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DYSREGULATION OF THE HIPPO PATHWAY SIGNALING IN AGING AND CANCER

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Abstract

Human beings are facing emerging degenerative and cancer diseases, in large part, as a consequence of increased life expectancy. In the near future, researchers will have to put even more effort into fighting these new challenges, one of which will be prevention of cancer while continuing to improve the aging process through this increased life expectancy. In the last few decades, relevance of the Hippo pathway on cancer has become an important study since it is a major regulator of organ size control and proliferation. However, its deregulation can induce tumors throughout the body by regulating cell proliferation, disrupting cell polarity, releasing YAP and TAZ from the Scribble complexes and facilitating survival gene expression via activation of TEAD transcription factors. This pathway is also involved in some of the most important mechanisms that control the aging processes, such as the AMP-activated protein kinase and sirtuin pathways, along with autophagy and oxidative stress response/antioxidant defense. This could be the link between two tightly connected processes that could open a broader range of targeted molecular therapies to fight aging and cancer. Therefore, available knowledge of the processes involved in the Hippo pathway during aging and cancer must necessarily be well understood.

Keywords: Aging, Hippo pathway, AMPK, Sirtuin, Autophagy, cancer

ABBREVATIONS

5-FU	=	Fluorouracil
AICAR	=	5-aminoimidazole-4-carboxamide-1-β-riboside
AMOT	=	Angiomotin
AMOTL1	=	Angiomotin like 1
AMPK	=	AMP-activated protein kinase
ANKRD1	=	Ankyrin repeat domain 1
AP-1	=	Activator protein 1
AREG	=	Amphiregulin
ATF4	=	Activating transcription factor 4
ATG5/7/8/12	=	Autophagy related 5/7/8/12
BAX	=	BCL2 associated X, apoptosis regulator
BDNF	=	Brain derived neurotrophic factor
BIRC5	=	Baculoviral IAP repeat containing 5
CASP	=	Caspase
CD44	=	CD44 molecule (Indian blood group)
CD98	=	CD98 Heavy Chain
CDX2	=	Caudal Type Homeobox 2
CNK1	=	Connector enhancer of kinase suppressor of ras 1
COX2	=	Cyclooxygenase 2
Crb	=	Crumbs
CSC	=	Cancer stem cells
CTGF	=	Connective tissue growth factor
CYR61	=	Cysteine rich angiogenic inducer 61/
EGF	=	Epidermal Growth Factor
EGFR	=	Epidermal Growth Factor Receptor
eIF2αP	=	Alpha (α) subunit of the translation initiation factor eIF2 at serine 51
EMT	=	Epithelial-to-mesenchymal transition
ER	=	Endoplasmic reticulum
ERK	=	Mitogen-activated protein kinase 1
ETS Family	=	E-twenty-six Family
Ex	=	Expanded
FGF1	=	Fibroblast growth factor 1
FGFR1	=	Fibroblast growth factor receptor 1
FOXA2	=	Forkhead box A2
FOXO1/3/4	=	Forkhead box O1/O3/O4
GABP	=	GA-binding protein
GATA3	=	GATA Binding Protein 3
GCLC	=	Glutamate-cysteine ligase catalytic subunit
GCLM	=	Glutamate-cysteine ligase modifier subunit
GH	=	Growth hormone
GLUT3	=	Glucose transporter 3

GSH	=	Glutathione
HCC	=	Hepatocellular carcinomas
HIF-1α	=	Hypoxia inducible factor 1 subunit alpha
HMGA1	=	High mobility group AT-hook 1
h-warts	=	Human warts
IL-6	=	Interleukin 6
JAK	=	Janus kinases (JAK)
Ki67	=	Antigen KI-67
KLF4	=	Kruppel-Like Factor 4
KRAS	=	KRAS proto-oncogene, GTPase
Ku70	=	X-ray repair cross complementing 6
Last	=	Large tumor suppressor kinase in Drosophila
LATS1/2	=	Large tumor suppressors 1/2
LC3II	=	Microtubule-associated protein 1A/1B-light chain 3
LIMK1	=	LIM Domain Kinase 1
LKB1	=	Serine/threonine kinase 11
LPA	=	Lysophosphatidic acid
MAP4Ks	=	Mitogen-activated protein kinase kinase kinase kinases
MEK1	=	Mitogen-activated protein kinase kinase 1
miRNA29	=	MicroRNA 29
MnSOD	=	Manganese superoxide dismutase
MOB	=	Adaptor proteins (homologues of Mats)
MST1/2	=	Mammalian STE20-like kinase
mTOR	=	Mechanistic target of rapamycin kinase
mTORC1/2	=	CREB-regulated transcription coactivator 1/2
MuSC	=	Muscle stem cells
NAD+	=	Nicotinamide adenine dinucleotide
NANOG	=	Homeobox Transcription Factor Nanog
NEDD4.2	=	Neural precursor cell expressed, developmentally down-regulated 4-like
NF2	=	Neurofibromin 2
NF-κβ	=	Nuclear factor kappa B
NQO1	=	NAD(P)H:quinone oxidoreductase
NRF-2	=	Nuclear factor erythroid 2 like 2
OCT3/4	=	Octamer-binding transcription factor 3/4
OEMES	=	Eomesodermin
OGT	=	O-GlcNAc transferase
p16	=	Cyclin-dependent kinase inhibitor 2A
p21	=	Cyclin-dependent kinase inhibitor 1
p53	=	Tumor protein p53
p62	=	Sequestosome 1
p65	=	Nuclear factor NF-kappa-B p65 subunit
p73	=	Tumor Protein P73
PAKs	=	P21 Activated Kinases

PERK	=	Eukaryotic translation initiation factor 2 alpha kinase 3
PGC1α	=	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K/Akt	=	Phosphatidylinosi- tol 3-kinase / Protein Kinase B
Pik3cb	=	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
PML	=	Promyelocytic Leukemia
PPARα	=	Peroxisome proliferator activated receptor alpha
RAF	=	Raf-1 Proto-Oncogene
RASSF1A	=	Ras association domain family proteins 1A
ROS	=	Reactive oxygen species
SAV1	=	Salvador family WW domain containing protein 1
SIRT	=	Sirtuin
SMAD2/3	=	SMAD family member 2 / 3
SOX2/9	=	SRY-box 2/9
STAT	=	Signal Transducer and Activator of Transcription protein
TAZ	=	Transcriptional co-activator with PDZ-binding motif
TBK1	=	TANK binding kinase 1
TEAD	=	TEA Domain Family Members
TNFα,	=	Tumour necrosis factor alpha-like
TXN1	=	Thioredoxin 1 (cytosolic)
TXN2	=	Thioredoxin 2 (mitochondrial)
UPR	=	Unfolded protein response
Wst	=	Warts
WWP1	=	WW domain containing E3 ubiquitin protein ligase 1
WWTR1	=	WW Domain Containing Transcription Factor
YAP	=	Yes associated protein
ZEB1	=	Zinc finger E-box binding homeobox 1
γ-H2AX	=	Gamma histone

1. INTRODUCTION

The age and population distribution of the European Union countries and their developed economies are expected to change dramatically in the upcoming decades. Life expectancy is projected to increase from 78.3 years (2016) to 86.1 (2070) for males and from 83.7–90.3 for females. The total elderly % of the population (65 & over) in 2016 was 19.3% and by 2070 it is projected to be 28.8% [1]. This increase in the average lifespan leads to an increase of the total cost of aging, i.e. education, unemployment benefits, public spending on pensioners: healthcare and long-term daily care, for example [1]. Aging is a multi-faceted process characterized by a progressive decline of physiological functions, which in turn promote the prevalence of age-related diseases, sometimes stimulating chronic disease growth; thus, increasing long-term care costs. One of these diseases is cancer, whose prevalence increases with age. According to the National Cancer Institute, age is the highest single risk factor for cancer, this risk increasing significantly after the age of 50. Furthermore, the percentage of newly diagnosed cancer cases by age group is expected to be 14.1% (45–54 years), 24.1% (55–64) and 25.4% (64–74 years), in which half of all "new" cases occur after age 66. In this context, a number of reports have recently summarized the link between aging and cancer [[2], [3], [4], [5], [6], [7]]. Accumulation of mutations and aberrant cell proliferation are typical characteristics of cancer initiation, promotion and progression [8]. The aging decline of DNA damage-repair machinery, loss of immune system efficiency, along with chronic inflammation, increase of reactive oxygen species (ROS) and multiple mutations in the genes, can contribute to cancer development. For example, it has recently been reported that decrease of the immune system response to aging (age-related decline in T cells) could be a more relevant event in the risk of developing cancer than in multiple mutations of DNA during aging [9]. To obtain a better understanding of the connection between aging and cancer it is necessary to develop more effective approaches to cancer prevention and treatment. The study of cellular signaling pathways is becoming increasingly as important as that of molecular targeted therapy in cancer. Consequently, it is important to know the mechanisms involved in this pathway. In this review, we will summarize recent findings that link the Hippo pathway to aging and cancer.

2. HIPPO PATHWAY SIGNALLING

The Hippo pathway is an evolutionarily conserved signal transduction pathway regulated by cell-cell contact, cell polarity, mechanical cues, ligands of G-protein coupled receptors, and cellular energy status [10]. This pathway is linked to development, cell proliferation, cell shape and growth [11], as well as tissue regeneration and stem cell regulation [12]. Moreover, the Hippo pathway has also been implicated in regulating cancer immunity, innate immune responses against pathogens, and autoimmune diseases (for details see review from [13]). The origin and discovery of the Hippo pathway began in 1995 with

Drosophila melanogaster. Justice and colleagues using a Drosophila model identified a new tumor suppressor gene, warts (wts) (also referred to as large tumor suppressor kinase, lats) [14]. The authors found that depletion of the wts gene resulted in increased cell proliferation, as well as abnormal morphogenesis. Four years later, two different laboratories identified two human homolog of the wts gene, large tumor suppressor kinase 1 (LATS1) [15] and h-warts (Human warts) [16]. In the early 2000s, several laboratories reported the core components of the Hippo pathway in Drosophila first, and soon after in mammalian species [11].

In the mammalian Hippo pathway, core components consist of Mammalian STE20-like kinase 1/2 (MST1/2) and an adaptor protein, Salvador family WW domain, containing protein 1 (SAV1), which can phosphorylate activate LATS1/2. Apart from MST1/2, two groups of mitogen-activated protein kinase kinase kinase kinases (MAP4Ks), MAP4K1/2/3/5 and MAP4K4/6/7, are also reported to directly phosphorylate LATS1/2 at their hydrophobic motifs. Once LATS1/2 is activated, its transcriptional coactivators, yes-associated protein (YAP) and WW Domain Containing Transcription Factor (WWTR1) (also known as TAZ), are phosphorylated and retained in the cytoplasm. When YAP and TAZ are dephosphorylated, they translocate to the nucleus and induce gene expression through their interaction with TEA Domain Family Members (TEAD), and the SMAD family of signal transduction proteins [17]. The Hippo pathway is summarized in Fig. 1, and a complete description of core components of the Hippo pathway, upstream signaling regulating it, mechanisms of activation and their transcriptional coactivators can be found in an excellent review of Meng and colleagues [11].

3. THE HIPPO PATHWAY SIGNALING LINK WITH AGING

The following section summarizes the link between the Hippo pathway and biological processes associated with aging, such as anti-aging pathways AMP-activated protein kinase (AMPK) and sirtuin (SIRT), autophagy and oxidative stress response/antioxidant defense.

3.1. AMPK.

AMPK is an ancestral energy sensor responsible for regulating metabolism and energy balance. In response to several stimuli such as metabolic stress (low energy status), exercise and drugs (metformin, resveratrol, rapamycin), AMPK modulates the production of adenosine triphosphate (ATP) as well as physiological processes including mitochondrial biogenesis, autophagy, lipogenesis and protein synthesis [18]. Recent advances in aging research have provided molecular evidence that the AMPK pathway is a key to signaling the promotion of healthy aging and longevity [18,19]. In this context Salminen and Colleagues reviewed mechanisms that correlate aging and dysregulation of AMPK [20]. The authors

summarized data showing that AMPK activity decreased with age in skeletal muscles. Moreover, AMPK (a, b and y isoforms) expression, phosphorylation of AMPKa and activated AMPK complex structures can also be affected by aging [20]. Although moderate AMPK activation is required to promote protective cell functions in order to enhance adaptive response, persistent AMPK activation stimulates irreversible senescence which leads to progressive age-related dysfunction and diseases [21].

The link between the Hippo pathway and AMPK signaling has been well-documented. For example, AMPK phosphorylates YAP on multiple sites and inhibits its transcriptional activity. Moderate activation of AMPK using glucose deprivation or AMPK activators such as metformin, phenformin and 5-aminoimidazole-4-carboxamide-1-β-riboside (AICAR) promotes YAP S127 phosphorylation and cytoplasmic retention and inhibits YAP-target genes ANKRD1, CTGF, and CYR61 expression [22]. Similarly, other reports have found that AMPK can inhibit YAP activity. In fact, it has been reported that AMPK induces YAP S94 phosphorylation, which disrupts the YAP/TEAD interaction and leads to inhibition of YAP target genes CTGF and CYR61 [23]. Another report shows that AMPK promotes YAP S61 phosphorylation, which does not disrupt the interaction YAP/TEAD but is able to suppress CTGF and CYR61 expressions [24]. In addition, resveratrol, an AMPK agonist, resveratrol, suppresses YAP protein expression and downregulates CTGF and CYR61 mRNA levels in pancreatic cancer cells [25]. However, a study using embryonic fibroblasts from AMPK-knockout mice shows only partial inhibition of CTGF and CYR61 transcription, suggesting that AMPK-independent regulation of the Hippo pathway could also exist [24]. In addition, Peng and colleagues found that O-GlcNAcylation of YAP by O-GlcNAc transferase (OGT) represses transcription of YAP target genes such as ANKRD1, CTGF, CYR61, and GLUT3 [26].

3.2. SIRT1.

SIRT1, a member of the sirtuin family of nicotinamide adenine dinucleotide (NAD+)–dependent deacetylases, plays a key role in aging and longevity by improving stress response, promoting cell survival and maintaining genomic stability [27]. It has been reported that the increased NAD+/NADH ratio, together with enhanced SIRT1 deacetylase activity, are associated with a prolonged life-span and a lower risk of developing several age-related pathologies including cancer, neurodegeneration, retinal degeneration or cardiovascular disease [28]. In addition, a number of genes relevant to regulation of aging and promotion of longevity including Ku70/BAX, p53, FOXO3/4, LKB1/AMPK, PGC1α and p65/NF-κβ, as well as biological processes such as cell proliferation, apoptosis, senescence and autophagy can also be affected by SIRT1 [29].

Few studies have been able to explain a direct link between the Hippo pathway and SIRT1. For example, in Mst1−/− knockout mice, MST1, a key component of the Hippo signaling pathway, upregulates the SIRT1 expression in the liver during fasting due to the inhibition of SIRT1 ubiquitination [30]. In addition, MST1 also promotes the p53 transcriptional activity and DNA damage-mediated apoptosis through SIRT1 phosphorylation, which can lead to the inhibition of both SIRT1/p53 interaction and SIRT1 deacetylation activity [31]. In the cardiovascular system, MST1 stimulates apoptosis and inhibits autophagy by impairing the protein quality control mechanisms [32]. Under high glucose condition, knockout of MST1 increases SIRT1 expression and reduces apoptosis in cardiac microvascular endothelial cells whereas overexpression of MST1 promotes apoptosis and coronary damage through SIRT1 inhibition [33]. Another study conducted by Hu and colleagues show MST1 activity is required for melatonin-mediated cardioprotective effects. The authors found that melatonin inhibits phosphorylation of MST1 resulting in SIRT1 upregulation, apoptosis reduction, autophagy stimulation, mitochondrial integrity as well as biogenesis modulation [34].

3.3. Autophagy.

Autophagy works mainly by removing damaged biomolecules from autophagosomes, which are then degraded by lysosomes. This biological process is essential in maintaining healthy aging and longevity; dysregulation of this process increases cellular stress, damage and death. In general, anti-aging pathways (AMPK and SIRT) induce autophagy and extend lifespan whereas pro-aging pathways (mTOR, Insulin/GH) inhibit autophagy and shorten lifespans [35]. Moreover, a set of autophagy-associated genes such as Atg5, Atg7, Atg8, Atg12 or Beclin-1 are downregulated with aging [36,37]. A recent work by Ravanan and colleagues provided an extensive review of autophagy. The authors summarized different autophagy stages: their molecular regulatory mechanisms, links to inflammation (NF-κβ, PPARα, TBK1), nutrient depletion/metabolism (AMPK, mTOR), hypoxia (HIF-1α), apoptosis and endoplasmic reticulum (ER) stress, and importantly, its contribution to developing pathologic conditions (cancer, neurodegeneration, metabolic disorders), and finally, the chemical modulators of autophagy [38].

The most established component in the Hippo pathway associated with autophagy comes from MST1/2 kinases; however, its role is controversial. For example, in cardiac cells, MST1, which is essential to autophagosome formation and autolysosome fusion, can directly phosphorylate Beclin1 and regulate its expression. MST1 also significantly attenuates Beclin1-Vps34 and Beclin1-Atg14 L interactions, proposing that MST1 induces autophagosome complex I dissociation [32,39]. Moreover, several cardioprotective compounds, including melatonin, nicorandil and luteolin, facilitate autophagy through MST1 inhibition [34,40,41]. Furthermore, in cardiac microvascular endothelial cells MST1 also inhibits

autophagy induction and lysosome-dependent degradation [33]. The above data show that in cardiac cells MST1 activation, in response to stress, inhibits autophagy. Using Mst-1-deficient mice, upregulation of autophagy-related genes Atg5, Atg7 and LC3II are observed after myocardial infarction, suggesting that MST1 negatively regulates autophagy and promotes cardiac dysfunction. Similarly, neurons in Mst-1-deficient mice were able to survive spinal cord injury by upregulation of LC3II and p62 levels, indicating a disruption of the autophagy-lysosome pathway [42]. These data indicate that Mst-1-deficient mice show elevated autophagy activity. In contrast, MST1/2 induces autophagy and lysosome-dependent degradation through phosphorylating LC3II. In human embryonic kidney cells 293, mouse embryonic fibroblasts and murine myoblasts, MST1/2 depletion represses autophagy, which is indicated by LC3II upregulation and p62 accumulation [43]. MST1 inhibits macrophage autophagy induction and lysosome-dependent degradation because MST1 depletion upregulate LC3II and downregulate p62 in the presence of lysosomal inhibitor [44].

3.4. Oxidative Stress Response / antioxidant defense

A number of reports have clarified an interdependent relationship between inflammation and oxidative stress. Oxidative stress promotes inflammation, and similarly, inflammation also induces oxidative stress through activation of numerous signaling pathways, resulting in a feedback loop [[45], [46], [47]]. More importantly, both inflammation and oxidative stress are associated with aging and age-related pathologies including cancer, neurodegenerative diseases, cardiovascular disease, and diabetes. In fact, one of the most popular explications of aging molecular mechanisms comes from an oxidative stress theory [48,49]. Previously, we have summarized how the Hippo pathway affects apoptosis and inflammation through regulation of FOXO1/3, TNFα, IL-6, COX2, HIF-1α, AP-1 and JAK/STAT in response to oxidative stress [17]. Especially important is the potential role of MST1 in regulating aging and lifespan through stimulation of FOXO3 nuclear translocation. FOXO3 leads to upregulation of pro-apoptotic genes, modulation of pro-inflammatory genes and regulation of NF-κβ, a master regulator of oxidative stress and inflammation [17]. Interestingly, the activation of MST1 promotes FOXO1 nuclear translocation and apoptosis upon survival factor deprivation in neurons [50] and accumulation of ROS in cancer cells [51]. In addition, oxidative stress stabilizes LATS1 and activates the Hippo pathway in the fibrosarcoma cell line. This promotes programmed cell death through upregulating eIF2αP-ATF4 expression and downregulation of E3 ubiquitin ligases, NEDD4.2 and WWP1 expression [52]. Oxidative stress also induces ER stress. Recently, it has been reported that transient ER stress induces PERK-eIF2αP signaling and promotes cell survival by stimulating ATF4 expression and increasing YAP and unfolded protein response (UPR) activities. In contrast, persistent ER stress promotes cell death by activating the Hippo pathway, inhibiting YAP and UPR activities and downregulating eIF2αP-ATF4 signaling [53].

Apart from the MST1 and LATS1 kinases, their downstream effectors TAZ and YAP are also affected by oxidative stress. For example, in HEK 293 T cells with mild oxidative stress, TAZ, TAZ S-glutathionylation and TAZ/TEAD4 trans-activation increase but YAP and YAP/TEAD4 trans-activation do not. This suggests that ROS could differentially regulate TAZ and YAP, this TAZ enhanced stability and activation leading to tissue repair [54]. In contrast, transcription of antioxidant genes, including catalase and MnSOD, can be upregulated by YAP-mediated FOXO1 activation in cardiomyocytes, whereas LATS2 overexpression suppresses their transcription [55]. The ETS family member, GA-binding protein (GABP), also known as nuclear (factor erythroid 2)-like 2 (NRF-2), binds to the YAP promoter and activates YAP transcription, which is essential for antioxidant defense as YAP markedly ameliorates oxidant-induced cell cycle arrest and apoptosis. The oxidant-induced inhibition of GABP is accompanied by MST1/2-induced depletion of YAP. In fact, levels of GSH associated enzymes including glutathione reductase (GSR), glutamate-cysteine ligase catalytic subunit (GCLC), glutamate-cysteine ligase modifier subunit (GCLM), NAD(P)H:quinone oxidoreductase (NQO1), cytosolic thioredoxin (TXN1) and mitochondrial thioredoxin (TXN2), are all increased in liver tissue with depleted MST1/2 [56].

4. HIPPO PATHWAY SIGNALING DYSREGULATED IN AGING

It is well known that a typical hallmark of aging is a steady increase of senescent cells. Stimuli such as DNA damage, oncogene, oxidative stress, mitochondrial dysfunction and DNA methylases/histone deacetylases inhibitors are all able to induce cell senescence [57]. If the cell is unable to control/reverse this process, the results are a pro-inflammatory microenvironment and a reduction of regenerative capacities in age-related dysfunction and diseases [57]. However, in cancer, cell senescence is a tumor suppressive mechanism. YAP/TAZ has been reported to play a key role in suppression of oncogene-RAS-induced senescence in human primary cells such as WI38 human primary lung fibroblasts, IMR90 human fibroblasts and HPNE ductal pancreatic cells. In fact, activation of YAP is enough to increase nucleotide metabolism and diminish senescent phenotypes including proliferation, morphological alterations, lysosomal activity and expression of SASP genes. Moreover, RAS and MEK1 inhibit YAP/TAZ transcriptional activity during induction of senescence while reduction of YAP/TAZ activity is enough to promote senescence-associated phenotypes [58]. Induction of senescence in human nucleus pulposus chondrocytes leads to an increase of the Hippo pathway activation and YAP phosphorylation and decrease of CTGF expression. In correspondence with this data, depletion of YAP promotes senescence through stimulation of p53/p21, and lysosomal activity [59]. In human periodontal ligament stem cells, YAP stimulates cell proliferation (assessed using EdU incorporation) and inhibits apoptosis whereas depletion of YAP promotes senescence [60]. Similarly, other studies have explained the role of the

transcriptional co-activators downstream of the Hippo pathway in regulating cell senescence. In ethanol-induced cellular senescence, upregulation of YAP decreases senescence markers (p16, p21, HMGA1 and DNA damage marker γ-H2AX) in hepatocytes [61]. In human fibroblast cells, progressive loss of YAP promotes concomitant increase of senescence through both the p53 and p16 pathways in a TEAD-dependent manner; in context of cancer, the authors reported that in mesothelioma and liver cancer YAP downregulation was also able to stimulate senescence [62]. When YAP is predominantly localized in the cytoplasm of senescent cells, the transcriptional activity of its target gene, its ability to self-repair and proliferate significantly decrease, its resistance to cellular senescence will also decrease.

CTGF is an established YAP/TAZ target gene which plays a central role in tissue remodeling. Downregulation of CTGF mediates collagen loss in chronologically-aged human skin whereas persistent activation of CTGF can result in excessive deposition of collagen and fibrotic disorders [63]. The authors found that TGF-β-activated Smad proteins are the main inducers of CTGF and type I procollagen in human dermal fibroblasts. In fact, downregulation of the TGF-β/Smad/CTGF/procollagen axis was identified in fibroblasts in aged human skin compared to young human skin in vivo [63]. Interestingly, it has also been reported that YAP/TAZ modulates the TGF-β/Smad3 pathway in primary human skin fibroblasts. The authors found that YAP/TAZ depletion promotes Smad7 via activation of AP-1 transcription factor, which in turn impairs TGF-β/Smad3 signaling [64]. The proliferative myogenecity capacity of muscle stem cells (MuSC) is essential to repair skeletal muscle after injury, while age-related dysfunction of MuSC can lead to fibrotic disorders and reduced recovery after injury [65]. Stearns-Reider and colleagues studied the effect of age and substrate stiffness on YAP/TAZ in fibroblasts and its influence on MuSC fate. In aged fibroblasts compared to young fibroblasts, the authors found an affiliated increase of stiffness and nuclear translocation of YAP/TAZ, which stimulated matricellular protein secretion leading to fibrogenic conversion of MuSCs and a diminished myogenicity [66]. The key role of the Hippo pathway in tissue repair and regeneration has been reported [67], and the intrinsic capacity to regenerate liver is well known. An interesting study by Mo and colleagues illuminated the modulation of the Hippo pathway in young and aged livers after partial hepatectomy. The authors found a modulation of the Hippo pathway and increased activity of YAP1 during liver regeneration. Aging was able to decrease hepatocyte proliferation, assayed as Ki67 and H&E, and increase pMST, pLATS and pYAP. Moreover, depletion of MTS1/2 recovered the regenerative capacity of liver in aged mice [68]. The study of regulation of MST1 in several tissues of aged mice has shown that MST1 mRNA expression in the heart, kidney, striatal and liver (only at 23–28 months) are reduced with aging. In the cortex and hippocampus MST1 mRNA expression increases initially then decreases with age. In contrast, in the spleen, an increase

of MST1 mRNA expression level is observed with aging. The authors also found that MST1 is cleaved by CASP3, 6, and 7, and protein levels of MST1 and its fragments increase during the aging process [69].

5. HIPPO PATHWAY SIGNALING AND LINK WITH CANCER

Cancer is a generic term for different types of diseases that can affect any part of the body. According to the World Health Organization, cancer is "the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs". Cancer can be divided into three main stages: initiation, promotion and progression [8]. The Hippo pathway, which originally was identified in Drosophila has functions of tumor suppression and emerging evidence suggests that its dysregulation can drive tumorigenesis forward [70]. In this section, the connection between the Hippo pathway and different cancer stages will be reviewed.

5.1. Cancer initiation

Cancer stem cells (CSCs), which are also called cancer initiating cells, have been described in multiple cancers including brain, breast, lung and prostate [[71], [72], [73], [74]]. CSCs are able to differentiate, self-renew and initiate tumorigenesis. Although the origin of the CSCs remains unclear, it is believed that they may be derived from progenitor cells. In this context, evidence suggests that the Hippo pathway plays an essential role in stem cell regulation. For example, the Hippo pathway controls cell fate and differentiation of progenitor cells during normal embryonic development and during cancer development [70]. Morin-Kensicki and colleagues showed that knockout of YAP, the main downstream effector of the Hippo pathway, caused embryonic defects at day 8.5 [75]. In addition, TEAD4, a YAP target transcription factor, regulates multiple trophoblast gene expression such as GATA3 and CDX2 and that, TEAD4 activity is correlated to nuclear localization of YAP [[76], [77], [78], [79], [80]]. Thus, suggesting that YAP and TEAD are the key players during embryogenesis. Recent studies also indicate that the Hippo pathway plays an important role in maintaining pluripotency. First, YAP and TEAD2, which are highly abundant in embryonic and hematopoietic stem cells, are able to stimulate expression of stem cell maintenance genes including OCT3/4, KLF4, NANOG and SOX2/9 [[81], [82], [83], [84]]. Apart from directly mediating stemness, YAZ can also promote pluripotency, together with other signaling. For example, Beyer and colleagues demonstrated that YAP-TAZ-TEAD could form a complex with SMAD2/3 and OCT4 in human embryonic stem cells. This complex can also suppress the expression of differentiation markers EOMES and FOXA2 and maintain the pluripotency of the human embryonic stem cells [85]. Taken together, this evidence indicates that the Hippo pathway contributes a major role in stem cell regulation and thus, cancer initiation.

5.2. Cancer promotion

Cancer promotion largely depends on abnormal cell proliferation. Uncontrolled cell growth, being one of the hallmarks of cancer, occurs when there is imbalance between cell proliferation and cell death. Recent studies indicate that the Hippo pathway plays a key role in cell fate decisions. Two independent studies carried out by Dong et al and Zhao et al demonstrated that the Hippo pathway is involved in cell contacted inhibition and tissue growth control [86,87]. Contact inhibition is a mechanism by which adherent cells stop the proliferation process once they come into contact with neighboring cells. Working with Drosophila, Dong and colleagues showed that phosphorylation of Yorkie, homolog of mammalian transcriptional coactivator family YAP/TAZ, at Serine 168 results in its cytoplasmic sequestration and reduces cell growth. On the other hand, mutation of the Hippo pathway in Drosophila, or wts, causes accumulation of Yorkie in the nucleus. In the same study, LATS1/2 mediated-phosphorylation of YAP at Serine 127 is found to be an equivalent mechanism in mammals. Another study conducted by Zhao and colleagues identified YAP-mediated cell growth to be affected by cell density. In sparse growing conditions, YAP is mainly located in the nucleus as a transcriptional coactivator that activates the expression of a wide range of cell proliferative genes such as CTGF, BDNF and FGF1. When cells are confluent, YAP is phosphorylated at Serine 127 and translocated to the cytoplasm, preventing transcription of genes involved in proliferation and inhibiting cell growth [86,88].

Apart from contact inhibition, the Hippo pathway can also affect cell polarity and cell-to-cell adhesion. Dysregulation of cell polarity is often associated with cancer. Cell polarity defines the asymmetric distribution of cellular components and is required to maintain proper structure and function of epithelial cells. Polarized cells can be divided into two domains, the basolateral domain facing the extracellular matrix and the apical domain that lines the lumen. Reports showed that a few key apical membrane determinants, including Crumbs (Crb) and Scribble, could negatively regulate the Hippo signaling [89,90]. In Drosophila, Crb is recruited to the apical membrane by interacting with Expanded (Ex) through the FERM-binding domain and thus, negatively regulates Crb activity. In mammals, Crb activates LATS which leads to cytoplasmic sequestration of YAP and TAZ. Consistently, knockdown of Crb increases the level of nuclear YAP and TAZ, leading to an upregulated transcription of target genes. Mammalian epithelial cells adhere to one another at both adherent and tight junctions. Numerous components of these junctions including α-catenin and E-cadherin have been shown to regulate cell proliferation through the Hippo pathway. Both α-catenin and E-cadherin can control the subcellular localization of YAP. α-catenin associates with YAP which is mediated by 14-3-3. These three molecules form a complex and prevent YAP dephosphorylation and thus, restraining it from entering the nucleus [91,92]. On the other hand, loss of α-catenin induces YAP/TAZ nuclear localization [89]. E-cadherin also

functions as an upstream regulator of the Hippo pathway. E-cadherin forms a complex with β-catenin, which induces YAP phosphorylation and causes cytoplasmic accumulation [93]. Taken together, the evidence indicates that the Hippo pathway plays a key part in cancer promotion through regulating cell proliferation and polarity.

5.3. Cancer progression

When cancer progresses, the cancer cells often spread to distant tissues or organs and become metastatic cancer. Metastasis is one of the features of cancer and is the major cause of cancer mortality [94]. In metastasis, tumor cells must detach from the primary tumor, invade surrounding tissues, and circulate through lymph or blood vessels followed by extravasation at a distant tissue, generating a secondary tumor. Epithelial-to-mesenchymal transition (EMT) is a fundamental process for cancer cells to confer stemness properties and trigger metastasis. Loss of cell polarity is an initial step of EMT. Hippo signaling can also promote metastasis by cell polarity disruption, releasing YAP and TAZ from the Scribble complexes and facilitating survival gene expression via activation of TEAD transcription factors [86,95]. In addition, stimuli such as TGF-β and HGF can active the Hippo pathway and induce EMT [96,97]. Interestingly, YAP/TAZ itself can also induce E-Cadherin, N-Cadherin and Vimentin gene expression through transcription factors SNAIL and TWIST and ZEB1 modifying the EMT process [[98], [99], [100]]. YAP induced EMT also triggers CSC characteristics which provide advantages to tumor cells so they can resist anoikis [101]. Therefore, increased CSC population has been associated with metastasis and poor prognosis [[102], [103], [104]]. This evidence suggests that the Hippo pathway plays an important role in cancer, at all stages of tumor development: initiation, growth and metastasis.

6. HIPPO PATHWAY SIGNALING DYSREGULATED IN CANCER

The Hippo pathway is crucial for maintaining a programmed cell proliferation and for restricting tissue growth. Dysregulation of this pathway has been reported in a wide range of human cancers including breast, lung, colorectal and liver. However, germline and somatic mutations in the Hippo pathway are rare, suggesting that the abnormal activity of the Hippo pathway in cancers is governed by molecular events rather than by mutation of the pathway components [105]. In this section, we discuss the effect of dysregulated core components in the Hippo pathway - NF2, MST, LATS and YAP/TAZ in cancer biology.

6.1. Neurofibromin 2 (NF2) mutation

NF2, which is also called Merlin, is a well-established tumor suppressor. It is the only Hippo pathway gene known to be inactivated by mutation in cancer. Type II neurofibromatosis is caused by NF2 mutations which are characterized by the growth of nonmalignant tumors of the nervous system,

sometimes inherited in an autosomal dominant manner. Apart from somatic mutation, epigenetic alteration of NF2 has also been reported in human cancers [[106], [107], [108]]. NF2 suppresses cancer growth through multiple mechanisms. Studies show that NF2 overexpression activates LATS and inhibits YAP transcription activity. Conditional NF2 knockout mice develop cholangiocellular and hepatocellular carcinoma which can be largely blocked by heterozygous deletion of YAP suggesting that NF2 is an upstream molecule of the Hippo pathway [109]. Furthermore, hetetrozygous deletion of NF2 develops metastatic osteosarcoma. Apart from the Hippo pathway, a wide range of downstream effectors of NF2, including EGFR, p21 Activated Kinases (PAKs) and RAS have also been reported in mammalian cells [[110], [111], [112]]. The Epidermal Growth Factor Receptor (EGFR) is one of the oncogenes that has been studied extensively in human carcinomas. Internalization of ligand-bound EGFR is the major mechanism to activate EGFR signaling that drives cell proliferation. Chiasson-Mackenzie and colleagues demonstrated that NF2 is a critical regulator of cortical actomyosin at the cell junction to inhibit EGFR internalization upon cell contact [111]. More importantly, pharmacological inhibition of EGFR suppresses the growth of NF2−/− cells both in vitro and in vivo [113]. Studies have also shown that NF2 can directly bind to PAKs and prevent it from activation. Elevated PAK expression has been identified in NF2-mediated schwannomas patients suggesting NF2-deficient tumors may rely on PAK signaling to survive [114]. Furthermore, NF2 also links with cell surface proteins such as β-catenin, CD44, and integrin and influences cell proliferation [110,115,116]. For example, phosphorylation of β-catenin leads to nucleus translocation and facilitates cell cycle gene transcription such as cyclin D1. NF2 can form a complex with β-catenin, localizes β-catenin in the plasma membrane and prevents gene transcription [110]. Taken together, in cell-based models, NF2 functions as a tumor suppressor mainly through contact inhibition.

6.2. MST and LATS downregulation.

MST1 and MST2 are mammalian homologs of Drosophila Hippo. MST1 and MST2 were originally identified as pro-apoptotic kinases controlling cell growth, proliferation and apoptosis. The tumor suppressor function of MST1 and MST2 is confirmed by genetic studies in mice. In vivo studies showed that both germline loss of heterozygosity MST2 and conditional knockout of MST1/2 in liver resulted in massive hepatocellular carcinomas (HCC) which could be reversed by knockdown of YAP [[117], [118], [119]]. Apart from HCC, increased undifferentiated cell population and enlarged crypts associated with enhanced YAP expression and nuclear localization have been observed in mouse intestinal and colonic tracts [120]. Downregulation of MST1/2 expression is well-established in soft tissue sarcoma, colorectal and prostate cancer [[121], [122], [123]]. In addition, analysis of adaptor proteins (MOB) phosphorylation, a downstream effector of MST1/2, showed that the activity of MST1/2 activity was

reduced in the majority of HCC samples [117]. All of these reduced MST levels have been associated with poor prognosis [[124], [125], [126]]. The MST family is rarely mutated in cancer; however, hypermethylation of the MST promoter has been identified [123,127]. MST can be positively regulated by RAS association domain family proteins 1 A (RASSF1 A). RASSF1 A can complex with MST1 and mediate cell cycle regulation and proapoptotic signaling through CNK1 [128,129]. In contrast, RASSF1 A promotes MST2 autophosphorylation and prevents its degradation [130]. Strikingly, RASSF1 A is one of the most frequently deleted or methylated genes in human cancer including breast, gastric, nasopharynx, liver, lung, pancreas, prostate and skin [[131], [132], [133], [134], [135], [136], [137], [138]].

Although in context of aging, SIRT1 is a key player responsible for promoting longevity, depending on environment, age, the cell type and their subcellular localization. It has been reported that SIRT1 can act as either a tumor-suppressor or an oncogene during cancer development [139]. In general, in the nucleus of cancer cells, YAP is regulated by SIRT1-mediated deacetylation, which leads to increased cell proliferation. For example, the HeLa cells response to specific DNA-damaging stimuli (SN2 alkylating agents), the decrease of YAP Ser-127 phosphorylation promoting the nuclear translocation and acetylation of YAP, and nuclear SIRT1-induced deacetylation of acetylated YAP [140]. Similarly, in hepatocellular carcinoma YAP deacetylation-mediated by SIRT1 promotes the YAP/TEAD association and increases YAP-target gene expression (CTGF) [141]. Finally, it has also been reported that there is a positive regulation of YAP activity by SITR1, increasing cell proliferation in obese mice of a murine gastric cancer model [142].

LATS is another kinase family in the Hippo pathway whose functions are related to tumor suppression. LATS1 and LATS2 can be phosphorylated by MST at Thr 1041 and 1079 residues with SAV1 as an adaptor protein. However, LATS must bind to MOB1 and undergo autophosphorylation at the Serine residues 872 and 909 before being fully activated [117]. Thereafter, LATS phosphorylates its substrates such as YAP and TAZ in the conserved HXRXXS motif [86]. In addition, LATS1/2 also regulates other proteins such as Angiomotin (AMOT) and LIMK1 [[143], [144], [145]]. Phosphorylation of AMOT inhibits cell migration by disrupting F-actin stress fibers and focal adhesion. Furthermore, LATS interact with LIMK1, affect its activity on actin polymerization and thus cell mitosis and migration come into being. LATS1/2 downregulation has been reported in human sarcomas, ovarian carcinoma, aggressive breast cancers, astrocytoma, retinoblastomas and acute lymphoblastic leukemia [[146], [147], [148]].

Similar to MTS, hypermethylation of LATS in human cancers has been reported [[149], [150], [151], [152], [153], [154]]. In addition, LATS2 can be inactivated by a functional mutation and is mutated in approximately 40% of mesothelioma [155]. Either LATS1 or LAT2 knockout is embryonic lethal. Information on conditional knockout of LATS in cancer development is still lacking; however, survivors of LATS1 knockout develop soft tissue sarcoma and ovarian tumors [156].

6.3. YAP1/TAZ amplification.

YAP itself is a potent oncogene and is the major target in the Hippo pathway. Unlike NF2, germline mutation of YAP is uncommon. In fact, whole genome sequencing only revealed 1.1% germline R331 W missense mutation of YAP in lung adenocarcinoma [157]. However, somatic amplification of YAP, chromosome region 11q22, has been reported in several human cancers including lung, pancreas, esophagus and liver cancer [[158], [159], [160], [161], [162]]. Consistently, a study conducted by Steinhardt and colleagues has also revealed that there were YAP overexpression and cytoplasmic accumulation in cancer tissues of the colon, lung and ovary suggesting that YAP might be a common activated oncogenic pathway in these cancers [163]. Importantly, analysis of clinical samples indicates that YAP amplification is an independent prognostic marker for overall survival in various cancer types [[164], [165], [166], [167]]. TAZ is a paralog of YAP, similarly, aberrant activity of TAZ has also been reported in different human cancers including brain, breast, lung and oral cancer [100,[168], [169], [170]].

As expected, hyperactivation of YAP causes ectopic cell proliferation. Constitutive active YAP also causes both growth factor-independent and anchorage-independent growth in non-transformed human MCF10 A mammary epithelial cell [158]. Similarly, mutations of either S127 or S381 residue in YAP promote transforming activity of YAP [171]. Furthermore, activation of YAP stimulates transcription of growth factors and cytokines AREG, CTGF, CYR61 and BIRC5 which can induce cell proliferation [86,88,172]. In 2011, two transgenic mice models showed that overexpression of YAP develops squamous cell carcinoma [91,173]. Increasing evidence suggests that there is crosstalk between the Hippo pathway and other cancer-related pathways. For example, it has been shown that EGFR signaling activates YAP via Phosphoinositide 3-kinase-Phosphoinositide dependent kinase-1 (PI3K-PDK1). In addition, the epidermal growth factor (EGF) promotes cell proliferation in a YAP dependent manner in Hepatocellular carcinoma [174]. It is also reported that YAP can work as a downstream transcription factor of KRAS in pancreatic cancer and upregulates RAF/MEK/ERK signaling in gastric cancer [164,175].

Apart from aberrant cell proliferation, high grade tumors are also characterized by a higher population of CSCs within the tumor. Gene profiling reveals that CSCs content is correlated with YAP induced gene expression. Moreover, YAP and TEAD has been found to be elevated in CSCs of several cancers such as medulloblastomas, bladder, breast, liver and lung [81,[176], [177], [178], [179], [180]]. TAZ is also required to maintain self-renewal and tumor initiation in breast CSC. Elevated TAZ expression, together with CD44high/CD24low has also been found in breast CSCs [90]. Increasing evidence also indicates that YAP plays a critical role in regulation of cancer stem cells. YAP activation can expand the population of progenitor cells in the intestine, which is differentiated upon cessation of YAP1 expression [181]. Another study conducted by Lu and colleagues showed that YAP and FGFR1 expression are correlated in lung cancer. The authors also demonstrate that YAP induces FGFR1 transcription by mediating TEAD transcription factor to FGFR promoter while maintaining CSC properties [182]. In addition to the association with TEAD, YAP can also interact with ZEB1 at its N- and C-terminals. ZEB1 is a well-known transcriptional repressor of epithelial genes. YAP-ZEB1 stimulates target gene expression and promotes cancer stem cell-related traits [98]. Moreover, YAP and TAZ mediated expression of SOX2/9, OCT4 and NANOG also induces CSC properties and population in numerous cancers such as lung, bladder and prostate [81,84,176,183,184]. Due to its role in CSC regulation, YAP expression can also affect the sensitivity of chemotherapeutic agents. In fact, several studies have highlighted that YAP/TAZ activation promotes cell survival against chemotherapeutic agents such as fluorouracil (5-FU), cisplatin and taxol in various cancers [[185], [186], [187]]. Furthermore, elevated levels of YAP leads to doxorubicin resistance [188]. As discussed earlier, other oncogenic signaling pathways can dependently or independently affect YAP activity. It is not surprising that YAP activation also contributes to the sensitivity of targeted therapies including tyrosine kinase, RAF and MEK inhibitors. In contrast, reduced YAP enhances sensitivity to cisplatin and tyrosine kinase inhibitors such as erlotinib and cetuximab [[189], [190], [191], [192], [193]].

Elevated YAP can also promote EMT and enhance tumor cell invasion. Significant correlations between elevated YAP/TAZ expressions and a high histological grade have been observed in various cancer types including breast, liver, lung and gastric [165,166,194,195]. YAP overexpression causes disruption of adherent junctions and induces mesenchymal gene expression profiles and morphological changes in pancreatic and oral cancer cells as well as cholangiocarcinoma cells [100,196,197]. Constitutively active TAZ also induces EMT transition and alters cell morphology [198]. In contrast, knockdown of TAZ in breast cancer cells inhibited cell migration and invasion [199]. Cordenonsi and colleagues found that TAZ activity is promoted by EMT and correlated with high stem cell content in breast cancer [90]. In 2012,

Lamar and colleagues first demonstrated that constitutively active YAP in melanoma cell causes lung metastasis in vivo [200]. Since then, multiple studies showed that YAP expression affects metastasis in different xenograft models including gastric, thyroid, and lung cancer [81,170,201]. In contrast, YAP also regulates cell motility and invasion independent of EMT. Loss- and gain- of function experiments in NSCLC cells demonstrate that YAP affects cell invasiveness without any significant changes in EMT markers [165].

So far, most of the evidence available strongly suggests YAP as an oncogene; however, YAP may also exhibit tumor suppressor activity by co-activating with p73 and induce pro-apoptotic gene expression such as BAX and PML [202,203]. In addition, hyperactivation of YAP in transgenic mice showed reduced WNT related gene expression, whereas knockout of YAP induces hyperplasia and stem cell expansion [204]. Therefore, it is likely that YAP could be both a tumor suppressor and an oncogene depending on cellular context. However, the detailed mechanism has yet to be determined.

7. PHARMACOLOGICAL ANTI-AGING APPROACHES AND THE HIPPO PATHWAY

Aging and age-related pathologies are the main causes of disabilities and death. As Magalhañes and colleagues suggest, the challenges of developing anti-aging pharmacological therapies may, in part, be due to the complexity of aging molecular mechanisms. There is no clear consensus on theories about aging. Experimental models available for aging research are performed in short-lived organisms. Most age-associated pathways have not been targeted pharmacologically as yet and anti-aging approaches in humans are difficult to address, requiring a long validation time [205]. Despite the importance of effective pharmacological approaches to an increased healthy lifespan and to delay age-related negative conditions, so far few pharmacological compounds including resveratrol, rapamicyn, spermidin and metformin have the ability to promote these desired conditions. This conclusion has been validated in at least three model organisms and confirmed by at least three different laboratories [206]. Here we summarize how the Hippo pathway can be modulated by anti-aging compounds.

7.1. Resveratrol.

Resveratrol is a class of polyphenol synthesized by a wide range of plant species including, grapes, berries, peanuts and legumes [207,208]. Numerous animal and human studies have shown its anti-aging effects: anti-cancer capacity in breast, lung, prostate, colorectal, skin and liver; an anti-inflammatory effect; a neuroprotective effect; protective effects on cardiovascular and cerebrovascular diseases; improve various symptoms of diabetic and obesity etc., [207,208]. Although the effect of resveratrol-induced regulation of the Hippo pathway in context of aging has not been described as yet, several reports

have suggested that resveratrol can directly regulate the Hippo pathway in context of cancer. For example, lysophosphatidic acid (LPA) and EGF promote breast cancer invasion by increasing the expression of the Hippo-YAP target genes. Indeed, Kim and colleagues reported that in the breast cancer cell, resveratrol was able to modulate the Hippo-YAP pathway. The authors found that resveratrol inhibits LPA- and EGF-induced YAP activation, which lead to a decrease of YAP target genes (AREG, CTGF, CYR61) resulting in a reduction of invasion and migration [209]. Moreover, Jiang and colleagues also suggest that AMPK has a crucial role in resveratrol-inhibition of YAP expression in pancreatic cancer cells. The authors found that resveratrol reduces proliferation, colony formation ability, and induced apoptosis through AMPK activation, which promoted the cytoplasmic retention of YAP by Ser 127 phosphorylation, decreasing YAP nuclear translocation in order to induce CTGF and CYR61 expression [25]. Additionally, the authors found that YAP contributed to chemotherapy resistance, and resveratrol treatment was able to decrease this chemoresistance to gemcitabine through inhibition of total YAP and upregulation of YAP phosphorylation at Ser127 [25].

7.2. Rapamycin.

Jahrling and Laberge (2015) reported that the beneficial effect of rapamycin in delaying signs of aging and age-related neurodegeneration is mediated by inhibition of mTORC1 [210]. The link between mTOR and the Hippo pathways seems to be a relevant modulator of growth and survival. It is known that mTOR, through activation of protein synthesis and inactivation of autophagy, stimulates cell growth, while depletion of YAP/TAZ through the Hippo pathway activation induces apoptosis and inhibits cell growth. For example, in the cardiac cells, while mTORC1 stimulates cardiac growth, MST1 inhibits cardiac growth. Moreover, to preserve cell survival in response to stress, mTORC2 is able to negatively regulate MST1 activity in the heart by increasing phosphorylation of MST1 at Serine 438, or through regulation of AKT activity, which inhibit MST1 [211]. mTORC depletion promotes cardiomyocyte apoptosis due to uncontrolled MST1 activation, although other authors have reported that cardiomyocyte apoptosis is not related to the increase of MST1 pro-apoptotic activity, because the pro-survival function of YAP1 did not change in mTORC1/2 depleted hearts [212]. Moreover, inhibition of the Hippo pathway contributes to increased nuclear levels of YAP, which through upregulation of YAP-target genes (such as CTGF, Pik3cb, miRNA29 and CD98) activates the PI3K/Akt/mTORC pathway and cell survival [213,214]. Rapamycin can regulate the Hippo pathway through different mechanisms. Indeed, in hepatocellular carcinoma rapamycin treatment promotes nuclear localization of TEAD1, and in the breast adenocarcinoma rapamycin increases the expression levels of TEAD1 without affecting intracellular localization. Rapamycin also reduces the expression levels of TAZ in hepatocellular carcinoma [215], and in Mst1/2−/− mice rapamycin decreased YAP1/TAZ-mediated tumor development [216].

7.3. Metformin.

Metformin has demonstrated positive effects on health and longevity by activating anti-aging pathways, inhibiting pro-aging pathways and protecting against age-related pathologies [217]. Regulation of the Hippo pathway by metformin has been extensively studied in context of cancer. For example, Chang and colleagues reported that obese mice expressing oncogenic KRAS have high pancreatic inflammation, pancreatic intraepithelial neoplasia and a higher incidence of pancreatic ductal adenocarcinoma, which may, in part, be because of an increased level of TAZ. The authors also found that metformin inhibits the TAZ upregulation in pancreatic lysates of obese mice possibly in an AMPK-dependent mechanism [218]. In hepatocellular carcinoma, metformin increases YAP phosphorylation and reduces YAP expression through an AMPK-dependent mechanism, which leads to YAP inhibition, cell proliferation decrease and increase sensitivity to chemotherapeutic agents [219]. In the human embryonic kidney, human mammary cells and in primary mouse hepatocellular carcinoma, metformin was able to decrease YAP nuclear localization and inhibit YAP target genes (CTGF and Cyr61) expression, through AMPK, LATS1/2 and AMOTL1 upregulation and stabilization, which resulted in decreased cell proliferation [22]. In addition to this, in human embryonic kidney, metformin reduced tumorigenesis by increasing YAP/TAZ phosphorylation and reducing the expression of YAP-TEAD target genes (CTGF and Cyr61) through AMPK or LATS1/2-dependent mechanisms [23]. Although in glioma cells metformin inhibits stemness and epithelial-mesenchymal transition by increasing YAP phosphorylation, decreasing nuclear localization of YAP and inhibiting the expression of YAP-target gene (CTGF), the phosphorylation and nuclear retention of TAZ were not affected [220]. Dysregulation of the Hippo pathway signaling in aging and cancer is summarized in Fig. 2, and regulation of the Hippo pathway by anti-aging compounds in Fig. 3.

8. CONCLUSIONS

Although studies have demonstrated association of the Hippo pathway with numerous signaling, the main contribution of the Hippo pathway is the regulation of cell proliferation and growth. In the context of aging process, AMPK pathway is able to regulate activity of the Hippo pathway, as well as the expression of its target genes, resulting in reduced cell proliferation and growth. Moreover, the Hippo pathway can promote oxidative stress-mediated cell death by inducing apoptosis or inhibiting oxidative stress-mediated cell death by increasing the expression of antioxidant genes. In cancer, low apoptosis promotes uncontrolled cell proliferation leading to cancer initiation and progression, while in aging, low apoptosis contributes to accumulation of the senescent cell. Given that effects of apoptosis in cancer and aging are opposite, future research is needed to elucidate the molecular mechanisms responsible for the Hippo pathway-mediated apoptosis in different cell types and under different environment conditions. Moreover,

experiments on various aging animal models are required to confirm/elucidate whether regulation of the Hippo pathway contributes to increasing lifespan and improving the healthspan. Interestingly, the effect of MST1 on autophagy is cell-type specific. For example, while still in embryonic cells, MST1 promotes autophagy, while in neuron, macrophages and cardiac cells and thyroid cancer, MST1 inhibits autophagy. Future studies elucidating the molecular mechanisms responsible of the "dual" effect of the Hippo pathway on autophagy and stress response should be done. In addition, whether direct manipulation of the Hippo pathway components have a positive effect on health and longevity should be clarified before utilizing pharmacological modulators of the Hippo pathway clinically. Similarly, the Hippo pathway also plays a crucial role in cell proliferation in cancer cells making it an attractive target for anticancer therapy. Inactivation of the Hippo pathway and the dysregulation of its downstream effectors, YAP and TAZ, were frequently observed in human cancers. Therefore, anticancer therapies targeting the Hippo pathway could either aim at restoring activity of the Hippo pathway or inhibiting the YAP and TAZ activities. MST1/2 and LATS1/2 are two pairs of core kinases in the Hippo pathway that suppress the function of YAP and TAZ. Reviews from Johnson et al and Guo et al have summarized small molecule agonists that stimulate these two kinase families [221,222]. Notably, the core components of the Hippo pathway are well-conserved and rarely exhibit genetic mutations. Future studies should aim at understanding the underlying mechanisms of the dysregulated activity of the Hippo pathway in cancer and aging. Moreover, in order to develop a tailored therapy to manipulate the Hippo activity in cancer patients, relationship between the dysregulated Hippo pathway and other major oncogenic driver mutations such as KRAS and EGFR should also be examined. Finally, YAP and TAZ do not confer any enzyme activity and their function is mediated by their interacting partners such as TEAD and AMOT. Consequently, pharmacological inhibition of YAP and TAZ mainly focuses on disrupting these protein-protein interactions. The co-crystal structure of YAP and TEAD has recently been determined and, therefore, it would not be surprising if numerous inhibitors were to be developed in the near future.

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FIGURE

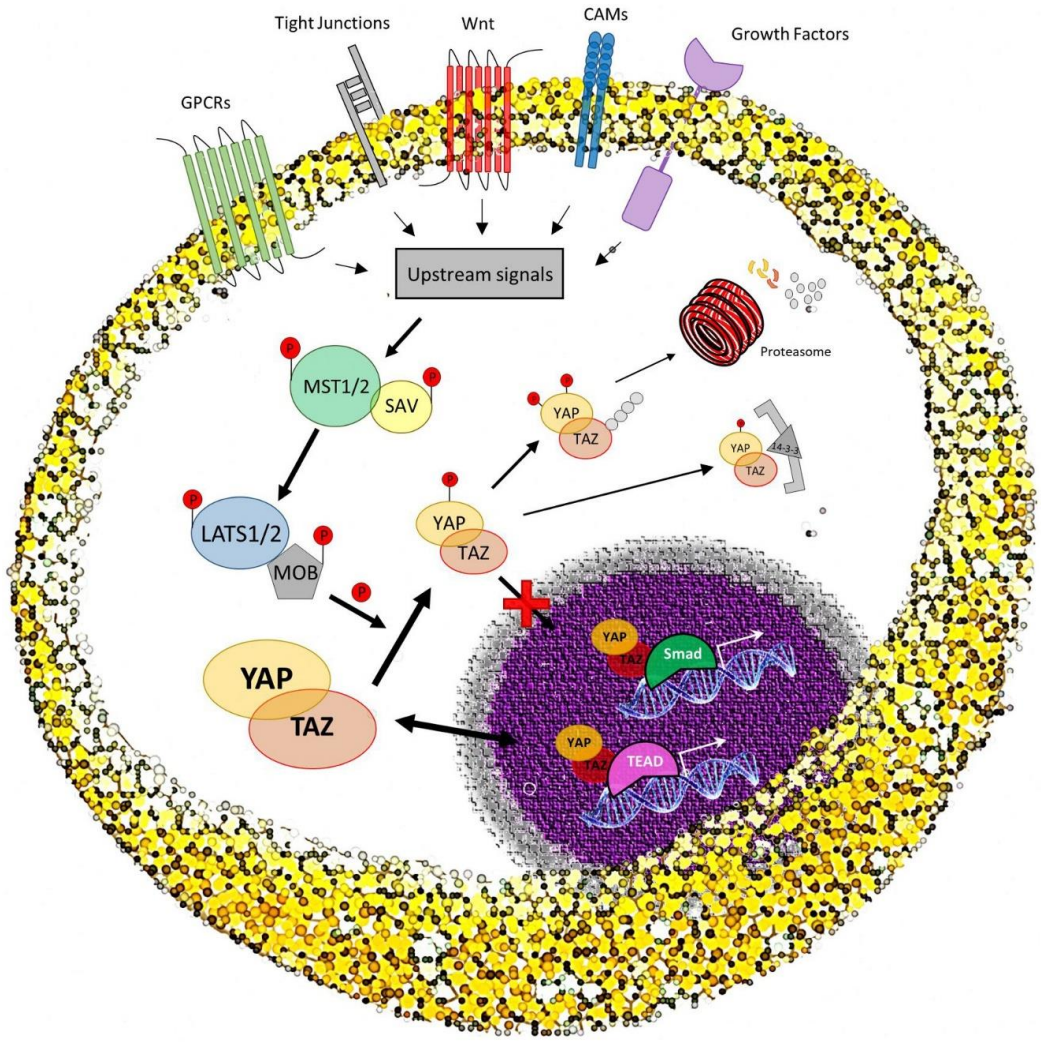

Figure 1. The mammalian Hippo pathway. Upstream signals (e.g. growth factors, tight junctions, GPCR signaling, CAMs and wnt signaling) induce activation of the Hippo pathway. Core components MST 1/2 and Sav1 phosphorylate and activate the kinase LATS 1/2 and the adaptor protein Mob. Then LATS 1/2/Mob phosphorylates and promote cytoplasm proteasome-mediated degradation and 14-3-3 mediated-retention of YAP and TAZ. The nuclear localization of dephosphorylated YAP and TAZ induce gene expression through their interaction with TEAD and SMAD family of transcription factors. G-protein-coupled receptor (**GPCR**); cell adhesion molecules (**CAM**); Ste-like kinase (**MST**); Salvador 1 (**Sav1**); large tumor suppressors (**LATS**); yes-associated protein (**YAP**); WW Domain Containing Transcription Factor (**TAZ**); TEA Domain Family Members (**TEAD**); family of signal transduction proteins (**SMAD**).

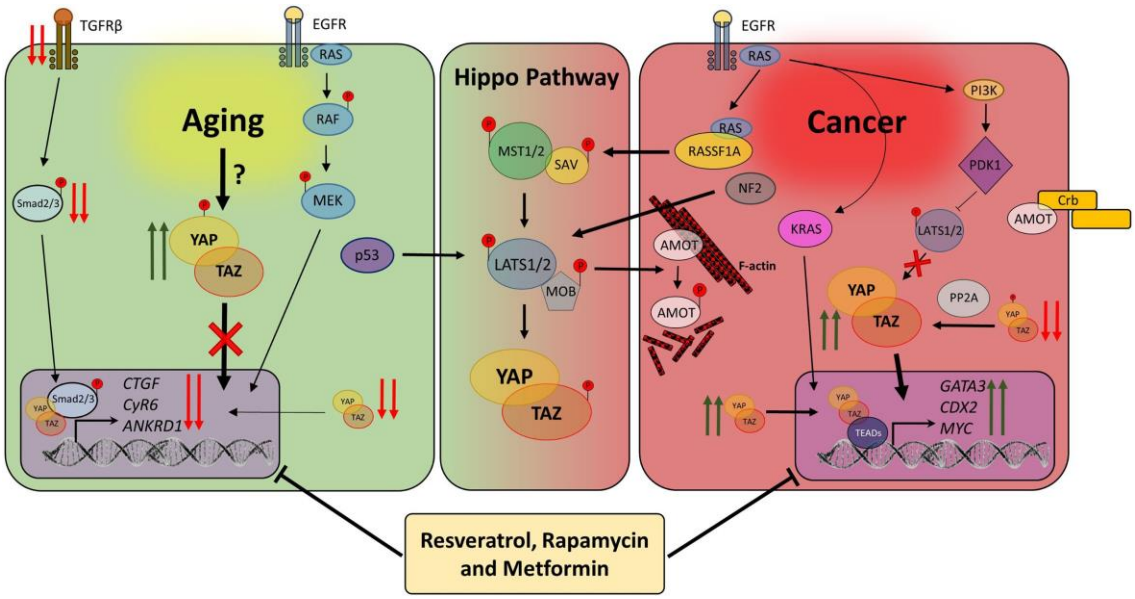

Figure 2. Dysregulation of the Hippo pathway signaling in aging and cancer. In general, during aging nuclear YAP/TAZ decrease. TGF-β/Smad/CTGF signaling is downregulated with age. Moreover, Ras and MEK1 inhibit YAP/TAZ transcriptional activity during induction of senescence. It is possible that during aging cytoplasm retention and YAP/TAZ phosphorylation increase because the expression of their target gene decrease. In cancer, aberrant oncogenic signaling including EGFR and Ras directly restrains YAP and TAZ in the nucleus. Inside the nucleus, non-phosphorylated YAP and TAZ together with TEAD transcription factor, stimulate target gene transcription such as GATA3, CDX2 and MYC, which are responsible for cancer cell proliferation and stemness maintenance. Inactivation or mutation of RASS1FA and NF2 is another mechanism results in insufficient Hippo signaling to phosphorylate YAP and TAZ. The PI3K-PDK1, a downstream effector of EGFR, also promotes nucleus accumulation of YAP and TAZ by inhibiting phosphorylation of LATS1/2. In contrast, upon activation, LATS1/2 is also able to phosphorylate AMOT and thus, inhibits cell migration by disrupting F-actin fibers. All these mechanisms contribute to the YAP-TAZ driven tumor progression. Interestingly, antiaging compounds such a Resveratrol, Rapamycin and Metformin in cancer cell decrease proliferation through inhibition of YAP/TAZ transcriptional activity. Transforming growth factor beta (**TGF-**β); family of signal transduction proteins (**SMAD**); Ste-like kinase (**MST**); Salvador 1 (**Sav1**); large tumor suppressors (**LATS**); yes-associated protein (**YAP**); WW Domain Containing Transcription Factor (**TAZ**); Epidermal Growth Factor Receptor (**EGFR**); Mitogen-Activated Protein Kinase (**MEK**); Connective tissue growth factor (**CTGF**); Cysteine-rich angiogenic inducer 61 (**Cyr61**); ankyrin repeat domain 1 (**ANKRD1**); Neurofibromin 2 (**NF2**); Angiomotin (**AMOT**); TEA Domain Family Members (**TEAD**); Phosphoinositide 3-kinase-Phosphoinositide dependent kinase-1 (**PI3K-PDK1**); Caudal Type Homeobox 2 (**CDX2**); Myc Proto-Oncogene Protein (**MYC**); Crumbs (**Crb**).

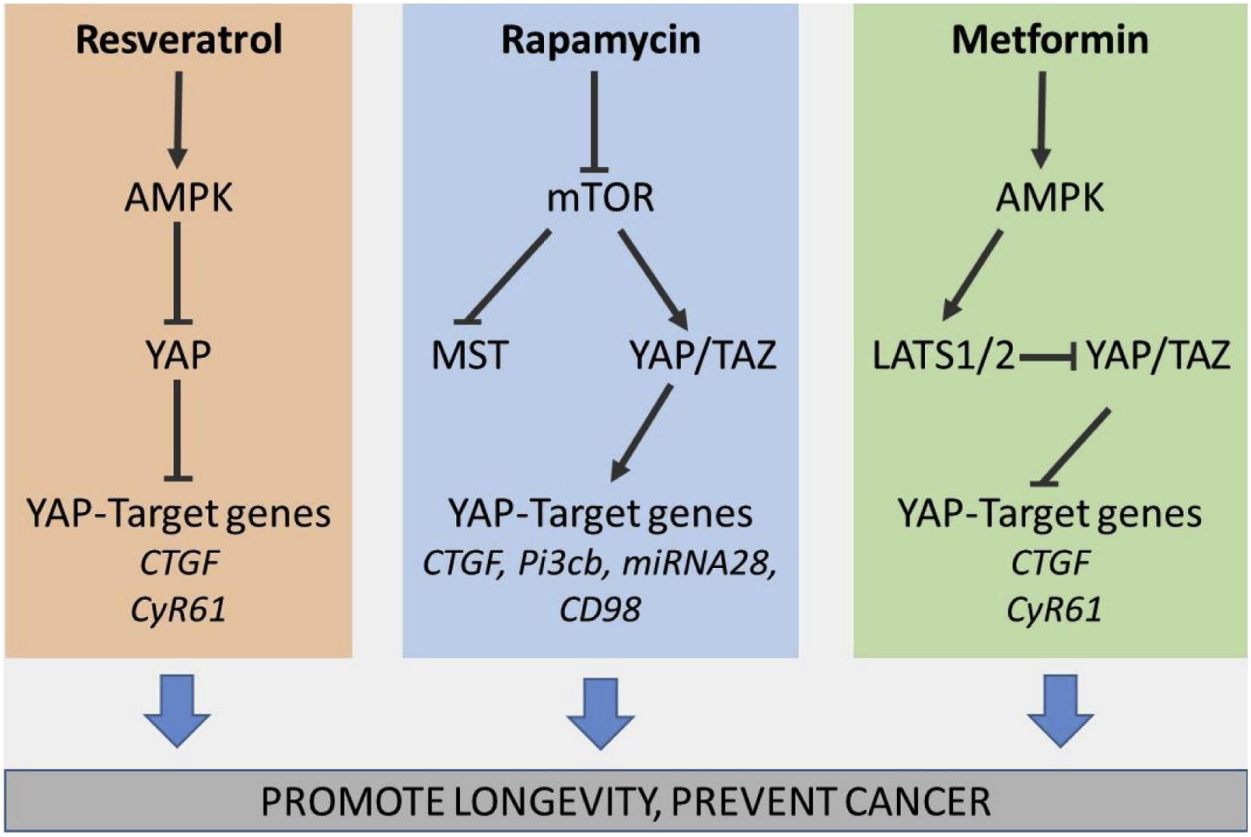

Figure 3. Regulation of the Hippo pathway by anti-aging compounds. To associate the regulation of the Hippo pathway with anti-aging pharmacological intervention, we selected only resveratrol, rapamycin and metformin because these compounds meet three relevant criteria: promote longevity, have been validated in at least three model organisms and confirmed by at least three different laboratories [206]. Resveratrol, rapamycin and metformin decrease the expression of YAP-target genes (*CTGF, CyR61, Pi3cb, miRNA28, CD98)*, which lead to promote longevity and prevent cancer. AMP-activated protein kinase (**AMPK**); Yes-associated protein (**YAP**); WW Domain Containing Transcription Factor (**TAZ**); Mammalian target of rapamycin kinase (**mTOR)**; Mammalian STE20-like kinase (**MST**); Large tumor suppressor kinase 1 (**LATS**); Connective tissue growth factor (**CTGF**); Cysteine rich angiogenic inducer 61 (**CyR61**); Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta (**Pi3cb**).