, P., & Cheng, S. Y. (1997). Dominant negative activity of mutant thyroid hormone alpha1 receptors from patients with hepatocellular carcinoma. *Endocrinology*, *138*, 5308–5315. https://doi.org/10.1210/endo.138.12.5625

Lin, K. H., Shieh, H. Y., Chen, S. L., & Hsu, H. C. (1999). Expression of mutant thyroid hormone nuclear receptors in human hepatocellular carcinoma cells. *Molecular Carcinogenesis*, *26*, 53–61. https://doi.org/10.1002/(sici)1098-2744(199909)26:1<53:aid-mc7>3.0.co;2-z

Lin, Y., & Sun, Z. (2011). Thyroid hormone potentiates insulin signaling and attenuates hyperglycemia and insulin resistance in a mouse model of type 2 diabetes. *British Journal of Pharmacology*, *162*, 597–610. https://doi.org/10.1111/j.1476-5381.2010.01056.x

Liu, X., Zheng, N., Shi, Y. N., Yuan, J., & Li, L. (2014). Thyroid hormone induced angiogenesis through the integrin alphavbeta3/protein kinase D/histone deacetylase 5 signaling pathway. *Journal of Molecular Endocrinology*, *52*, 245–254. https://doi.org/10.1530/JME-13-0252

Liu, Y. C., Yeh, C. T., & Lin, K. H. (2019). Molecular functions of thyroid hormone signaling in regulation of cancer progression and anti-apoptosis. *International Journal of Molecular Sciences*, *20*, https://doi.org/10.3390/ijms20204986

Lonard, D. M., & O'Malley, B. W. (2007). Nuclear receptor coregulators: Judges, juries, and executioners of cellular regulation. *Molecular Cell*, *27*, 691–700. https://doi.org/10.1016/j.molcel.2007.08.012

Lonardo, A., Nascimbeni, F., Targher, G., Bernardi, M., Bonino, F., Bugianesi, E., Casini, A., Gastaldelli, A., Marchesini, G., Marra, F., Miele, L., Morisco, F., Petta, S., Piscaglia, F., Svegliati-Baroni, G., Valenti, L., & Bellentani, S. (2017). AISF position paper on nonalcoholic fatty liver disease (NAFLD): Updates and future directions. *Digestive and Liver Disease*, *49*(5), 471–483. https://doi.org/10.1016/j.dld.2017.01.147

Lopez-Noriega, L., Capilla-González, V., Cobo-Vuilleumier, N., Martín-Vázquez, E., Lorenzo, P. I., Martinez-Force, E., Soriano-Navarro, M., García-Fernández, M. G., Romero-Zerbo, S. Y., Bermúdez-Silva, F. J., Díaz-Contreras, I., Sánchez-Cuesta, A., Santos-Ocaña, C., Hmadcha, A., Soria, B., Martín, F., Gauthier, B. R., & Martín-Montalvo, A. (2019). Inadequate control of thyroid hormones sensitizes to hepatocarcinogenesis and unhealthy aging. *Aging*, *11*, 7746–7779. https://doi.org/10.18632/aging.102285

López-Noriega, L., Cobo-Vuilleumier, N., Narbona-Pérez, Á. J., Araujo-Garrido, J. L., Lorenzo, P. I., Mellado-Gil, J. M., Moreno, J. C., Gauthier, B. R., & Martín-Montalvo, A. (2017). Levothyroxine enhances glucose clearance and blunts the onset of experimental type 1 diabetes mellitus in mice. *British Journal of Pharmacology*, *174*, 3795–3810. https://doi.org/10.1111/bph.13975

Ludwig, U., Holzner, D., Denzer, C., Greinert, A., Haenle, M. M., Oeztuerk, S., Koenig, W., Boehm, B. O., Mason, R. A., Kratzer, W., Graeter, T., & EMIL-Study et al. (2015). Subclinical and clinical hypothyroidism and non-alcoholic fatty liver disease: A cross-sectional study of a random population sample aged 18 to 65 years. *BMC Endocrine Disorders*, *15*, 41. https://doi.org/10.1186/s12902-015-0030-5

Ma, S., Yang, J., Song, C., Ge, Z., Zhou, J., Zhang, G., & Hu, Z. (2017). Expression quantitative trait loci for PAX8 contributes to the prognosis of hepatocellular carcinoma. *PLoS One*, *12*, e0173700. https://doi.org/10.1371/journal.pone.0173700

Mancini, A., Di Segni, C., Raimondo, S., Olivieri, G., Silvestrini, A., Meucci, E., & Currò, D. (2016). Thyroid hormones, oxidative stress, and inflammation. *Mediators of Inflammation*, *2016*, 1–12. https://doi.org/10.1155/2016/6757154

Mansouri, A., Chowdhury, K., & Gruss, P. (1998). Follicular cells of the thyroid gland require Pax8 gene function. *Nature Genetics*, *19*, 87–90. https://doi.org/10.1038/ng0598-87

Maratou, E., Hadjidakis, D. J., Peppa, M., Alevizaki, M., Tsegka, K., Lambadiari, V., Mitrou, P., Boutati, E., Kollias, A., Economopoulos, T., Raptis, S. A., & Dimitriadis, G. (2010). Studies of insulin resistance in patients with clinical and subclinical hyperthyroidism. *European Journal of Endocrinology*, *163*, 625–630. https://doi.org/10.1530/EJE-10-0246

Marsili, A., Aguayo-Mazzucato, C., Chen, T., Kumar, A., Chung, M., Lunsford, E. P., Harney, J. W., Van-Tran, T., Gianetti, E., Ramadan, W., Chou, C., Bonner-Weir, S., Larsen, P. R., Silva, J. E., & Zavacki, A. M. (2011). Mice with a targeted deletion of the type 2 deiodinase are insulin resistant and susceptible to diet induced obesity. *PLoS One*, *6*, e20832. https://doi.org/10.1371/journal.pone.0020832

Martagon, A. J., Lin, J. Z., Cimini, S. L., Webb, P., & Phillips, K. J. (2015). The amelioration of hepatic steatosis by thyroid hormone receptor agonists is insufficient to restore insulin sensitivity in ob/ob mice. *PLoS One*, *10*, e0122987. https://doi.org/10.1371/journal.pone.0122987

Martin, U., Davies, C., Hayavi, S., Hartland, A., & Dunne, F. (1999). Is normal pregnancy atherogenic? *Clinical Science*, *96*, 421–425.

Martinez-Iglesias, O., Garcia-Silva, S., Regadera, J., & Aranda, A. (2009). Hypothyroidism enhances tumor invasiveness and metastasis development. *PLoS One*, *4*, e6428. https://doi.org/10.1371/journal.pone.0006428

Martinez-Iglesias, O., Garcia-Silva, S., Tenbaum, S. P., Regadera, J., Latcher, F., Paramio, J. M., Vennstrom, B., & Aranda, A. (2009). Thyroid hormone receptor beta1 acts as a potent suppressor of

tumor invasiveness and metastasis. *Cancer Research*, 69, 501–509. https://doi.org/10.1158/0008-5472.CAN-08-2198

Martin-Montalvo, A., López-Noriega, L., Jimenez-Moreno, C., Herranz, A., Lorenzo, P. I., Cobo-Vuilleumier, N., Tamayo, A., González-Guerrero, C., Hofsteede, J. S. W., Lebreton, F., Bosco, D., García Toscano, M., Herranz, L., Anselmo, J., Moreno, J. C., & Gauthier, B. R. (2019). Transient PAX8 expression in islets during pregnancy correlates with beta-cell survival, revealing a novel candidate gene in gestational diabetes mellitus. *Diabetes*, 68, 109–118. https://doi.org/10.2337/db18-0285

Mastracci, T. L., & Evans-Molina, C. (2014). Pancreatic and islet development and function: the role of thyroid hormone. *Journal of Endocrinology, Diabetes & Obesity 2*.

Mazzoccoli, G., Pazienza, V., Piepoli, A., Muscarella, L. A., Inglese, M., De Cata, A., Giuliani, F., & Tarquini, R. (2010). Hypothalamus-hypophysis-thyroid axis function in healthy aging. *Journal of Biological Regulators and Homeostatic Agents*, 24, 433–439.

McCabe, C. J., Gittoes, N. J., Sheppard, M. C., & Franklyn, J. A. (1999). Thyroid receptor alpha1 and alpha2 mutations in nonfunctioning pituitary tumors. *The Journal of Clinical Endocrinology and Metabolism*, 84, 649–653. https://doi.org/10.1210/jcem.84.2.5469

Medina-Gomez, G., Calvo, R. M., & Obregon, M. J. (2008). Thermogenic effect of triiodothyroacetic acid at low doses in rat adipose tissue without adverse side effects in the thyroid axis. *American Journal of Physiology. Endocrinology and Metabolism*, 294, E688–697. https://doi.org/10.1152/ajpendo.00417.2007

Mentuccia, D., Proietti-Pannunzi, L., Tanner, K., Bacci, V., Pollin, T. I., Poehlman, E. T., Shuldiner, A. R., & Celi, F. S. (2002). Association between a novel variant of the human type 2 deiodinase gene Thr92Ala and insulin resistance: evidence of interaction with the Trp64Arg variant of the beta-3-adrenergic receptor. *Diabetes*, 51, 880–883. https://doi.org/10.2337/diabetes.51.3.880

Meyer, E. L., Goemann, I. M., Dora, J. M., Wagner, M. S., & Maia, A. L. (2008). Type 2 iodothyronine deiodinase is highly expressed in medullary thyroid carcinoma. *Molecular and Cellular Endocrinology*, 289, 16–22. https://doi.org/10.1016/j.mce.2008.04.009

Michalakis, K., Goulis, D., Vazaiou, A., Mintziori, G., Polymeris, A., & Abrahamian-Michalakis, A. (2013). Obesity in the ageing man. *Metabolism: Clinical and Experimental*, 62, 1341–1349. https://doi.org/10.1016/j.metabol.2013.05.019

Mishra, A., Zhu, X. G., Ge, K., & Cheng, S. Y. (2010). Adipogenesis is differentially impaired by thyroid hormone receptor mutant isoforms. *Journal of Molecular Endocrinology*, 44, 247–255. https://doi.org/10.1677/JME-09-0137

Mitrou, P., Boutati, E., Lambadiari, V., Tsegka, A., Raptis, A. E., Tountas, N., Economopoulos, T., Raptis, S. A., & Dimitriadis, G. (2010). Insulin resistance in hyperthyroidism: the role of IL6 and TNF alpha. *European Journal of Endocrinology*, 162, 121–126. https://doi.org/10.1530/EJE-09-0622

Morley, J. E. (2003). Hormones and the aging process. *Journal of the American Geriatrics Society*, 51, S333–337. https://doi.org/10.1046/j.1365-2389.2003.51344.x

Mousa, S., Glinsky, G., Lin, H.-Y., Ashur-Fabian, O., Hercbergs, A., Keating, K., & Davis, P. (2018). Contributions of thyroid hormone to cancer metastasis. *Biomedicines*, 6, https://doi.org/10.3390/biomedicines6030089

Mousa, S. A., Yalcin, M., Bharali, D. J., Meng, R., Tang, H.-Y., Lin, H.-Y., Davis, F. B., & Davis, P. J. (2012). Tetraiodothyroacetic acid and its nanoformulation inhibit thyroid hormone stimulation of non-small cell lung cancer cells in vitro and its growth in xenografts. *Lung Cancer*, 76, 39–45. https://doi.org/10.1016/j.lungcan.2011.10.003

Muller, M. J., Enderle, J., Pourhassan, M., Braun, W., Eggeling, B., Lagerpusch, M., Glüer, C., Kehayias, J. J., Kiosz, D., & Bosy-Westphal, A. (2015). Metabolic adaptation to caloric restriction and subsequent refeeding: the Minnesota Starvation Experiment revisited. *The American Journal of Clinical Nutrition*, 102, 807–819. https://doi.org/10.3945/ajcn.115.109173

Mullur, R., Liu, Y. Y., & Brent, G. A. (2014). Thyroid hormone regulation of metabolism. *Physiological Reviews*, 94, 355–382. https://doi.org/10.1152/physrev.00030.2013

Nanda, N., Bobby, Z., Hamide, A., Koner, B. C., & Sridhar, M. G. (2007). Association between oxidative stress and coronary lipid risk factors in hypothyroid women is independent of body mass index. *Metabolism: Clinical and Experimental*, 56, 1350–1355. https://doi.org/10.1016/j.metabol.2007.05.015

Ng, L., Kelley, M. W., & Forrest, D. (2013). Making sense with thyroid hormone–the role of T(3) in auditory development. *Nature Reviews. Endocrinology*, 9, 296–307. https://doi.org/10.1038/nrendo.2013.58

Nicholls, J. J., Brassill, M. J., Williams, G. R., & Bassett, J. H. (2012). The skeletal consequences of thyrotoxicosis. *The Journal of Endocrinology*, 213, 209–221. https://doi.org/10.1530/JOE-12-0059

Nunez, J., Celi, F. S., Ng, L., & Forrest, D. (2008). Multigenic control of thyroid hormone functions in the nervous system. *Molecular and Cellular Endocrinology*, 287, 1–12. https://doi.org/10.1016/j.mce.2008.03.006

Ochs, N., Auer, R., Bauer, D. C., Nanchen, D., Gussekloo, J., Cornuz, J., & Rodondi, N. (2008). Meta-analysis: Subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Annals of Internal Medicine*, 148, 832–845. https://doi.org/10.7326/0003-4819-148-11-200806030-00225

Ooka, H., & Shinkai, T. (1986). Effects of chronic hyperthyroidism on the lifespan of the rat. *Mechanisms of Ageing and Development*, 33, 275–282. https://doi.org/10.1016/0047-6374(86)90052-7

Oppenheimer, J. H., Schwartz, H. L., Lane, J. T., & Thompson, M. P. (1991). Functional relationship of thyroid hormone-induced lipogenesis, lipolysis, and thermogenesis in the rat. *The Journal of Clinical Investigation*, 87, 125–132. https://doi.org/10.1172/JCI114961

Pagadala, M. R., Zein, C. O., Dasarathy, S., Yerian, L. M., Lopez, R., & McCullough, A. J. (2012). Prevalence of hypothyroidism in nonalcoholic fatty liver disease. *Digestive Diseases and Sciences*, 57, 528–534. https://doi.org/10.1007/s10620-011-2006-2

Palkowska-Gozdzik, E., Lachowicz, K., & Rosolowska-Huszcz, D. (2017). Effects of dietary protein on thyroid axis activity. *Nutrients*, 10, https://doi.org/10.3390/nu10010005

Park, E. A., Song, S., Vinson, C., & Roesler, W. J. (1999). Role of CCAAT enhancer-binding protein beta in the thyroid hormone and cAMP induction of phosphoenolpyruvate carboxykinase gene transcription. *The Journal of Biological Chemistry*, 274, 211–217. https://doi.org/10.1074/jbc.274.1.211

Park, Y. J., Lee, E. J., Lee, Y. J., Choi, S. H., Park, J. H., Lee, S. B., Lim, S., Lee, W. W., Jang, H. C., Cho, B. Y., Woo, J. I., & Kim, K. W. (2010). Subclinical hypothyroidism (SCH) is not associated with metabolic derangement, cognitive impairment, depression or poor quality of life (QoL) in elderly subjects. *Archives of Gerontology and Geriatrics*, 50, e68–73. https://doi.org/10.1016/j.archger.2009.05.015

Parle, J. V., Maisonneuve, P., Sheppard, M. C., Boyle, P., & Franklyn, J. A. (2001). Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: A 10-year cohort study. *Lancet*, 358, 861–865. https://doi.org/10.1016/S0140-6736(01)06067-6

Pearce, E. N. (2004). Hypothyroidism and dyslipidemia: modern concepts and approaches. *Current Cardiology Reports*, 6, 451–456. https://doi.org/10.1007/s11886-004-0054-3

Pearce, E. N. (2012). Update in lipid alterations in subclinical hypothyroidism. *The Journal of Clinical Endocrinology and Metabolism*, 97, 326–333. https://doi.org/10.1210/jc.2011-2532

Pepino, M. Y., Kuda, O., Samovski, D., & Abumrad, N. A. (2014). Structure-function of CD36 and importance of fatty acid signal transduction in fat metabolism. *Annual Review of Nutrition*, 34, 281–303. https://doi.org/10.1146/annurev-nutr-071812-161220

Perissi, V., Jepsen, K., Glass, C. K., & Rosenfeld, M. G. (2010). Deconstructing repression: Evolving models of co-repressor action. *Nature Reviews Genetics*, 11, 109–123. https://doi.org/10.1038/nrg2736

Perra, A., Simbula, G., Simbula, M., Pibiri, M., Kowalik, M. A., Sulas, P., Cocco, M. T., Ledda-Columbano, G. M., & Columbano, A. (2008). Thyroid hormone (T3) and TRbeta agonist GC-1 inhibit/reverse nonalcoholic fatty liver in rats. *FASEB Journal*, 22, 2981–2989. https://doi.org/10.1096/fj.08-108464

Perra, A., Kowalik, M. A., Pibiri, M., Ledda-Columbano, G. M., & Columbano, A. (2009). Thyroid hormone receptor ligands induce regression of rat preneoplastic liver lesions causing their reversion to a differentiated phenotype. *Hepatology*, 49, 1287–1296. https://doi.org/10.1002/hep.22750

Petra, I. L., Martin-Montalvo, A., Cobo Vuilleumier, N., & Gauthier, B. R. (2019). Molecular modelling of islet beta-cell adaptation to inflammation in pregnancy and gestational diabetes mellitus. *International Journal of Molecular Sciences* 20, https://doi.org/10.3390/ijms20246171

Piekielko-Witkowska, A., Master, A., Wojcicka, A., Boguslawska, J., Brozda, I., Tanski, Z., & Nauman, A. (2009). Disturbed expression of type 1 iodothyronine deiodinase splice variants in human renal cancer. *Thyroid*, 19(10), 1105–1113. https://doi.org/10.1089/thy.2008.0284

Pinter, M., Haupt, L., Hucke, F., Bota, S., Bucsics, T., Trauner, M., Peck-Radosavljevic, M., & Sieghart, W. (2017). The impact of thyroid hormones on patients with hepatocellular carcinoma. *PLoS One*, 12, e0181878. https://doi.org/10.1371/journal.pone.0181878

Potenza, M., Via, M. A., & Yanagisawa, R. T. (2009). Excess thyroid hormone and carbohydrate metabolism. *Endocrine Practice*, 15, 254–262. https://doi.org/10.4158/EP.15.3.254

Pucci, E., Chiovato, L., & Pinchera, A. (2000). Thyroid and lipid metabolism. *International Journal of Obesity and Related Metabolic Disorders*, 24(Suppl 2), S109–S112. https://doi.org/10.1038/sj.ijo.0801292

Puzianowska-Kuznicka, M., Krystyniak, A., Madej, A., Cheng, S. Y., & Nauman, J. (2002). Functionally impaired TR mutants are present in thyroid papillary cancer. *The Journal of Clinical Endocrinology and Metabolism*, 87, 1120–1128. https://doi.org/10.1210/jcem.87.3.8296

Radaideh, A. R., Nusier, M. K., Amari, F. L., Bateiha, A. E., El-Khateeb, M. S., Naser, A. S., & Ajlouni, K. M. (2004). Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. *Saudi Medical Journal*, 25, 1046–1050.

Ravussin, E., Redman, L. M., Rochon, J., Das, S. K., Fontana, L., Kraus, W. E., Romashkan, S., Williamson, D. A., Meydani, S. N., Villareal, D. T., Smith, S. R., Stein, R. I., Scott, T. M., Stewart, T. M., Saltzman, E., Klein, S., Bhapkar, M., Martin, C. K., Gilhooly, C. H., … Roberts, S. B. (2015). A 2-year randomized controlled trial of human caloric restriction: Feasibility and effects on predictors of health span and longevity. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 70, 1097–1104. https://doi.org/10.1093/gerona/glv057

Reddy, A., Dash, C., Leerapun, A., Mettler, T. A., Stadheim, L. M., Lazaridis, K. N., Roberts, R. O., & Roberts, L. R. (2007). Hypothyroidism: A possible risk factor for liver cancer in patients with no known underlying cause of liver disease. *Clinical Gastroenterology and Hepatology*, 5, 118–123. https://doi.org/10.1016/j.cgh.2006.07.011

Rennert, G., Rennert, H. S., Pinchev, M., & Gruber, S. B. (2010). A case-control study of levothyroxine and the risk of colorectal cancer. *Journal of the National Cancer Institute*, 102, 568–572. https://doi.org/10.1093/jnci/djq042

Revekka, G., Christina, L., Ekaterini, P., Michalis, L., Katerina, S., Theocharis, P., Nikolaos, T., Dimitrios, H., Alexandros, R., Maria, A., Aristotelis, B., & Athanasios, D. M. (2014). Differential transcriptional and protein expression of thyroid-stimulating hormone receptor in ovarian carcinomas. *International Journal of Gynecological Cancer*, 24, 851–856. https://doi.org/10.1097/IGC.0000000000000139

Rochon, C., Tauveron, I., Dejax, C., Benoit, P., Capitan, P., Fabricio, A., Berry, C., Champredon, C., Thieblot, P., & Grizard, J. (2003). Response of glucose disposal to hyperinsulinaemia in human hypothyroidism and hyperthyroidism. *Clinical Science*, 104, 7–15. https://doi.org/10.1042/CS20020154

Rodolico, C., Toscano, A., Benvenga, S., Mazzeo, A., Bartolone, S., Bartolone, L., Girlanda, P., Monici, M. C., Migliorato, A., Trimarchi, F., & Vita, G. (1998). Myopathy as the persistently isolated symptomatology of primary autoimmune hypothyroidism. *Thyroid*, 8, 1033–1038. https://doi.org/10.1089/thy.1998.8.1033

Rosen, M. D., & Privalsky, M. L. (2011). Thyroid hormone receptor mutations in cancer and resistance to thyroid hormone: Perspective and prognosis. *Journal of Thyroid Research*, 2011, 1–20. https://doi.org/10.4061/2011/361304

Rosenberg, A. G., Dexeus, F., Swanson, D. A., & von Eschenbach, A. C. (1990). Relationship of thyroid disease to renal cell carcinoma. An epidemiologic study. *Urology*, 35, 492–498. https://doi.org/10.1016/0090-4295(90)80101-r

Rozing, M. P., Houwing-Duistermaat, J. J., Slagboom, P. E., Beekman, M., Frölich, M., de Craen, A. J. M., Westendorp, R. G. J., & van Heemst, D. (2010). Familial longevity is associated with decreased thyroid function. *The Journal of Clinical Endocrinology and Metabolism*, 95, 4979–4984. https://doi.org/10.1210/jc.2010-0875

Rozing, M. P., Westendorp, R. G. J., de Craen, A. J. M., Frolich, M., Heijmans, B. T., Beekman, M., Wijsman, C., Mooijaart, S. P., Blauw, G.-J., Slagboom, P. E., & van Heemst, D. (2010). Low serum free triiodothyronine levels mark familial longevity: the Leiden Longevity Study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 65, 365–368. https://doi.org/10.1093/gerona/glp200

Russell, S. J., & Kahn, C. R. (2007). Endocrine regulation of ageing. *Nature Reviews. Molecular Cell Biology*, 8, 681–691. https://doi.org/10.1038/nrm2234

Russo, D., Arturi, F., Schlumberger, M., Caillou, B., Monier, R., Filetti, S., & Suárez, H. G. (1995). Activating mutations of the TSH receptor in differentiated thyroid carcinomas. *Oncogene*, 11, 1907–1911.

Samuels, M. H. (2000) Hyperthyroidism in aging. In K. R. Feingold et al. *Endotext* (eds). MD Text.com, Inc.

Sawin, C. T., Bigos, S. T., Land, S., & Bacharach, P. (1985). The aging thyroid. Relationship between elevated serum thyrotropin level and thyroid antibodies in elderly patients. *The American Journal of Medicine*, 79, 591–595. https://doi.org/10.1016/0002-9343(85)90056-7

Schmohl, K. A., Mueller, A. M., Dohmann, M., Spellerberg, R., Urnauer, S., Schwenk, N., Ziegler, S. I., Bartenstein, P., Nelson, P. J., & Spitzweg, C. (2019). Integrin alphavbeta3-mediated effects of thyroid hormones on mesenchymal stem cells in tumor angiogenesis. *Thyroid*, 29, 1843–1857. https://doi.org/10.1089/thy.2019.0413

Schrack, J. A., Simonsick, E. M., Chaves, P. H., & Ferrucci, L. (2012). The role of energetic cost in the age-related slowing of gait speed. *Journal of the American Geriatrics Society*, 60, 1811–1816. https://doi.org/10.1111/j.1532-5415.2012.04153.x

Schrack, J. A., Zipunnikov, V., Simonsick, E. M., Studenski, S., & Ferrucci, L. (2016). Rising energetic cost of walking predicts gait speed decline with aging. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 71, 947–953. https://doi.org/10.1093/gerona/glw002

Schulze, K., Imbeaud, S., Letouzé, E., Alexandrov, L. B., Calderaro, J., Rebouissou, S., Couchy, G., Meiller, C., Shinde, J., Soysouvanh, F., Calatayud, A., Pinyol, R., Pelletier, L., Balabaud, C., Laurent, A., Blanc, J., Mazzaferro, V., Calvo, F., Villanueva, A., … Zucman-Rossi, J. (2015). Exome sequencing of hepatocellular carcinomas

identifies new mutational signatures and potential therapeutic targets. *Nature Genetics*, *47*, 505–511. https://doi.org/10.1038/ng.3252

Schweizer, U., Weitzel, J. M., & Schomburg, L. (2008). Think globally: Act locally. *Molecular and Cellular Endocrinology*, *289*(1-2), 1–9. https://doi.org/10.1016/j.mce.2008.04

Seely, E. W., & Solomon, C. G. (2003). Insulin resistance and its potential role in pregnancy-induced hypertension. *The Journal of Clinical Endocrinology and Metabolism*, *88*, 2393–2398. https://doi.org/10.1210/jc.2003-030241

Sell, M. A., Schott, M., Tharandt, L., Cissewski, K., Scherbaum, W. A., & Willenberg, H. S. (2008). Functional central hypothyroidism in the elderly. *Aging Clinical and Experimental Research*, *20*, 207–210. https://doi.org/10.1007/bf03324770

Selmer, C., Olesen, J. B., Hansen, M. L., von Kappelgaard, L. M., Madsen, J. C., Hansen, P. R., Pedersen, O. D., Faber, J., Torp-Pedersen, C., & Gislason, G. H. (2014). Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: A large population study. *The Journal of Clinical Endocrinology and Metabolism*, *99*, 2372–2382. https://doi.org/10.1210/jc.2013-4184

Sharma, P., Levesque, T., Boilard, E., & Park, E. A. (2014). Thyroid hormone status regulates the expression of secretory phospholipases. *Biochemical and Biophysical Research Communications*, *444*, 56–62. https://doi.org/10.1016/j.bbrc.2014.01.003

Sherman, S. I., Ringel, M. D., Smith, M. J., Kopelen, H. A., Zoghbi, W. A., & Ladenson, P. W. (1997). Augmented hepatic and skeletal thyromimetic effects of tiratricol in comparison with levothyroxine. *The Journal of Clinical Endocrinology and Metabolism*, *82*, 2153–2158. https://doi.org/10.1210/jcem.82.7.4054

Shih, Y. L., Huang, Y. H., Lin, K. H., Chu, Y. D., & Yeh, C. T. (2018). Identification of functional thyroid stimulating hormone receptor and TSHR Gene mutations in hepatocellular carcinoma. *Anticancer Research*, *38*, 2793–2802. https://doi.org/10.21873/anticanres.12523

Shoemaker, T. J., Kono, T., Mariash, C. N., & Evans-Molina, C. (2012). Thyroid hormone analogues for the treatment of metabolic disorders: New potential for unmet clinical needs? *Endocrine Practice*, *18*, 954–964. https://doi.org/10.4158/EP12086.RA

Shun, C. B., Donaghue, K. C., Phelan, H., Twigg, S. M., & Craig, M. E. (2014). Thyroid autoimmunity in Type 1 diabetes: Systematic review and meta-analysis. *Diabetic Medicine*, *31*, 126–135. https://doi.org/10.1111/dme.12318

Simonsick, E. M. (2009). Subclinical hypothyroidism and functional mobility in older adults. *Archives of Internal Medicine*, *169*, 2011–2017. https://doi.org/10.1001/archinternmed.2009.392

Simonsick, E. M., Chia, C. W., Mammen, J. S., Egan, J. M., & Ferrucci, L. (2016). Free thyroxine and functional mobility, fitness, and fatigue in euthyroid older men and women in the baltimore longitudinal study of aging. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *71*, 961–967. https://doi.org/10.1093/gerona/glv226

Singer, R. B. (2006). Mortality in a complete 4-year follow up of 85-year-old residents of Leiden, classified by serum level of thyrotropin and thyroxine. *Journal of Insurance Medicine*, *38*, 14–19.

Singh, B. K., Sinha, R., Tripathi, M., Mendoza, A., Ohba, K., Sy, J. A. C., Xie, S. Y., Zhou, J., Ho, J. P., Chang, C., Wu, Y., Giguere, V., Bay, B., Vanacker, J., Ghosh, S., Gauthier, K., Holleberg, A. N., McDonnell, D. P., & Yen, P. M. (2018). Thyroid hormone receptor and ERRalpha coordinately regulate mitochondrial fission, mitophagy, biogenesis, and function. *Science Signaling*, *11*, https://doi.org/10.1126/scisignal.aam5855

Sinha, R. A., Bruinstroop, E., Singh, B. K., & Yen, P. M. (2019). Nonalcoholic fatty liver disease and hypercholesterolemia: Roles of thyroid hormones, metabolites, and agonists. *Thyroid*, *29*, 1173–1191. https://doi.org/10.1089/thy.2018.0664

Sinha, R. A., Singh, B. K., & Yen, P. M. (2018). Direct effects of thyroid hormones on hepatic lipid metabolism. *Nature Reviews. Endocrinology*, *14*, 259–269. https://doi.org/10.1038/nrendo.2018.10

Sjouke, B., Langslet, G., Ceska, R., Nicholls, S. J., Nissen, S. E., Öhlander, M., Ladenson, P. W., Olsson, A. G., Hovingh, G. K., & Kastelein, J. J. P. (2014). Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): A randomised, double-blind, placebo-controlled phase 3 study. *The Lancet. Diabetes & Endocrinology*, *2*, 455–463. https://doi.org/10.1016/S2213-8587(14)70006-3

Skarulis, M. C., Celi, F. S., Mueller, E., Zemskova, M., Malek, R., Hugendubler, L., Cochran, C., Solomon, J., Chen, C., & Gorden, P. (2010). Thyroid hormone induced brown adipose tissue and amelioration of diabetes in a patient with extreme insulin resistance. *The Journal of Clinical Endocrinology and Metabolism*, *95*, 256–262. https://doi.org/10.1210/jc.2009-0543

Stekovic, S., Hofer, S. J., Tripolt, N., Aon, M. A., Royer, P., Pein, L., Stadler, J. T., Pendl, T., Prietl, B., Url, J., Schroeder, S., Tadic, J., Eisenberg, T., Magnes, C., Stumpe, M., Zuegner, E., Bordag, N., Riedl, R., Schmidt, A., ... Madeo, F. (2020). Alternate day fasting improves physiological and molecular markers of aging in healthy, non-obese humans. *Cell Metabolism*, *31*, 878–881. https://doi.org/10.1016/j.cmet.2020.02.011

Supale, S., Li, N., Brun, T., & Maechler, P. (2012). Mitochondrial dysfunction in pancreatic beta cells. *Trends in Endocrinology and Metabolism: TEM*, *23*, 477–487. https://doi.org/10.1016/j.tem.2012.06.002

Surks, M. I., & Hollowell, J. G. (2007). Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: Implications for the prevalence of subclinical hypothyroidism. *The Journal of Clinical Endocrinology and Metabolism*, *92*, 4575–4582. https://doi.org/10.1210/jc.2007-1499

Tatar, M. (2001). A mutant Drosophila insulin receptor homolog that extends life-span and impairs neuroendocrine function. *Science*, *292*, 107–110. https://doi.org/10.1126/science.1057987

Taub, R., Chiang, E., Chabot-Blanchet, M., Kelly, M. J., Reeves, R. A., Guertin, M., & Tardif, J. (2013). Lipid lowering in healthy volunteers treated with multiple doses of MGL-3196, a liver-targeted thyroid hormone receptor-beta agonist. *Atherosclerosis*, *230*, 373–380. https://doi.org/10.1016/j.atherosclerosis.2013.07.056

Taylor, A. H., Stephan, Z. F., Steele, R. E., & Wong, N. C. (1997). Beneficial effects of a novel thyromimetic on lipoprotein metabolism. *Molecular Pharmacology*, *52*, 542–547. https://doi.org/10.1124/mol.52.3.542

Taylor, P. N., Razvi, S., Pearce, S. H., & Dayan, C. M. (2013). Clinical review: A review of the clinical consequences of variation in thyroid function within the reference range. *The Journal of Clinical Endocrinology and Metabolism*, *98*, 3562–3571. https://doi.org/10.1210/jc.2013-1315

Terry, D. F., Wilcox, M., McCormick, M. A., Lawler, E., & Perls, T. T. (2003). Cardiovascular advantages among the offspring of centenarians. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *58*, M425–431. https://doi.org/10.1093/gerona/58.5.m425

Thvilum, M., Brandt, F., Brix, T. H., & Hegedus, L. (2012). A review of the evidence for and against increased mortality in hypothyroidism. *Nature Reviews. Endocrinology*, *8*, 417–424. https://doi.org/10.1038/nrendo.2012.29

Tian, L., Song, Y., Xing, M., Zhang, W., Ning, G., Li, X., Yu, C., Qin, C., Liu, J., Tian, X., Sun, X., Fu, R., Zhang, L., Zhang, X., Lu, Y., Zou, J., Wang, L., Guan, Q., Gao, L., & Zhao, J. (2010). A novel role for thyroid-stimulating hormone: Up-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein pathway. *Hepatology*, *52*, 1401–1409. https://doi.org/10.1002/hep.23800

Tiedge, M., Lortz, S., Drinkgern, J., & Lenzen, S. (1997). Relation between antioxidant enzyme gene expression and antioxidative defense

status of insulin-producing cells. *Diabetes*, 46, 1733–1742. https://doi.org/10.2337/diab.46.11.1733

Torrance, C. J., Usala, S. J., Pessin, J. E., & Dohm, G. L. (1997). Characterization of a low affinity thyroid hormone receptor binding site within the rat GLUT4 gene promoter. *Endocrinology*, 138, 1215–1223. https://doi.org/10.1210/endo.138.3.4982

Totoki, Y., Tatsuno, K., Covington, K. R., Ueda, H., Creigton, C. J., Kato, M., Tsuji, S., Donehower, L. A., Slagle, B. L., Nakamura, H., Yamamoto, S., Shinbrot, E., Hama, N., Lehmkuhl, M., Hosoda, F., Arai, Y., Walker, K., Dahdouli, M., Gotoh, K., ... Shibata, T. (2014). Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. *Nature Genetics*, 46, 1267–1273. https://doi.org/10.1038/ng.3126

Tran, T. V., Kitahara, C. M., de Vathaire, F., Boutron-Ruault, M. C., & Journy, N. (2020). Thyroid dysfunction and cancer incidence: A systematic review and meta-analysis. *Endocrine-related Cancer*, 27(4), 245–259. https://doi.org/10.1530/ERC-19-0417

Tseng, F.-Y., Lin, W.-Y., Li, C.-I., Li, T.-C., Lin, C.-C., & Huang, K.-C. (2015). Subclinical hypothyroidism is associated with increased risk for cancer mortality in adult Taiwanese-a 10 years population-based cohort. *PLoS One*, 10, e0122955. https://doi.org/10.1371/journal.pone.0122955

Tully, T., & Lambert, A. (2011). The evolution of postreproductive life span as an insurance against indeterminacy. *Evolution; International Journal of Organic Evolution*, 65, 3013–3020. https://doi.org/10.1111/j.1558-5646.2011.01347.x

Tzotzas, T., Krassas, G. E., Konstantinidis, T., & Bougoulia, M. (2000). Changes in lipoprotein(a) levels in overt and subclinical hypothyroidism before and during treatment. *Thyroid*, 10, 803–808. https://doi.org/10.1089/thy.2000.10.803

Umezu, T., Kita, T., & Morita, M. (2020). Dataset on effects of perinatal exposure to propylthiouracil on serum T4, body weight gain, day of eye opening and brain monoamine contents in offspring mice. *Data in Brief*, 28, 104900. https://doi.org/10.1016/j.dib.2019.104900

van den Beld, A. W., Visser, T. J., Feelders, R. A., Grobbee, D. E., & Lamberts, S. W. J. (2005). Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. *The Journal of Clinical Endocrinology and Metabolism*, 90, 6403–6409. https://doi.org/10.1210/jc.2005-0872

van der Valk, F., Hassing, C., Visser, M., Thakkar, P., Mohanan, A., Pathak, K., Dutt, C., Chauthaiwale, V., Ackermans, M., Nederveen, A., Serlie, M., Nieuwdorp, M., & Stroes, E. (2014). The effect of a diiodothyronine mimetic on insulin sensitivity in male cardiometabolic patients: A double-blind randomized controlled trial. *PLoS One*, 9, e86890. https://doi.org/10.1371/journal.pone.0086890

Venditti, P., De Rosa, R., & Di Meo, S. (2003). Effect of thyroid state on H2O2 production by rat liver mitochondria. *Molecular and Cellular Endocrinology*, 205, 185–192. https://doi.org/10.1016/s0303-7207(02)00332-5

Venediktova, N. I., Mashchenko, O. V., Talanov, E. Y., Belosludtseva, N. V., & Mironova, G. D. (2020). Energy metabolism and oxidative status of rat liver mitochondria in conditions of experimentally induced hyperthyroidism. *Mitochondrion*, 52, 190–196. https://doi.org/10.1016/j.mito.2020.04.005

Verga Falzacappa, C., Patriarca, V., Bucci, B., Mangialardo, C., Michienzi, S., Moriggi, G., Stigliano, A., Brunetti, E., Toscano, V., & Misiti, S. (2009). The TRbeta1 is essential in mediating T3 action on Akt pathway in human pancreatic insulinoma cells. *Journal of Cellular Biochemistry*, 106, 835–848. https://doi.org/10.1002/jcb.22045

Vestergaard, P., & Mosekilde, L. (2003). Hyperthyroidism, bone mineral, and fracture risk–a meta-analysis. *Thyroid*, 13, 585–593. https://doi.org/10.1089/105072503322238854

Videla, L. A., Fernández, V., Cornejo, P., Vargas, R., Carrasco, J., Fernández, J., & Varela, N. (2015). Causal role of oxidative stress in unfolded protein response development in the hyperthyroid state. *Free Radical Biology & Medicine*, 89, 401–408. https://doi.org/10.1016/j.freeradbiomed.2015.09.004

Villicev, C. M., Freitas, F. R. S., Aoki, M. S., Taffarel, C., Scanlan, T. S., Moriscot, A. S., Ribeiro, M. O., Bianco, A. C., & Gouveia, C. H. A. (2007). Thyroid hormone receptor beta-specific agonist GC-1 increases energy expenditure and prevents fat-mass accumulation in rats. *The Journal of Endocrinology*, 193, 21–29. https://doi.org/10.1677/joe.1.07066

Wang, C. (2013). The Relationship between type 2 diabetes mellitus and related thyroid diseases. *Journal of Diabetes Research*, 2013, 390534. https://doi.org/10.1155/2013/390534

Wang, F., Tan, Y., Wang, C., Zhang, X., Zhao, Y., Song, X., Zhang, B., Guan, Q., Xu, J., Zhang, J., Zhang, D., Lin, H., Yu, C., & Zhao, J. (2012). Thyroid-stimulating hormone levels within the reference range are associated with serum lipid profiles independent of thyroid hormones. *The Journal of Clinical Endocrinology and Metabolism*, 97, 2724–2731. https://doi.org/10.1210/jc.2012-1133

Waring, A. C., Arnold, A. M., Newman, A. B., Bùžková, P., Hirsch, C., & Cappola, A. R. (2012). Longitudinal changes in thyroid function in the oldest old and survival: the cardiovascular health study all-stars study. *The Journal of Clinical Endocrinology and Metabolism*, 97, 3944–3950. https://doi.org/10.1210/jc.2012-2481

Waring, A. C., Rodondi, N., Harrison, S., Kanaya, A. M., Simonsick, E. M., Miljkovic, I., Satterfield, S., Newman, A. B., & Bauer, D. C. (2012). Thyroid function and prevalent and incident metabolic syndrome in older adults: The Health, Ageing and Body Composition Study. *Clinical Endocrinology*, 76, 911–918. https://doi.org/10.1111/j.1365-2265.2011.04328.x

Weiner, J., Kranz, M., Klöting, N., Kunath, A., Steinhoff, K., Rijntjes, E., Köhrle, J., Zeisig, V., Hankir, M., Gebhardt, C., Deuther-Conrad, W., Heiker, J. T., Kralisch, S., Stumvoll, M., Blüher, M., Sabri, O., Hesse, S., Brust, P., Tönjes, A., & Krause, K. (2016). Thyroid hormone status defines brown adipose tissue activity and browning of white adipose tissues in mice. *Scientific Reports*, 6, 38124. https://doi.org/10.1038/srep38124

Weingarten, C., Jenudi, Y., Tshuva, R. Y., Moskovich, D., Alfandari, A., Herbergs, A., Davis, P. J., Ellis, M., & Ashur-Fabian, O. (2018). The interplay between epithelial-mesenchymal transition (EMT) and the thyroid hormones-alphavbeta3 axis in ovarian cancer. *Hormones & Cancer*, 9, 22–32. https://doi.org/10.1007/s12672-017-0316-3

Weinstein, S. P., Watts, J., & Haber, R. S. (1991). Thyroid hormone increases muscle/fat glucose transporter gene expression in rat skeletal muscle. *Endocrinology*, 129, 455–464. https://doi.org/10.1210/endo-129-1-455

Westendorp, R. G., Heemst, D. V., Rozing, M. P., Frölich, M., Mooijaart, S. P., Blauw, G., Beekman, M., Heijmans, B. T., de Craen, A. J. M., Slagboom, P. E., & Leiden Longevity Study Group et al. (2009). Nonagenarian siblings and their offspring display lower risk of mortality and morbidity than sporadic nonagenarians: The Leiden Longevity Study. *Journal of the American Geriatrics Society*, 57, 1634–1637. https://doi.org/10.1111/j.1532-5415.2009.02381.x

Wiesenborn, D. S., Ayala, J. E., King, E., & Masternak, M. M. (2014). Insulin sensitivity in long-living Ames dwarf mice. *Age*, 36, 9709. https://doi.org/10.1007/s11357-014-9709-1

Xu, C., Xu, L., Yu, C., Miao, M., & Li, Y. (2011). Association between thyroid function and nonalcoholic fatty liver disease in euthyroid elderly Chinese. *Clinical Endocrinology*, 75, 240–246. https://doi.org/10.1111/j.1365-2265.2011.04016.x

Yang, Y., Chen, Y., Chen, J., Zhang, D., Wang, J., Mao, X., Wei, X., Li, X., Ma, X., Liu, C., & Wang, K. (2019). The adverse effects of thyrotropin absence on pancreatic beta cell function in mice. *Journal of Diabetes Research*, 2019, 9536032. https://doi.org/10.1155/2019/9536032

Yen, C.-C., Huang, Y.-H., Liao, C.-Y., Liao, C.-J., Cheng, W.-L., Chen, W.-J., & Lin, K.-H. (2006). Mediation of the inhibitory effect of thyroid hormone on proliferation of hepatoma cells by transforming

growth factor-beta. *Journal of Molecular Endocrinology, 36*, 9–21. https://doi.org/10.1677/jme.1.01911

Zambrano, A., García-Carpizo, V., Gallardo, M. E., Villamuera, R., Gómez-Ferrería, M. A., Pascual, A., Buisine, N., Sachs, L. M., Garesse, R., & Aranda, A. (2014). The thyroid hormone receptor beta induces DNA damage and premature senescence. *The Journal of Cell Biology, 204*, 129–146. https://doi.org/10.1083/jcb.201305084

Zhang, G.-Y., Langan, E. A., Meier, N. T., Funk, W., Siemers, F., & Paus, R. (2019). Thyroxine (T4) may promote re-epithelialisation and angiogenesis in wounded human skin ex vivo. *PLoS One, 14*, e0212659. https://doi.org/10.1371/journal.pone.0212659

Zhang, Q., Miao, Q., Ye, H., Zhang, Z., Zuo, C., Hua, F., Guan, Y., & Li, Y. (2014). The effects of thyroid hormones on brown adipose tissue in humans: A PET-CT study. *Diabetes/metabolism Research and Reviews, 30*, 513–520. https://doi.org/10.1002/dmrr.2556

Zhao, P., Hu, Z., Ma, W., Zang, L., Tian, Z., & Hou, Q. (2020). Quercetin alleviates hyperthyroidism-induced liver damage via Nrf2 Signaling pathway. *BioFactors, 46*(4), 608–619https://doi.org/10.1002/biof.1626