Cancer Letters 461 (2019) 112–122

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

The tumour microenvironment as an integrated framework to understand cancer biology

Rebeca Burgos-Panadero[a,b,1], Federico Lucantoni[a,1], Esther Gamero-Sandemetrio[a,b], Luis de la Cruz-Merino[c], Tomás Álvaro[b,d,**], Rosa Noguera[a,b,*]

[a] Departament of Pathology, Medical School, University of Valencia - INCLIVA Biomedical Health Research Institute, Valencia, Spain
[b] CIBERONC, Madrid, Spain
[c] Departament of Oncology, Hospital Universitario Virgen Macarena, Sevilla, Spain
[d] Hospital Verge de la Cinta, Tortosa, Tarragona, Spain

ARTICLE INFO

Keywords:
Biophysics
Bioelectric
Metabolism
Cancer treatment
Extracellular matrix
Stromal classification

ABSTRACT

Cancer cells all share the feature of being immersed in a complex environment with altered cell-cell/cell-extracellular element communication, physicochemical information, and tissue functions. The so-called tumour microenvironment (TME) is becoming recognised as a key factor in the genesis, progression and treatment of cancer lesions. Beyond genetic mutations, the existence of a malignant microenvironment forms the basis for a new perspective in cancer biology where connections at the system level are fundamental. From this standpoint, different aspects of tumour lesions such as morphology, aggressiveness, prognosis and treatment response can be considered under an integrated vision, giving rise to a new field of study and clinical management. Nowadays, somatic mutation theory is complemented with study of TME components such as the extracellular matrix, immune compartment, stromal cells, metabolism and biophysical forces. In this review we examine recent studies in this area and complement them with our own research data to propose a classification of stromal changes. Exploring these avenues and gaining insight into malignant phenotype remodelling, could reveal better ways to characterize this disease and its potential treatment.

1. Introduction

Cancer remains a major public health threat and one of the leading causes of death worldwide. Great effort has been invested into characterising and understanding this disease at a cellular, molecular and clinical level, and many achievements in the field have helped shape the therapies in use nowadays. However, most conventional chemotherapeutic drugs developed so far display only a narrow therapeutic window, due to their inability to distinguish cancerous from normal cells [89]. Developing new therapies against cancer often starts with use of non-physiological models of the disease such as cell monocultures, with no contribution from extracellular matrix (ECM) components. Unsurprisingly, this has meant that observations on cellular network functions do not translate readily into *in vivo* models. This reductionist approach hinders attempts to turn novel interventions to correct dysfunctional cellular behaviour into effective therapies that can be successfully translated to the clinic.

The majority of solid tumours have complex three-dimensional (3D) architecture, comprising different populations of abnormal cells divided into parenchymal and stromal compartments. The ECM that constitutes the stroma has a complex composition and is rich in growth factors and metabolites [20,33,100,140,144]. Communication between cancer cells and their surroundings contributes to changes and a high degree of heterogeneity at the phenotypic and genotypic level. Integrating the stromal components with the immune system, the non-cancerous niche and the consequent interplay of metabolic pathways sheds a different light on our understanding of cancer properties. This integrated view, termed the tumour microenvironment (TME), has modified our vision

Abbreviations: ECM, Extracellular matrix; TME, tumour microenvironment; PG, proteoglycans; GAG, glycosaminoglycans; GP, glycoproteins; TAM, tumour-associated macrophages; TANs, tumour-associated neutrophils; CAF, cancer associated fibroblast; CSC, cancer stem cells; OXPHOS, oxidative phosphorylation; EMT, epithelial-mesenchymal transition

* Corresponding author. Department of Pathology, Medical School, University of Valencia-INCLIVA, Valencia, Spain.
** Corresponding author. Hospital Verge de la Cinta, Tarragona, Spain.
E-mail addresses: talvaro.ebre.ics@gencat.cat (T. Álvaro), rnoguera@uv.es (R. Noguera).
[1] Authors contributed equally.

https://doi.org/10.1016/j.canlet.2019.07.010
Received 29 May 2019; Received in revised form 11 July 2019; Accepted 14 July 2019

of cancer towards a phenomenon that develops via cellular cooperation, moving away from a purely gene-centric framework [13].

The architectural role of ECM components is clear and central to tissue homeostasis [138]. In fact, scaffold architecture has been found to have a significant impact on cell growth [91]. Anomalous cell-microenvironment interaction results in an aberrant cellular networks. The interaction between physical and chemical properties establishes a dynamic reciprocity between neoplastic cells, stromal cells, microvascularization, innervation, ECM scaffolding, bioelectric fields and soluble factors of tumour growth control [50]. In this review we highlight how different biological phenomena drive the development of the TME and consequently tumour malignancies. Providing an integrated perspective of the different components of the TME might yield insights into cancer as a whole.

2. The TME niche

The ECM is composed of soluble factors and a network of biopolymer fibres of proteins, proteoglycans (PG), glycosaminoglycans (GAG) and glycoproteins (GP), that differ in composition and structure according to the organ and tissue [42]. The size and density of the fibre network determine mechanical properties, as well as morphology, porosity and size of the mesh. The spatial organisation of this network provides a mode of communication thanks to its elasticity, which depends on the intricate biophysical properties of its components, and provides movement and contraction to the matrix [118]. ECM rigidity, which depends on the presence of the molecular elements mentioned above with the consequent pore size, viscoelasticity, cross-linking, cellular density and interstitial pressure, influences the reprogramming of the tumour cell [101]. Additionally, electrical charges carried by protein elements such as collagen have a powerful impact on the function and diffusion of substances and stimuli transmission [83]. PGs, which are glycosylated proteins with covalently attached highly anionic GAG, contribute to tissue hydration and swelling pressure, and allow it to tolerate compression forces [86]. Fibrous proteins of the ECM include collagen, elastin, fibronectin, vitronectin and laminin among other elements [42]. Collagen provides the principal structural component of the ECM and is the most abundant protein in the human body [70]. Elastin cooperates with collagen and confers elasticity to tissues [84]. GPs have a similar fibril organisation to collagen and are bound to integrins, mediating cell processes such as cell adhesion [42]. Immersed in the ECM are the blood and lymphatic vessels and the stromal cells that synthesize the matrix and facilitate the immune response. Neoangiogenesis in particular determines blood and lymphatic flow, oxygen and nutrient supply, interstitial pH and the bioelectrical and metabolic state of the tumour [131]. Intriguingly, the TME is also permeated by nerves, which have been shown to have an impact on cancer development [62].

The TME is infiltrated with a number of different cells that contribute to the progression of malignancy, enabling some cancer hallmarks [50]. Among the inflammatory cells of TME, tumour-associated macrophages (TAM) represent the most abundant population of infiltrating cells and participate in both antitumor control (M1 phenotype) and in malignant progression (M2 phenotype) [46], promoting vascularization, invasion, growth, cancer cell survival and immunosuppression [149]. Indeed, it has recently been found that increased levels of $CD163^+$ TAM at the invasive front are indicative of poor prognosis and are responsible for releasing mesenchymal circulating tumour cells [143]. Throughout tumour progression, tumour-associated neutrophils (TANs) change from an antitumor function to a pro-tumorigenic phenotype, under the influence of the TME [49,105]. Conversely, T and B lymphocytes are also found within the TME and correlate with good prognosis [8]. Another cell type abundant in the stroma which has antitumor to pro-tumour switching properties is the fibroblast; cancer associated fibroblast (CAF) modifies the TME by secreting ECM remodelling enzymes [3]. Finally, cancer stem cells (CSC) represent the source of heterogeneity in the tumour, the reason for resistance to chemotherapy and the origin of distant metastasis [27]. The inflammatory TME is a determinant of CSC and both are tightly linked [156].

2.1. Biophysical interactions in the TME

The mechanical properties and the bioelectric signals of the tumour stroma determine cellular, biological and clinical behaviour.

2.1.1. Stiffness of the ECM

One classic characteristic of tumours is stromal stiffness, which allows cancer detection through palpation or radiological examination and is associated with altered ECM profile in the TME [44]. Indeed, increased ECM protein deposition can be employed as a prognostic factor [58,78,135,136]. On a similar note, previous studies from our group highlighted that ECM composition and architecture can define an ultra-high-risk patient subgroup with 5-year survival rate < 15% in neuroblastoma [130]. Additionally, neuroblastoma patients with poor prognosis possess a reticular and poorly porous ECM [132]. Stiffness has been shown to increase from healthy to malignant tissues, together with fibrosis, and to be accompanied by chemo-resistance [111]. This increase in matrix stiffness reduces the elastic modulus and the 3D environment affects cell rheology [7]. Cancer cells have shown increased proliferation in a softer matrix that could be linked to the initial growth of a tumour lesion, before the development of tumour vasculature [26]. Likewise, during the invasion process, cancer cells showed increased intracellular viscosity, suggesting a mechanism that could facilitate cell motility in a dense matrix [147].

Increased tumour stiffness depends not only on the amount and organization of the fibrous elements and other components of the ECM but also on increased interstitial fluid pressure [122]. These elements, together with the stromal cellular infiltrate, determine phenotypic diversity, gene expression and the therapeutic response of cancer cells [4,47]. Physical stimulus of the tissue has a significant effect on the chemical signals of the tumour cell, which is able to perceive the mechanics of the substrate and transduce this information to the molecular signalling pathways [47]. The rigidity of the matrix profoundly influences cellular morphology and behaviour and vice versa [66,121]. Indeed, it has been found that pancreatic stellate cell activation and durotactic response depends on the stiffness of the substrate [72]. Further investigation has linked the retinoic acid receptor to mechanosensing response process [36].

Intracellular signalling in response to the mechanics of the TME mainly uses the integrin family and affects cancer gene expression, showing how tissue mechanics affect carcinogenesis [120]. In this context, it has been proposed that actin binds to integrin β3 by competing with talin protein; once this happens and mature adhesion has been established, forces are transmitted to the ECM thereby activating downstream signalling [112]. Partial inhibition of integrin results in a softer intracellular state [7] and revert tumour phenotype [108]. Mechanosensing of the TME also depends on focal adhesion proteins whose signalling cascades promote changes in tumorigenicity [66]. The same pathways modulate compression forces, as cancer cells are often subjected to mechanical deformation during proliferation [131].

2.1.2. Bioelectric TME

Cells are able to generate and receive biological information in the form of bioelectric signals [34]. Cellular membranes provide an anchor for ion channels and protein pumps; through these avenues, cells can establish action potentials and depolarisation levels throughout the human body. Membrane potential develops a bioelectric field that enables cell-cell and cell-tissue communication. Tissues undergoing proliferation possess a positive charge when compared to quiescent cells [1]. Indeed, when negative charges are induced experimentally, cellular proliferation is inhibited [76]. Temporal variations in the membrane

potential exert a fundamental impact on cell cycle progression: cells become hyperpolarised before S phase and depolarise during mitosis, while G1 and G2 phases fluctuate between the two conditions [150]. The cyclic behaviour of the membrane potential during cell cycle can be linked to the dynamic properties of the cellular microenvironment [14]. Bioelectric gradients form an important part of the morphogenetic information transmitted to structural tissue organisation to coordinate cell-cell interaction [28]. A quiescent non-transformed cell can modify its voltage threshold when switching to proliferative or malignant phenotype [1]. A negative membrane potential allows passive Ca^{2+} influx through specific ion channels, with an increase in actin polymerisation, myosin contraction and adhesion decrease [88]. The repulsion of Ca^{2+} to the anodal side of the cell, mediated by the voltage-gated Na^{+} channel, causes asymmetry in Ca^{2+} concentration, resulting in actin polymerisation and myosin contraction [19].

Negative charges contract the cytoskeleton and deploy a tensional force with a determined directional and migratory vector. In this context, ions fluxes have been found to drive cell migration and metastasis initiation in several types of cancer [119]. Cancer cells are affected by several transcriptional changes that are activated by membrane potential depolarisation, such as motility regulation induced by serotonin, Ca^{2+} and inositol triphosphate fluxes through gap junctions [126]. Membrane depolarisation also triggers the process of metastasis which is mediated by the transcriptional and epigenetic dynamics induced by serotonin and butyrate fluxes coupled with electrical changes [79]. Moreover, forced hyperpolarization has been found to inhibit the formation of induced tumour structures, even in cells distant from the tumour site [35].

Ion channels, protein pumps and gap junctions are part of the oncogene family [9] and are considered predictive biomarkers [106], supporting a more integrated vision of cancer development, where the TME, rather than the mutation of single specific genes, is fundamental in establishing carcinogenesis. Indeed, a recent study highlighted that biopotential levels are significantly different in cancerous tissue to paired non-malignant tissue; this characteristic was shown to be influenced by ECM stiffness, and high biopotential values correlated with advanced epithelial ovarian cancer stage [31]. Emerging theories view cancer as a coherent subsystem with the ability to control information exchange with the surrounding environment [125]. Thus, tumour lesions gain independence by creating primitive morphogenetic fields such the one observed in the histopathological structure of a metastasis. Indeed, cancer cells can “prime” the environment at a distal site in order to set the foundation for metastasis establishment in the pre-metastatic niche [97]. Endogenous membrane potentials make up the bioelectric TME, an important element with the ability to increase or normalise malignancy [75]. In this scenario, the bioelectric code applied to the reprogramming of cancer-TME interaction constitutes a malignant phenotype that can be used to develop new treatments to inhibit cancer membrane potential [74].

2.2. Role of metabolism in TME interaction

The physiological complexity of the TME and the 3D cellular organization of a tumour also depends on existing metabolic differences. Varying oxygen, nutrient and waste diffusion gradients develop within the cancer tissue and contribute to its pathogenesis [24,73]. These gradients shape the TME and generate subcellular cancer populations with different gene expression patterns (Fig. 1) [29].

Altered metabolism is an emerging hallmark of cancer, proving essential to a diverse range of cellular properties in malignant lesions [51]. As a result of poor or aberrant vascularisation, cancers have limited access to oxygen and nutrients [104]. Thus, tumour cells can use a diverse range of nutrients to fuel proliferation, invasion and treatment resistance [139]. Furthermore, cancer metabolism has a high degree of plasticity, as malignant cells can switch from different sources to obtain the energy needed [87]. TME stiffness exacerbates the harsh

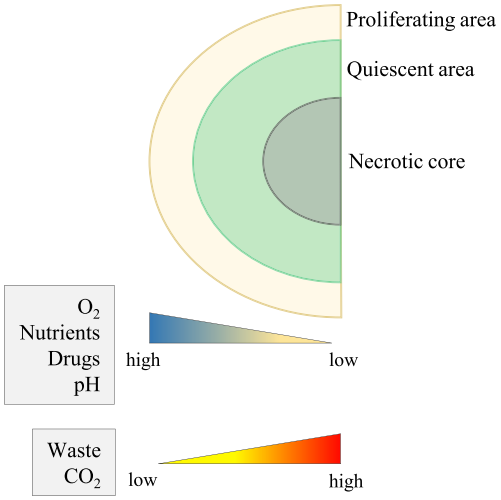

Fig. 1. Tumour architecture in relation to extracellular gradients. Most solid tumours are organized in 3D structures made up of a central core with a high prevalence of necrotic cells, a quiescent area with tumour cells in G0 phase, and an external area with cells undergoing proliferation. As a consequence of this multicellular environment and the presence of an external ECM, a set of gradients are established. Typically O2, nutrients, pH and drugs are mostly concentrated at the outer zones, while their concentration decreases as they diffuse inside the tumour mass. On the other hand, waste and CO2 are highly concentrated inside the tumour mass, while outer cells can easily diffuse them in the surrounding TME.

environment for these cells; the extensive fibrosis produced by the accumulation of ECM proteins increases interstitial pressure and the content of macromolecules, which contributes towards sustaining cancer cells by recycling these cellular elements [41]. This is particularly evident in pancreatic cancer, where glucose and glutamine are comparatively low and amino acids are scavenged from extracellular proteins such as albumin [37,68]. A similar process occurs in breast cancer, where stromal cells deposit large amounts of ECM proteins, which sustain metabolism and metastasis initiation [59].

A higher glycolytic rate is a prominent feature of cancer, due to defective oxidative phosphorylation (OXPHOS) and limited oxygen availability: a phaenomenon called Warburg's effect [77]. While this is a widely accepted process, an emerging idea termed “reverse Warburg effect” has flourished. In this scenario, CAFs are metabolically impaired by H_20_2 produced by cancer cells, with the consequent switch to aerobic glycolysis and the synthesis of metabolites such as lactate, pyruvate, ketone bodies and fatty acids. These nutrients are employed by tumour cells through active OXPHOS [6,17,95,99,124,145]. Cancer cells internalise the lactate which in turn modify NAD+/NADH ratio and increase mitochondrial mass and activity, resulting in Krebs cycle deregulation and accumulation of oncometabolites [57]. There is a high degree of variability between different cancers in estimated levels of ATP production through glycolysis or OXPHOS [159]. The switch between OXPHOS and glycolysis is a key process in immune cell activation in the TME. Quiescent T cells use fatty acid oxidation and glutamine and move towards glycolysis when activated [5].

Fatty acids are also required for a rapid cell division process and are in high demand among cancer cells to support their survival [2]. It has been found that hypoxic and Ras-driven cancer cells scavenge fatty acid from the TME as they possess reduced fatty acid biogenesis [67]. Furthermore, adipocytes are abundant in the TME [93] and sustain cancer progression and metabolism [92,148,155]. Another example of communication between components of the stroma and cancer cells has been described in leukaemia, where adipose tissue stimulates lipolysis in malignancies and protects against chemotherapy [151].

An aberrant metabolism provides for a set of cancer hallmarks; for example, it can promote epithelial-mesenchymal transition (EMT),

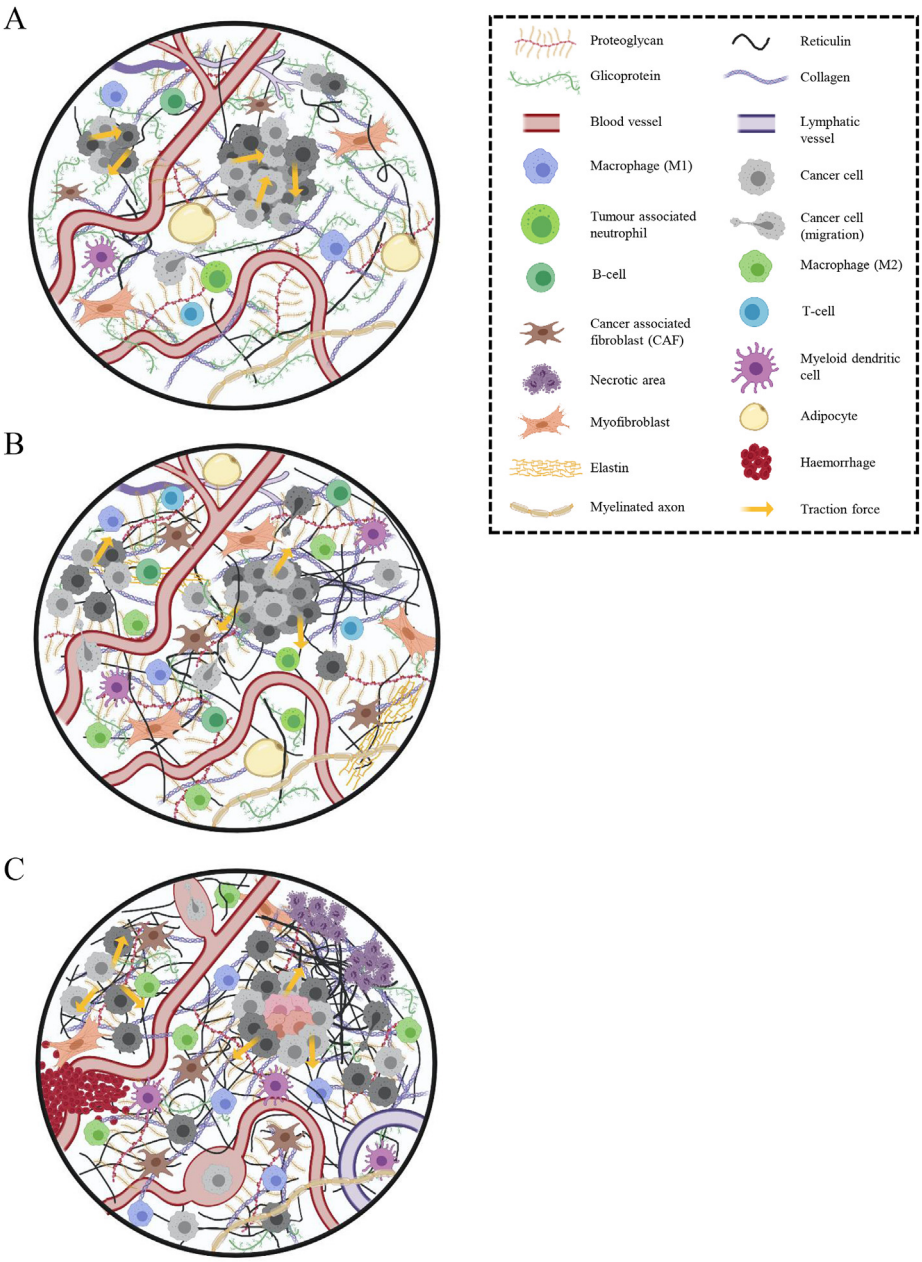

Fig. 2. Stromal alteration grades. Graphical representation of the three proposed levels of stromal alteration. **(A)** Grade I represents a lax and porous ECM with a low immune response and without modification in the tumoural vasculature system. **(B)** In grade II the ECM increases in rigidity and distribution, allowing cancer migration and decreasing diffusion of therapeutic agents. A moderate immune response is displayed, together with a vasculature system that permits cell migration. **(C)** Grade III is characterized by a significant increase in rigidity, and as a consequence, augmented cancer migration and heterogeneity with decreased diffusion of chemotherapy. A severe immune response is encountered, together with an increase in the vasculature system which allows blood extravasation, haemorrhage and area of cellular necrosis.

which increases glycolysis through the key EMT regulator Snail [154]. Indeed, glycolysis has been identified as the main metabolic route utilised for cell motility [123] and its upregulation is important to maintain cancer stemness and EMT phenotypes [158]. More importantly, the metabolites and waste gradient produced by cancer cells provide spatial information on vasculature position and modulate cell phenotypes within the TME [25].

3. Stromal alteration grades

Combining the available information with our own findings, the data presented shows how the tumour stroma is progressively transformed as the tumour phenotype advances. We propose classifying these changes into the three levels outlined in Fig. 2, according to the intensity of their alteration, clinical and therapeutic implications.

Slight changes in tumour stroma, grade I (Fig. 2A). Good prognosis, associated with early stages of various carcinomas and localized sarcomas. TME elements confer a minimal increase in stromal rigidity that does not stimulate tumour progression and allows diffusion of therapeutic agents. Morphologically, this corresponds to a lax and porous ECM, with few type I collagen fibres and poor reticular fibre cross-linking, high PG and low GP content, and absence of desmoplasia or perineural invasion [21,40,66,132]. Among the ECM elements it is possible to observe numerous CAF (without myofibroblasts), limited numbers of tumour stem cells and a mild inflammatory response, with a low proportion of macrophages. M2 macrophages are not identified, and there is a low to moderate number of T and NK lymphocytes [8]. A network of regular blood capillaries, open lymphatics and collecting vessels that show little or no change in the interstitial pressure of the ECM can be observed [21,128].

Moderate changes in tumour stroma, grade II (Fig. 2B). Uncertain prognosis associated with carcinomas and advanced regional sarcomas. TME elements generate stromal disruption that serves as a cleavage plane for tumour migration and lodges microscopic residual disease. Increased stiffness hinders the diffusion of therapeutic agents. There is incipient desmoplasia and a certain degree of tension due to the increase in the content of type I collagen fibres, cross-linking of reticular fibres, decrease in PG and increase in GP content [21,40,132]. CAFs are

found, with occasional myofibroblasts and limited tumour stem cells. There is a variable inflammatory response, characterized by infiltration of type M1 and M2 macrophages, T lymphocytes and natural killers (NK) cells. The vascular system is made up of regular blood capillaries together with tortuous sinusoids, and a moderate presence of small calibre lymphatic capillaries, frequently collapsed due to increased interstitial pressure in the ECM [21].

Severe changes in tumour stroma, grade III (Fig. 2C). Poor prognosis associated with various carcinomas, sarcomas, melanomas, lymphomas and neural tumours. Taken together, the TME elements confer an appearance of high tumour heterogeneity, showing a remarkable increase in stromal rigidity, migratory capacity of tumour cells, poor response to treatment and very low diffusion of chemotherapeutic agents [132]. Perineural invasion and desmoplasia are frequently observed, associated with a rigid ECM due to the cross-linking and increased content of collagen I and reticular fibres, low PG and high GP content, with the presence of CAFs, myofibroblasts, tumour stem cells and a severe inflammatory response characterized especially by infiltration of M1 and M2 macrophages [107]. The vascular system presents abundant sinusoids, long and irregular vascular lakes, intermediate lymphatic capillaries and small collecting vessels [130,133,134]. High interstitial pressure in the ECM leads to frequent blood extravasation areas, haemorrhage and areas of necrosis.

4. Cancer progression depends on the TME and vice-versa

Previous research examined spatial growth and genetic evolution to model tumour progression, without considering the support provided from the surrounding environment [141]. While TME it is now considered a key player in cancer evolution, there are several concerns that have not been resolved regarding the extent of its contribution.

The impact of the TME in modulating carcinogenesis, tumour development and progression has been documented by studying the effect of the physiological microenvironment on cancers. Based on this, a non-malignant phenotype could be restored if cancer cells receive adequate signals from a physiological environment rather than a malignant one. Metastatic breast cancer cells were found to behave like “normal” cells when transplanted into a mammary gland microenvironment without forming tumours and contributing to tissue development [22]. Another report highlighted that embryonic stem cell preconditioned microenvironment suppresses breast cancer tumorigenicity through the Stat3 pathway [52]. Exposure of cancer cells to Lefty, a Nodal-signalling inhibitor secreted from the embryonic microenvironment, reduces their metastatic potential [103]. On a similar note, the embryonic chick microenvironment is able to reprogram the metastatic potential of melanoma cells following a neural fate [71]. Likewise, culturing primary cells from lung tumour resections in *in vitro* TME-mimetic conditions made it possible to efficiently obtain and amplify tumour-associated stromal progenitors which increased tumour malignancy [115].

Mutation and proliferation rates are not the only players in cancer progression: tumour development estimates are also influenced by the differential effect of selection processes on different cancer cell subpopulations. Under these circumstances, adaptive therapy modulated by chemotherapy minimises the competitive advantages between cancer cells to the extent that tumour size is not reduced but rather maintained. Notably, this approach increased therapy efficacy, as the fittest cancer cells are restrained and tumour proliferation is reduced [43]. It is plausible to suppose that the oncosuppressive functions of the embryonic microenvironment could be due to evolutionary competition between malignant and non-malignant cells [98].

The nutrients in the TME also have the ability to reprogram cancer cells into a more invasive phenotype. Cancer cells have nutrient-sensing mechanisms to track the surrounding environment and fine-tune the metabolism accordingly [94]. It has been found that extracellular pyruvate regulates collagen hydroxylation and promotes growth of breast cancer lung metastasis [39]. Stromal and cancer cells compete with each other to scavenge nutrients such as glucose from the TME. Increased glucose consumption uptake by tumours outsources and restricts metabolism in T cells, allowing cancer to progress [32,54].

Importantly, both the TME and associated cancer change during therapy. Indeed, it has been reported that immune checkpoint inhibitors alter the mutational landscape of the tumour and T-cell repertoire [110]. The immune TME can constrain cancer progression or not based on its composition, and different TMEs can co-exist, showing highly heterogeneous therapeutic responses [65]. A case-study highlighted a high-grade serous ovarian cancer patient with several metastases who showed progression or regression depending on immune exclusion or infiltration, respectively [61]. Similarly, tumour stroma also evolves with cancer starting from an increase in vasculature and leading to the transformation of the stroma into the desmoplastic environment [23]. A recent study analysing the human metastatic microenvironment in ovarian cancer found matrisome genes and proteins to have prognostic significance. Extension of the disease was accompanied by an increase in fibrinogen, fibronectin, PG and affiliated proteins, indicating that the ECM evolves during metastasis [96].

5. Current methods to study TME-tumour cell interactions

Cell monolayers have been employed for decades to study the cellular pathways involved in cancer progression and as a starting point of the drug discovery process. However, several other methods, as multicellular tumour spheroids (MCTS), tumour explants, *in vivo* models, digital pathology and *in silico* models have been developed to better study the TME.

2D cell cultures are easy to set up and relatively cheap. Importantly and in relation with the ECM, 2D cultures can be used to analyse the mechanical properties at a single cell level. This model also allows to understand how down/upregulations of certain proteins/genes intervene in the TME. Nonetheless, there are a number of issues such as lack of three dimensionality and absence of ECM, even when employing co-cultures to increase the physiological cell heterogeneity found in the TME.

To overcome these limitations MCTS have been developed using mono or co-cultures. These add the dimensionality needed to develop the cellular and treatment gradients described previously. Spheroids co-cultures are fundamental to study the immune cells interaction with a solid tumour. However, this model is not as fast as standard monolayers, in terms of usage and the researcher needs to carefully select the best protocol to fit a specific biological question [90]. Another disadvantage would be the lack of a physiological ECM architecture. In this context, scaffolded MCTS have been developed in order to reproduce ECM contributions, but low reproducibility and cost are major disadvantages [30].

The tumor tissue explants are based on tumor tissue biopsies, which are placed in a collagen matrix or gelatin sponges after necrotic tissue clearance. Disadvantages include the reduced reproducibility of tumour heterogeneity and maintenance of the culture for more than three weeks [113]. An approach to overcome all the limitation mentioned above relies on organoids model from tissue explants: 3D tissues derived from patient-derived pluripotent stem cells, which mimic complex feature of the malignant cells, but poorly recapitulate TME characteristics. Further advances, known as "tumor on a chip", have been aimed at developing a more TME physiological environment with tumor perfusion and mechanical stimuli such as shear stress [137]. In this context, 3D cell cultures are placed in microfluidic devices connected to perfusion systems with the possibility to regulate both fluids (medium, nutrients and waste) and gasses (CO_2 and O_2).

An *in vivo* model that enables to study tumourigenesis in a natural immune microenvironment is the genetically engineered mouse model (GEMM). De novo tumors developed in GEMM share molecular and histopathological properties with the human counterpart and capture

intrinsic and extrinsic factors necessary for tumor initiations and metastasis [142]. Nonetheless, the validation and experimentation with GEMMs is costly, time-consuming and intricate.

An important model in the study of the TME is patient samples analysis with digital pathology. This rely on performing serial sections from a biopsy with the pertinent stains and consequent digital analysis. This technique is relatively easy to perform and can highlight an approximate profile of the TME-cell interaction. With the correct staining it is possible to visualise the ECM components or the stromal cells for quantitative/qualitative analysis. The sectioning process of paraffin-embedded tissue can almost capture the full three dimensionality of the tumour architecture through overlapping the images derived of the digital analysis.

Finally, all the biological data coming from different methods in the era of "omics" techniques and personalized medicine, need to be properly integrated. *In silico* approaches using mathematical modelling and systems biology are increasingly being considered in the cancer biology field, because they capture the complexity of cellular systems as a whole. These rely on building biological networks using ordinary differential equations to analyse high throughput data, build predictive models and refine experimental hypothesis. Nonetheless, computational models of all TME-cancer cell interactions needs to be carefully validated.

6. Targeting TME as an anti-cancer strategy

Given both the complexity of the TME, and its interaction with cancer and stromal cells, it is essential to identify targetable microenvironmental modules (Fig. 3 and Table 1 – reviewed in Refs. [11,113]) and, if present, any synergistic interaction with standard of care [65]. Several approaches have aimed at perturbing either the recruitment or function of stromal cells. As an example, modulation of the mesenchymal stromal cell compartment with tyrosine kinase inhibitors or immunosuppressive therapy could be a potential approach to limit the effect of the TME on cancer progression [102]. Blockage of macrophages by altering CSF1/CSF1R signalling can enhance the efficacy of conventional cytotoxic therapies [114]. CSF-1R inhibition acts synergistically with platinum-based chemotherapy, releasing an intratumoral type I interferon response [116]. Notably, iron metabolism, which is important for macrophage polarisation, has attracted interest in the development of new therapies [38]. Additionally, emerging elements are acquiring a key role in reprogramming the TME; vitamin D receptor has been found to have a role in metastatic cancer cells, stromal/immune compartment and the microbiota [60].

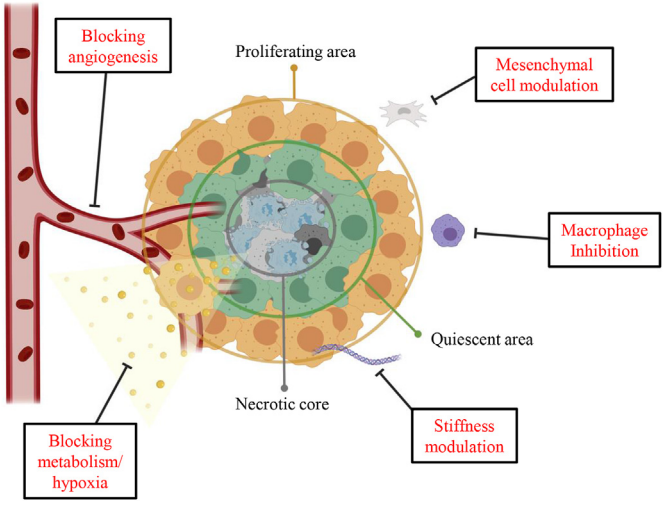

Fig. 3. Therapeutic modules of TME. The stratified cancer environment provides the basis for treatment resistance, as cells in the quiescent domain are more refractory to chemo- or immunotherapy. The extent of a drug's ability to penetrate the cancer 3D structure also affects treatment resistance. Among the therapies being developed nowadays, research has focused on blocking tumour angiogenesis, modulating stiffness to decrease cell migration and metastasis formation and inhibiting macrophage activity and other mesenchymal cells. Finally, several studies are concentrated on altering cellular metabolism to block cell proliferation, induce cell death and modulate interaction between cancer and immune cells.

Table 1
Major strategies used to target tumour microenvironment for cancer therapy[a].

TME element	Therapy strategies
Desmoplasia	
Activation TGF- β signaling pathway/ Increased secretion collagen I	Angiotensin II receptor agonists
Increased expression of MMPs/collagen cross-linkers	Targeting MMPs
Presence of Cancer-Associated Fibroblasts	Targeting FAP-α and TGF-β
Hypoxia and acidosis	
Oxygen deficit	Tackle HIF-1 or its targets
Warburg effect	Inhibitor of proton exchangers/ transporters or carbonic anhydrase
Vascularization	
Proliferation endothelial cells and pericytes inhibitor	anti-VEGF/VEGFR and m-TOR
Altered immune system	
Active macrophages recruitment and differentiation	anti-CSF1/CSF1R Tyrosine kinase inhibitor
Chronic inflammation	anti-IL-1/IL-1R/IL-6
Pro-tumoural activity of immune system	GM-CSF, CTLA-4, PD-1 and PD-L1
Combined	
Immune check point PD-1 and angiogenesis	anti-PD-1 plus anti-VEGF/PD-L1 plus anti-VEGF

[a] Reviewed in Belli et al. and Roma-Rodrigues et al. CTLA-4: cytotoxic T-lymphocyte-associated protein 4; CSF1: colony-stimulating factor-1; CSF1R: CSF-1 receptor; FAP-α: fibroblast activation protein α; GM-CSF: Granulocyte-macrophage colony-stimulating factor; GTP: guanine nucleotides guanosine triphosphate; HIF-1: transcriptional factor hypoxia-induced factor-1; IL-1: interleukin-1; IL-1R: IL-1 receptor; IL-6: interleukin-6; MMPs: matrix metalloproteinases; m-TOR: mammalian Target of Rapamycin; PD-1: programmed death 1 receptor; PD-L1: PD-1 ligand; TGF-β: transforming growth factor beta; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor.

Several groups have focused on modulating angiogenesis as a targeted therapy against the TME. Modulation of VEGFR2 signalling can improve therapeutic efficacy [146]. Alteration of hypoxia-related signalling might return aberrant vasculature to normal while decreasing tumour malignancy [82]. Promoting normal vasculature could also increase chemotherapy uptake in the hypoxic TME and avoid boosting the more aggressive cancer cell subpopulation [146,153]. Conversely, vasculature reduction by inhibiting tumour stiffness using β-aminopropionitrile decreased metastasis [18].

Modulating ECM stiffness and the prosurvival signals derived from the TME is another approach to improve the efficacy of conventional therapies. Treatment of melanoma-associated fibroblasts with BRAF inhibitor PLX4720 resulted in ECM deposition and resistance to treatment; thus, modulation of integrin β1 or FAK signalling in combination with BRAF inhibition induced cell death in melanoma [53]. Furthermore, it has been shown that overexpression of laminin-411 correlates with poor outcome in glioblastoma multiforme and its inhibition increased *in vivo* survival [127]. In pancreatic cancer, depletion of βIG-H3, an ECM component, reduced tumour size and increased cancer cell clearance [45]. Inhibition of the GP vitronectin binding to its ligands (αvβ3 integrin, uPAR or PAI-1) has been tested as a potential therapeutic [55,81,109].

Several approaches have aimed at efficiently blocking aberrant metabolism and its interaction with the TME. Hypoxia, a potent barrier in radiotherapy, chemotherapy and immunotherapy, has been used to develop targeted drugs [48]. Several reports showed the efficacy of HIF-1α blockade on tumour progression [15,80,152]. Lactate production,

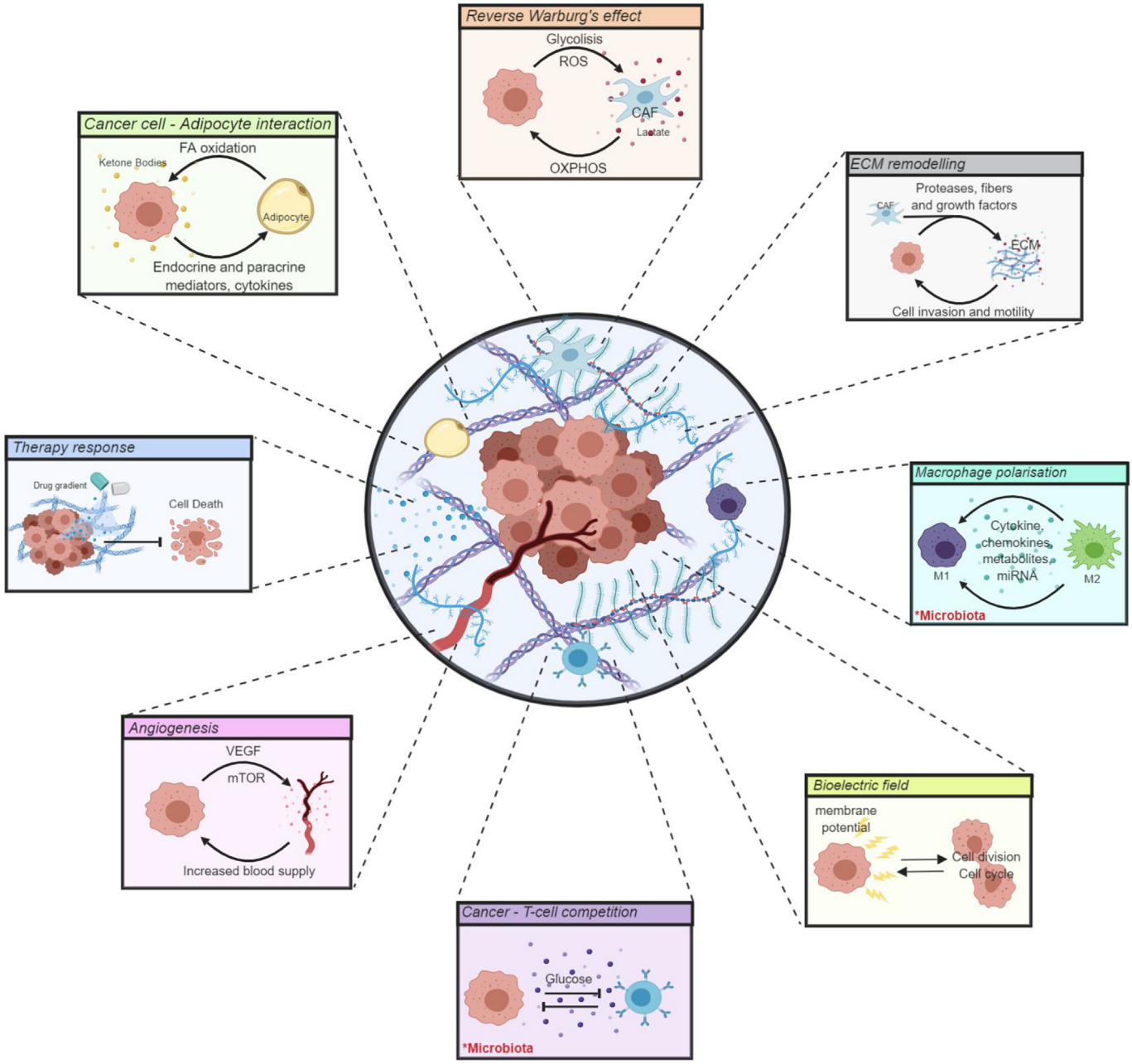

Fig. 4. TME as an integrated platform to understand cancer. Despite the classical view of cancer as a disease driven by mutation accumulation, emerging evidence highlights the role of the TME in tumorigenesis. In order to identify new biomarkers, improve drug development and better characterize this disease, cancer researchers need to keep in mind the integrated vision of a malignant lesion immersed in all the elements of the TME, the most important of which are showcased in this figure. A malignant metabolism contributes to carcinogenesis and cancer cell interaction with the immune system and mesenchymal cell compartments (with the help of the microbiota). Remodelling the ECM allows cancer migration and metastasis formation, and impedes chemotherapy diffusion. The bioelectric field generated in the TME regulates cell division and cell cycle. Finally, new blood vessel formation facilitates nutrient diffusion and creates a hub for cancer cells to disseminate from the primary tumour site.

which correlates with tumour aggressiveness, increases in the TME as a consequence of the Warburg effect [117]. Indeed, inhibition of lactate uptake through MCT transporters has been found to reduce cancer growth, alone and in combination with current therapies [10,12,16,56,85]. The acidic TME has also been employed for specific targeting of cancer cells. In this context, a tumour acidic microenvironment targeted drug delivery system has been developed to carry doxorubicin to breast cancer [157]. Similar studies also focused on the production of pH/redox dual stimuli-responsive polymeric micelles for the intracellular delivery of doxorubicin [63,64].

7. Conclusions and perspectives

An optimal strategy to avoid therapeutic obstinacy and superfluous tests in cancer patients could be to develop new terminology to replace the word cancer in conditions showing low clinical aggressiveness. From a general point of view, carcinogenesis appears to be a differentiation phenomenon, which also includes proliferation and senescence alterations. The fact that cancer cells rewire their malignant phenotype to a normal one when grafted into a healthy microenvironment allows us to view carcinogenesis from a developmental change perspective (Fig. 4). This is in line with recent tissue

organization field theory, where cancer is viewed as a disease affecting the entire tissue rather than single cells [129].

Cells with similar proteomic and genomic profiles possess different physiological properties, and vice-versa. The biophysical forces that maintain the structural integrity of a tumour greatly influence cell adhesion, motility and proliferation. Changes in the bioelectric field can control tumorigenesis and cancer progression without major DNA damage. The metabolic interaction of cancer cells with the surrounding microenvironment shape not only the ECM architecture, but also the cellular/immune niche. The different TME elements promote angiogenesis and a set of changes that alter the tumour stroma. Moreover, therapeutic cytotoxic damage allows the tissue to remodel the environment with different oncogenic changes such as growth factor expression, cytokines and stromal disruption that ultimately generate new migratory signals for cancer cells [69].

In summary, integrating all these information levels could lead to tumour normalisation by remodelling to healthy tissue morphogenesis (including the stromal and cellular compartment) in a non-malignant bioelectric/biophysical field and metabolism. With an integrated perspective, it is possible to view carcinogenesis as a reversible process which is not necessarily linked to mutation. In order to achieve this objective, it would be helpful to record the integrated TME information in a standardized and homogeneous manner. The framework proposed in this review could be useful in finding new biomarkers and treatments that could potentially benefit cancer patients.

Funding disclosure

This work was supported by grants from ISCIII (FIS) and FEDER (European Regional Development Fund) PI17/01558; CIBERONC (contract CB16/12/00484); Fundación Científica de la Asociación Española contra el Cáncer (FAECC2015/006); NEN Association (Nico contra el cancer infantil 2017 – PVR00157) and the Neuroblastoma Foundation (PVR00166). The funders had no involvement in the research process nor in the preparation and submission of the article.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

The authors would like to thank Kathryn for english correction.

References

[1] L. Abdul Kadir, M. Stacey, R. Barrett-Jolley, Emerging roles of the membrane potential: action beyond the action potential, Front. Physiol. 9 (2018) 1661.
[2] D. Ackerman, M.C. Simon, Hypoxia, lipids, and cancer: surviving the harsh tumor microenvironment, Trends Cell Biol. 24 (2014) 472–478.
[3] T. Alkasalias, L. Moyano-Galceran, M. Arsenian-Henriksson, K. Lehti, Fibroblasts in the tumor microenvironment: shield or spear? Int. J. Mol. Sci. 19 (2018) 1532.
[4] T. Alvaro, L. de la Cruz-Merino, F. Henao-Carrasco, J.L. Villar Rodriguez, D. Vicente Baz, M. Codes Manuel de Villena, M. Provencio, Tumor microenvironment and immune effects of antineoplastic therapy in lymphoproliferative syndromes, J. Biomed. Biotechnol. (2010) 2010.
[5] K.E. Allison, B.L. Coomber, B.W. Bridle, Metabolic reprogramming in the tumour microenvironment: a hallmark shared by cancer cells and T lymphocytes, Immunology 152 (2017) 175–184.
[6] A. Arcucci, M.R. Ruocco, G. Granato, A.M. Sacco, S. Montagnani, Cancer: an oxidative crosstalk between solid tumor cells and cancer associated fibroblasts, BioMed Res. Int. 2016 (2016) 4502846.
[7] E.L. Baker, R.T. Bonnecaze, M.H. Zaman, Extracellular matrix stiffness and architecture govern intracellular rheology in cancer, Biophys. J. 97 (2009) 1013–1021.
[8] F.R. Balkwill, M. Capasso, T. Hagemann, The tumor microenvironment at a glance, J. Cell Sci. 125 (2012) 5591–5596.
[9] A. Becchetti, Ion channels and transporters in cancer. 1. Ion channels and cell proliferation in cancer, Am. J. Physiol. Cell Physiol. 301 (2011) C255–C265.
[10] M. Beloueche-Babari, S. Wantuch, T. Casals Galobart, M. Koniordou, H.G. Parkes, V. Arunan, Y.L. Chung, T.R. Eykyn, P.D. Smith, M.O. Leach, MCT1 inhibitor AZD3965 increases mitochondrial metabolism, facilitating combination therapy and noninvasive magnetic resonance spectroscopy, Cancer Res. 77 (2017) 5913–5924.
[11] C. Belli, D. Trapani, G. Viale, P. D'Amico, B.A. Duso, P. Della Vigna, F. Orsi, G. Curigliano, Targeting the microenvironment in solid tumors, Cancer Treat Rev. 65 (2018) 22–32.
[12] D. Benjamin, D. Robay, S.K. Hindupur, J. Pohlmann, M. Colombi, M.Y. El-Shemerly, S.M. Maira, C. Moroni, H.A. Lane, M.N. Hall, Dual inhibition of the lactate transporters MCT1 and MCT4 is synthetic lethal with metformin due to NAD+ depletion in cancer cells, Cell Rep. 25 (2018) 3047–3058 e3044.
[13] M. Bertolaso, A.M. Dieli, Cancer and intercellular cooperation, R. Soc. Open Sci. 4 (2017) 170470.
[14] D.J. Blackiston, K.A. McLaughlin, M. Levin, Bioelectric controls of cell proliferation: ion channels, membrane voltage and the cell cycle, Cell Cycle 8 (2009) 3527–3536.
[15] K.M. Block, H. Wang, L.Z. Szabo, N.W. Polaske, L.K. Henchey, R. Dubey, S. Kushal, C.F. Laszlo, J. Makhoul, Z. Song, E.J. Meuillet, B.Z. Olenyuk, Direct inhibition of hypoxia-inducible transcription factor complex with designed dimeric epidithiodiketopiperazine, J. Am. Chem. Soc. 131 (2009) 18078–18088.
[16] B.M. Bola, A.L. Chadwick, F. Michopoulos, K.G. Blount, B.A. Telfer, K.J. Williams, P.D. Smith, S.E. Critchlow, I.J. Stratford, Inhibition of monocarboxylate transporter-1 (MCT1) by AZD3965 enhances radiosensitivity by reducing lactate transport, Mol. Cancer Ther. 13 (2014) 2805–2816.
[17] G. Bonuccelli, D. Whitaker-Menezes, R. Castello-Cros, S. Pavlides, R.G. Pestell, A. Fatatis, A.K. Witkiewicz, M.G. Vander Heiden, G. Migneco, B. Chiavarina, P.G. Frank, F. Capozza, N. Flomenberg, U.E. Martinez-Outschoorn, F. Sotgia, M.P. Lisanti, The reverse Warburg effect: glycolysis inhibitors prevent the tumor promoting effects of caveolin-1 deficient cancer associated fibroblasts, Cell Cycle 9 (2010) 1960–1971.
[18] F. Bordeleau, B.N. Mason, E.M. Lollis, M. Mazzola, M.R. Zanotelli, S. Somasegar, J.P. Califano, C. Montague, D.J. LaValley, J. Huynh, N. Mencia-Trinchant, Y.L. Negron Abril, D.C. Hassane, L.J. Bonassar, J.T. Butcher, R.S. Weiss, C.A. Reinhart-King, Matrix stiffening promotes a tumor vasculature phenotype, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 492–497.
[19] P. Borys, On the biophysics of cathodal galvanotaxis in rat prostate cancer cells: Poisson-Nernst-Planck equation approach, Eur. Biophys. J. 41 (2012) 527–534.
[20] R.M. Bremnes, T. Donnem, S. Al-Saad, K. Al-Shibli, S. Andersen, R. Sirera, C. Camps, I. Marinez, L.T. Busund, The role of tumor stroma in cancer progression and prognosis: emphasis on carcinoma-associated fibroblasts and non-small cell lung cancer, J. Thorac. Oncol. : Off. Publ. Int. Assoc. Stud. Lung Canc. 6 (2011) 209–217.
[21] F. Broders-Bondon, T.H. Nguyen Ho-Bouldoires, M.E. Fernandez-Sanchez, E. Farge, Mechanotransduction in tumor progression: the dark side of the force, J. Cell Biol. 217 (2018) 1571–1587.
[22] K.M. Bussard, G.H. Smith, Human breast cancer cells are redirected to mammary epithelial cells upon interaction with the regenerating mammary gland microenvironment in-vivo, PLoS One 7 (2012) e49221.
[23] F. Cammarota, M.O. Laukkanen, Mesenchymal stem/stromal cells in stromal evolution and cancer progression, Stem Cell. Int. (2016) 4824573 2016.
[24] J.R. Cantor, D.M. Sabatini, Cancer cell metabolism: one hallmark, many faces, Cancer Discov. 2 (2012) 881–898.
[25] C. Carmona-Fontaine, M. Deforet, L. Akkari, C.B. Thompson, J.A. Joyce, J.B. Xavier, Metabolic origins of spatial organization in the tumor microenvironment, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 2934–2939.
[26] M. Cavo, M. Fato, L. Penuela, F. Beltrame, R. Raiteri, S. Scaglione, Microenvironment complexity and matrix stiffness regulate breast cancer cell activity in a 3D in vitro model, Sci. Rep. 6 (2016) 35367.
[27] M.E. Ciurea, A.M. Georgescu, S.O. Purcaru, S.A. Artene, G.H. Emami, M.V. Boldeanu, D.E. Tache, A. Dricu, Cancer stem cells: biological functions and therapeutically targeting, Int. J. Mol. Sci. 15 (2014) 8169–8185.
[28] W.H. Clark Jr., The nature of cancer: morphogenesis and progressive (self)-disorganization in neoplastic development and progression, Acta Oncol. (Stockh.) 34 (1995) 3–21.
[29] E.C. Costa, A.F. Moreira, D. de Melo-Diogo, V.M. Gaspar, M.P. Carvalho, I.J. Correia, 3D tumor spheroids: an overview on the tools and techniques used for their analysis, Biotechnol. Adv. 34 (2016) 1427–1441.
[30] X. Cui, Y. Hartanto, H. Zhang, Advances in multicellular spheroids formation, J. R. Soc. Interface 14 (2017) 20160877.
[31] P. Cunnea, T. Gorgy, K. Petkos, S.A.N. Gowers, H. Lu, C. Morera, W. Wu, P. Lawton, K. Nixon, C.L. Leong, F. Sorbi, L. Domenici, A. Paterson, E. Curry, H. Gabra, M.G. Boutelle, E.M. Drakakis, C. Fotopoulou, Clinical value of bioelectrical properties of cancerous tissue in advanced epithelial ovarian cancer patients, Sci. Rep. 8 (2018) 14695.
[32] C.H. Chang, J. Qiu, D. O'Sullivan, M.D. Buck, T. Noguchi, J.D. Curtis, Q. Chen, M. Gindin, M.M. Gubin, G.J. van der Windt, E. Tonc, R.D. Schreiber, E.J. Pearce, E.L. Pearce, Metabolic competition in the tumor microenvironment is a driver of cancer progression, Cell 162 (2015) 1229–1241.
[33] F. Chen, X. Zhuang, L. Lin, P. Yu, Y. Wang, Y. Shi, G. Hu, Y. Sun, New horizons in tumor microenvironment biology: challenges and opportunities, BMC Med. 13 (2015) 45.
[34] B. Chernet, M. Levin, Endogenous voltage potentials and the microenvironment: bioelectric signals that reveal, induce and normalize cancer, J. Clin. Exp. Oncol. Suppl 1 (2013) S1–S002.
[35] B.T. Chernet, M. Levin, Transmembrane voltage potential of somatic cells controls oncogene-mediated tumorigenesis at long-range, Oncotarget 5 (2014) 3287–3306.
[36] A. Chronopoulos, B. Robinson, M. Sarper, E. Cortes, V. Auernheimer,

D. Lachowski, S. Attwood, R. Garcia, S. Ghassemi, B. Fabry, A. Del Rio Hernandez, ATRA mechanically reprograms pancreatic stellate cells to suppress matrix remodelling and inhibit cancer cell invasion, Nat. Commun. 7 (2016) 12630.
[37] S.M. Davidson, O. Jonas, M.A. Keibler, H.W. Hou, A. Luengo, J.R. Mayers, J. Wyckoff, A.M. Del Rosario, M. Whitman, C.R. Chin, K.J. Condon, A. Lammers, K.A. Kellersberger, B.K. Stall, G. Stephanopoulos, D. Bar-Sagi, J. Han, J.D. Rabinowitz, M.J. Cima, R. Langer, M.G. Vander Heiden, Direct evidence for cancer-cell-autonomous extracellular protein catabolism in pancreatic tumors, Nat. Med. 23 (2017) 235–241.
[38] D. Dong, G. Zhang, J. Yang, B. Zhao, S. Wang, L. Wang, G. Zhang, P. Shang, The role of iron metabolism in cancer therapy focusing on tumor-associated macrophages, J. Cell. Physiol. 234 (2019) 8028–8039.
[39] I. Elia, M. Rossi, S. Stegen, D. Broekaert, G. Doglioni, M. van Gorsel, R. Boon, C. Escalona-Noguero, S. Torrekens, C. Verfaillie, E. Verbeken, G. Carmeliet, S.M. Fendt, Breast cancer cells rely on environmental pyruvate to shape the metastatic niche, Nature (2019) 117–121.
[40] B. Emon, J. Bauer, Y. Jain, B. Jung, T. Saif, Biophysics of tumor microenvironment and cancer metastasis - a mini review, Comput. Struct. Biotechnol. J. 16 (2018) 279–287.
[41] B.T. Finicle, V. Jayashankar, A.L. Edinger, Nutrient scavenging in cancer, Nat. Rev. Cancer 18 (2018) 619–633.
[42] C. Frantz, K.M. Stewart, V.M. Weaver, The extracellular matrix at a glance, J. Cell Sci. 123 (2010) 4195–4200.
[43] R.A. Gatenby, A.S. Silva, R.J. Gillies, B.R. Frieden, Adaptive therapy, Cancer Res. 69 (2009) 4894–4903.
[44] V. Gkretsi, T. Stylianopoulos, Cell adhesion and matrix stiffness: coordinating cancer cell invasion and metastasis, Front Oncol. 8 (2018) 145.
[45] D. Goehrig, J. Nigri, R. Samain, Z. Wu, P. Cappello, G. Gabiane, X. Zhang, Y. Zhao, I.S. Kim, M. Chanal, R. Curto, V. Hervieu, C. de La Fouchardiere, F. Novelli, P. Milani, R. Tomasini, C. Bousquet, P. Bertolino, A. Hennino, Stromal protein betaig-h3 reprogrammes tumour microenvironment in pancreatic cancer, Gut 68 (2019) 693–707.
[46] K. Gollapudi, C. Galet, T. Grogan, H. Zhang, J.W. Said, J. Huang, D. Elashoff, S.J. Freedland, M. Rettig, W.J. Aronson, Association between tumor-associated macrophage infiltration, high grade prostate cancer, and biochemical recurrence after radical prostatectomy, Am. J. Canc. Res. 3 (2013) 523–529.
[47] D.M. Graham, K. Burridge, Mechanotransduction and nuclear function, Curr. Opin. Cell Biol. 40 (2016) 98–105.
[48] K. Graham, E. Unger, Overcoming tumor hypoxia as a barrier to radiotherapy, chemotherapy and immunotherapy in cancer treatment, Int. J. Nanomed. 13 (2018) 6049–6058.
[49] Z. Granot, Z.G. Fridlender, Plasticity beyond cancer cells and the "immunosuppressive switch, Cancer Res. 75 (2015) 4441–4445.
[50] D. Hanahan, L.M. Coussens, Accessories to the crime: functions of cells recruited to the tumor microenvironment, Cancer Cell 21 (2012) 309–322.
[51] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[52] N. He, G. Feng, Y. Li, Y. Xu, X. Xie, H. Wang, Y. Wang, L. Ou, X. Pei, N. Liu, Z. Li, Embryonic stem cell preconditioned microenvironment suppresses tumorigenic properties in breast cancer, Stem Cell Res. Ther. 7 (2016) 95.
[53] E. Hirata, M.R. Girotti, A. Viros, S. Hooper, B. Spencer-Dene, M. Matsuda, J. Larkin, R. Marais, E. Sahai, Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin beta1/FAK signaling, Cancer Cell 27 (2015) 574–588.
[54] P.C. Ho, J.D. Bihuniak, A.N. Macintyre, M. Staron, X. Liu, R. Amezquita, Y.C. Tsui, G. Cui, G. Micevic, J.C. Perales, S.H. Kleinstein, E.D. Abel, K.L. Insogna, S. Feske, J.W. Locasale, M.W. Bosenberg, J.C. Rathmell, S.M. Kaech, Phosphoenolpyruvate is a metabolic checkpoint of anti-tumor T cell responses, Cell 162 (2015) 1217–1228.
[55] A.W. Holle, J.L. Young, J.P. Spatz, In vitro cancer cell-ECM interactions inform in vivo cancer treatment, Adv. Drug Deliv. Rev. 97 (2016) 270–279.
[56] C.S. Hong, N.A. Graham, W. Gu, C. Espindola Camacho, V. Mah, E.L. Maresh, M. Alavi, L. Bagryanova, P.A.L. Krotee, B.K. Gardner, I.S. Behbahan, S. Horvath, D. Chia, I.K. Mellinghoff, S.A. Hurvitz, S.M. Dubinett, S.E. Critchlow, S.K. Kurdistani, L. Goodglick, D. Braas, T.G. Graeber, H.R. Christofk, MCT1 modulates cancer cell pyruvate export and growth of tumors that Co-express MCT1 and MCT4, Cell Rep. 14 (2016) 1590–1601.
[57] L. Ippolito, A. Morandi, M.L. Taddei, M. Parri, G. Comito, A. Iscaro, M.R. Raspollini, F. Magherini, E. Rapizzi, J. Masquelier, G.G. Muccioli, P. Sonveaux, P. Chiarugi, E. Giannoni, Cancer-associated fibroblasts promote prostate cancer malignancy via metabolic rewiring and mitochondrial transfer, Oncogene (2019).
[58] V. Izzi, J. Lakkala, R. Devarajan, E.R. Savolainen, P. Koistinen, R. Heljasvaara, T. Pihlajaniemi, Expression of a specific extracellular matrix signature is a favorable prognostic factor in acute myeloid leukemia, Leuk. Res. Rep. 9 (2018) 9–13.
[59] M.K. Jena, J. Janjanam, Role of extracellular matrix in breast cancer development: a brief update, F1000Res. 7 (2018) 274.
[60] S.M. Jeon, E.A. Shin, Exploring vitamin D metabolism and function in cancer, Exp. Mol. Med. 50 (2018) 20.
[61] A. Jimenez-Sanchez, D. Memon, S. Pourpe, H. Veeraraghavan, Y. Li, H.A. Vargas, M.B. Gill, K.J. Park, O. Zivanovic, J. Konner, J. Ricca, D. Zamarin, T. Walther, C. Aghajanian, J.D. Wolchok, E. Sala, T. Merghoub, A. Snyder, M.L. Miller, Heterogeneous tumor-immune microenvironments among differentially growing metastases in an ovarian cancer patient, Cell 170 (2017) 927–938 e920.
[62] P. Jobling, J. Pundavela, S.M. Oliveira, S. Roselli, M.M. Walker, H. Hondermarck, Nerve-cancer cell cross-talk: a novel promoter of tumor progression, Cancer Res. 75 (2015) 1777–1781.
[63] J.V. John, S. Uthaman, R. Augustine, H. Chen, I.-K. Park, I. Kim, pH/redox dual stimuli-responsive sheddable nanodaisies for efficient intracellular tumour-triggered drug delivery, J. Mater. Chem. B 5 (2017) 5027–5036.
[64] J.V. John, S. Uthaman, R. Augustine, K. Manickavasagam Lekshmi, I.-K. Park, I. Kim, Biomimetic pH/redox dual stimuli-responsive zwitterionic polymer block poly(L-histidine) micelles for intracellular delivery of doxorubicin into tumor cells, J. Polym. Sci. A Polym. Chem. 55 (2017) 2061–2070.
[65] M.R. Junttila, F.J. de Sauvage, Influence of tumour micro-environment heterogeneity on therapeutic response, Nature 501 (2013) 346–354.
[66] M. Kalli, T. Stylianopoulos, Defining the role of solid stress and matrix stiffness in cancer cell proliferation and metastasis, Front Oncol. 8 (2018) 55.
[67] J.J. Kamphorst, J.R. Cross, J. Fan, E. de Stanchina, R. Mathew, E.P. White, C.B. Thompson, J.D. Rabinowitz, Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 8882–8887.
[68] J.J. Kamphorst, M. Nofal, C. Commisso, S.R. Hackett, W. Lu, E. Grabocka, M.G. Vander Heiden, G. Miller, J.A. Drebin, D. Bar-Sagi, C.B. Thompson, J.D. Rabinowitz, Human pancreatic cancer tumors are nutrient poor and tumor cells actively scavenge extracellular protein, Cancer Res. 75 (2015) 544–553.
[69] G.S. Karagiannis, J.S. Condeelis, M.H. Oktay, Chemotherapy-induced metastasis: mechanisms and translational opportunities, Clin. Exp. Metastasis 35 (2018) 269–284.
[70] J.K. Kular, S. Basu, R.I. Sharma, The extracellular matrix: structure, composition, age-related differences, tools for analysis and applications for tissue engineering, J. Tissue Eng. 5 (2014) 2041731414557112.
[71] P.M. Kulesa, J.C. Kasemeier-Kulesa, J.M. Teddy, N.V. Margaryan, E.A. Seftor, R.E. Seftor, M.J. Hendrix, Reprogramming metastatic melanoma cells to assume a neural crest cell-like phenotype in an embryonic microenvironment, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 3752–3757.
[72] D. Lachowski, E. Cortes, D. Pink, A. Chronopoulos, S.A. Karim, P.M.J, A.E. Del Rio Hernandez, Substrate rigidity controls activation and durotaxis in pancreatic stellate cells, Sci. Rep. 7 (2017) 2506.
[73] S.A. Langhans, Three-dimensional in vitro cell culture models in drug discovery and drug repositioning, Front. Pharmacol. 9 (2018) 6.
[74] M. Levin, Reprogramming cells and tissue patterning via bioelectrical pathways: molecular mechanisms and biomedical opportunities, Wiley Interdiscip. Rev. Syst. Biol. Med. 5 (2013) 657–676.
[75] M. Levin, Molecular bioelectricity: how endogenous voltage potentials control cell behavior and instruct pattern regulation in vivo, Mol. Biol. Cell 25 (2014) 3835–3850.
[76] M. Levin, C.J. Martyniuk, The bioelectric code: an ancient computational medium for dynamic control of growth and form, Biosystems 164 (2018) 76–93.
[77] M.V. Liberti, J.W. Locasale, The Warburg effect: how does it benefit cancer cells? Trends Biochem. Sci. 41 (2016) 211–218.
[78] S.B. Lim, S.J. Tan, W.T. Lim, C.T. Lim, An extracellular matrix-related prognostic and predictive indicator for early-stage non-small cell lung cancer, Nat. Commun. 8 (2017) 1734.
[79] M. Lobikin, B. Chernet, D. Lobo, M. Levin, Resting potential, oncogene-induced tumorigenesis, and metastasis: the bioelectric basis of cancer in vivo, Phys. Biol. 9 (2012) 065002.
[80] N.J. Mabjeesh, D. Escuin, T.M. LaValle, V.S. Pribluda, G.M. Swartz, M.S. Johnson, M.T. Willard, H. Zhong, J.W. Simons, P. Giannakakou, 2ME2 inhibits tumor growth and angiogenesis by disrupting microtubules and dysregulating HIF, Cancer Cell 3 (2003) 363–375.
[81] T. Masuda, N. Hattori, T. Senoo, S. Akita, N. Ishikawa, K. Fujitaka, Y. Haruta, H. Murai, N. Kohno, SK-216, an inhibitor of plasminogen activator inhibitor-1, limits tumor progression and angiogenesis, Mol. Cancer Ther. 12 (2013) 2378–2388.
[82] M. Mazzone, D. Dettori, R.L. de Oliveira, S. Loges, T. Schmidt, B. Jonckx, Y.M. Tian, A.A. Lanahan, P. Pollard, C.R. de Almodovar, F. De Smet, S. Vinckier, J. Aragones, K. Debackere, A. Luttun, S. Wyns, B. Jordan, A. Pisacane, B. Gallez, M.G. Lampugnani, E. Dejana, M. Simons, P. Ratcliffe, P. Maxwell, P. Carmeliet, Heterozygous deficiency of PHD2 restores tumor oxygenation and inhibits metastasis via endothelial normalization, Cell 136 (2009) 839–851.
[83] P. Mesquida, D. Kohl, O.G. Andriotis, P.J. Thurner, M. Duer, S. Bansode, G. Schitter, Evaluation of surface charge shift of collagen fibrils exposed to glutaraldehyde, Sci. Rep. 8 (2018) 10126.
[84] S.M. Mithieux, A.S. Weiss, Elastin, Adv. Protein Chem. 70 (2005) 437–461.
[85] F. Morais-Santos, S. Granja, V. Miranda-Goncalves, A.H. Moreira, S. Queiros, J.L. Vilaca, F.C. Schmitt, A. Longatto-Filho, J. Paredes, F. Baltazar, C. Pinheiro, Targeting lactate transport suppresses in vivo breast tumour growth, Oncotarget 6 (2015) 19177–19189.
[86] J.K. Mouw, G. Ou, V.M. Weaver, Extracellular matrix assembly: a multiscale deconstruction, Nat. Rev. Mol. Cell Biol. 15 (2014) 771–785.
[87] A. Muir, M.G. Vander Heiden, The nutrient environment affects therapy, Science (New York, N.Y.) 360 (2018) 962–963.
[88] M.E. Mycielska, M.B. Djamgoz, Cellular mechanisms of direct-current electric field effects: galvanotaxis and metastatic disease, J. Cell Sci. 117 (2004) 1631–1639.
[89] M. Najafi, N.H. Goradel, B. Farhood, E. Salehi, S. Solhjoo, H. Toolee, E. Kharazinejad, K. Mortezaee, Tumor microenvironment: interactions and therapy, J. Cell. Physiol. 234 (2019) 5700–5721.
[90] S. Nath, G.R. Devi, Three-dimensional culture systems in cancer research: focus on tumor spheroid model, Pharmacol. Ther. 163 (2016) 94–108.
[91] M.R. Ng, J.S. Brugge, A stiff blow from the stroma: collagen crosslinking drives tumor progression, Cancer Cell 16 (2009) 455–457.

[92] K.M. Nieman, H.A. Kenny, C.V. Penicka, A. Ladanyi, R. Buell-Gutbrod, M.R. Zillhardt, I.L. Romero, M.S. Carey, G.B. Mills, G.S. Hotamisligil, S.D. Yamada, M.E. Peter, K. Gwin, E. Lengyel, Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth, Nat. Med. 17 (2011) 1498–1503.
[93] K.M. Nieman, I.L. Romero, B. Van Houten, E. Lengyel, Adipose tissue and adipocytes support tumorigenesis and metastasis, Biochim. Biophys. Acta 1831 (2013) 1533–1541.
[94] W. Palm, C.B. Thompson, Nutrient acquisition strategies of mammalian cells, Nature 546 (2017) 234–242.
[95] S. Pavlides, D. Whitaker-Menezes, R. Castello-Cros, N. Flomenberg, A.K. Witkiewicz, P.G. Frank, M.C. Casimiro, C. Wang, P. Fortina, S. Addya, R.G. Pestell, U.E. Martinez-Outschoorn, F. Sotgia, M.P. Lisanti, The reverse Warburg effect: aerobic glycolysis in cancer associated fibroblasts and the tumor stroma, Cell Cycle 8 (2009) 3984–4001.
[96] O.M.T. Pearce, R.M. Delaine-Smith, E. Maniati, S. Nichols, J. Wang, S. Bohm, V. Rajeeve, D. Ullah, P. Chakravarty, R.R. Jones, A. Montfort, T. Dowe, J. Gribben, J.L. Jones, H.M. Kocher, J.S. Serody, B.G. Vincent, J. Connelly, J.D. Brenton, C. Chelala, P.R. Cutillas, M. Lockley, C. Bessant, M.M. Knight, F.R. Balkwill, Deconstruction of a metastatic tumor microenvironment reveals a common matrix response in human cancers, Cancer Discov. 8 (2018) 304–319.
[97] H. Peinado, H. Zhang, I.R. Matei, B. Costa-Silva, A. Hoshino, G. Rodrigues, B. Psaila, R.N. Kaplan, J.F. Bromberg, Y. Kang, M.J. Bissell, T.R. Cox, A.J. Giaccia, J.T. Erler, S. Hiratsuka, C.M. Ghajar, D. Lyden, Pre-metastatic niches: organ-specific homes for metastases, Nat. Rev. Cancer 17 (2017) 302–317.
[98] J.W. Pepper, C. Scott Findlay, R. Kassen, S.L. Spencer, C.C. Maley, Cancer research meets evolutionary biology, Evol. Appl. 2 (2009) 62–70.
[99] N. Pertega-Gomes, J.R. Vizcaino, J. Attig, S. Jurmeister, C. Lopes, F. Baltazar, A lactate shuttle system between tumour and stromal cells is associated with poor prognosis in prostate cancer, BMC Canc. 14 (2014) 352.
[100] F. Petitprez, C.M. Sun, L. Lacroix, C. Sautes-Fridman, A. de Reynies, W.H. Fridman, Quantitative analyses of the tumor microenvironment composition and orientation in the era of precision medicine, Front Oncol. 8 (2018) 390.
[101] M.W. Pickup, J.K. Mouw, V.M. Weaver, The extracellular matrix modulates the hallmarks of cancer, EMBO Rep. 15 (2014) 1243–1253.
[102] A. Poggi, S. Varesano, M.R. Zocchi, How to hit mesenchymal stromal cells and make the tumor microenvironment immunostimulant rather than immunosuppressive, Front. Immunol. 9 (2018) 262.
[103] L.M. Postovit, N.V. Margaryan, E.A. Seftor, D.A. Kirschmann, A. Lipavsky, W.W. Wheaton, D.E. Abbott, R.E. Seftor, M.J. Hendrix, Human embryonic stem cell microenvironment suppresses the tumorigenic phenotype of aggressive cancer cells, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 4329–4334.
[104] J. Pouysségur, F. Dayan, N.M. Mazure, Hypoxia signalling in cancer and approaches to enforce tumour regression, Nature 441 (2006) 437.
[105] D.R. Powell, A. Huttenlocher, Neutrophils in the tumor microenvironment, Trends Immunol. 37 (2016) 41–52.
[106] N. Prevarskaya, R. Skryma, Y. Shuba, Ion channels and the hallmarks of cancer, Trends Mol. Med. 16 (2010) 107–121.
[107] D.F. Quail, J.A. Joyce, Microenvironmental regulation of tumor progression and metastasis, Nat. Med. 19 (2013) 1423–1437.
[108] S. Raab-Westphal, J.F. Marshall, S.L. Goodman, Integrins as therapeutic targets: successes and cancers, Cancers 9 (2017) 110.
[109] V.E. Rea, A. Lavecchia, C. Di Giovanni, F.W. Rossi, A. Gorrasi, A. Pesapane, A. de Paulis, P. Ragno, N. Montuori, Discovery of new small molecules targeting the vitronectin-binding site of the urokinase receptor that block cancer cell invasion, Mol. Cancer Ther. 12 (2013) 1402–1416.
[110] N. Riaz, J.J. Havel, V. Makarov, A. Desrichard, W.J. Urba, J.S. Sims, F.S. Hodi, S. Martin-Algarra, R. Mandal, W.H. Sharfman, S. Bhatia, W.J. Hwu, T.F. Gajewski, C.L. Slingluff Jr., D. Chowell, S.M. Kendall, H. Chang, R. Shah, F. Kuo, L.G.T. Morris, J.W. Sidhom, J.P. Schneck, C.E. Horak, N. Weinhold, T.A. Chan, Tumor and microenvironment evolution during immunotherapy with nivolumab, Cell 171 (2017) 934–949 e916.
[111] A.J. Rice, E. Cortes, D. Lachowski, B.C.H. Cheung, S.A. Karim, J.P. Morton, A. del Río Hernández, Matrix stiffness induces epithelial–mesenchymal transition and promotes chemoresistance in pancreatic cancer cells, Oncogenesis 6 (2017) e352.
[112] P. Roca-Cusachs, A. del Rio, E. Puklin-Faucher, N.C. Gauthier, N. Biais, M.P. Sheetz, Integrin-dependent force transmission to the extracellular matrix by alpha-actinin triggers adhesion maturation, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) E1361–E1370.
[113] C. Roma-Rodrigues, R. Mendes, P.V. Baptista, A.R. Fernandes, Targeting tumor microenvironment for cancer therapy, Int. J. Mol. Sci. 20 (2019) 840.
[114] B. Ruffell, D. Chang-Strachan, V. Chan, A. Rosenbusch, C.M. Ho, N. Pryer, D. Daniel, E.S. Hwang, H.S. Rugo, L.M. Coussens, Macrophage IL-10 blocks CD8+ T cell-dependent responses to chemotherapy by suppressing IL-12 expression in intratumoral dendritic cells, Cancer Cell 26 (2014) 623–637.
[115] D. Saforo, L. Omer, A. Smolenkov, A. Barve, L. Casson, N. Boyd, G. Clark, L. Siskind, L. Beverly, Primary lung cancer samples cultured under microenvironment-mimetic conditions enrich for mesenchymal stem-like cells that promote metastasis, Sci. Rep. 9 (2019) 4177.
[116] C. Salvagno, M. Ciampricotti, S. Tuit, C.S. Hau, A. van Weverwijk, S.B. Coffelt, K. Kersten, K. Vrijland, K. Kos, T. Ulas, J.Y. Song, C.H. Ooi, D. Ruttinger, P.A. Cassier, J. Jonkers, J.L. Schultze, C.H. Ries, K.E. de Visser, Therapeutic targeting of macrophages enhances chemotherapy efficacy by unleashing type I interferon response, Nat. Cell Biol. 21 (2019) 511–521.
[117] I. San-Millan, G.A. Brooks, Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect, Carcinogenesis 38 (2017) 119–133.
[118] L. Sapir, S. Tzlil, Talking over the extracellular matrix: how do cells communicate mechanically? Semin. Cell Dev. Biol. 71 (2017) 99–105.
[119] A. Schwab, C. Stock, Ion channels and transporters in tumour cell migration and invasion, Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (2014) 20130102.
[120] L. Seguin, J.S. Desgrosellier, S.M. Weis, D.A. Cheresh, Integrins and cancer: regulators of cancer stemness, metastasis, and drug resistance, Trends Cell Biol. 25 (2015) 234–240.
[121] A.C. Shieh, Biomechanical forces shape the tumor microenvironment, Ann. Biomed. Eng. 39 (2011) 1379–1389.
[122] A.C. Shieh, M.A. Swartz, Regulation of tumor invasion by interstitial fluid flow, Phys. Biol. 8 (2011) 015012.
[123] T. Shiraishi, J.E. Verdone, J. Huang, U.D. Kahlert, J.R. Hernandez, G. Torga, J.C. Zarif, T. Epstein, R. Gatenby, A. McCartney, J.H. Elisseeff, S.M. Mooney, S.S. An, K.J. Pienta, Glycolysis is the primary bioenergetic pathway for cell motility and cytoskeletal remodeling in human prostate and breast cancer cells, Oncotarget 6 (2015) 130–143.
[124] F. Sotgia, D. Whitaker-Menezes, U.E. Martinez-Outschoorn, N. Flomenberg, R.C. Birbe, A.K. Witkiewicz, A. Howell, N.J. Philp, R.G. Pestell, M.P. Lisanti, Mitochondrial metabolism in cancer metastasis: visualizing tumor cell mitochondria and the "reverse Warburg effect" in positive lymph node tissue, Cell Cycle 11 (2012) 1445–1454.
[125] A.M. Soto, C. Sonnenschein, The tissue organization field theory of cancer: a testable replacement for the somatic mutation theory, Bioessays 33 (2011) 332–340.
[126] J.P. Stains, R. Civitelli, Gap junctions regulate extracellular signal-regulated kinase signaling to affect gene transcription, Mol. Biol. Cell 16 (2005) 64–72.
[127] T. Sun, R. Patil, A. Galstyan, D. Klymyshyn, H. Ding, A. Chesnokova, W.K. Cavenee, F.B. Furnari, V.A. Ljubimov, E.S. Shatalova, S. Wagner, D. Li, A.N. Mamelak, S.I. Bannykh, C.G. Patil, J.D. Rudnick, J. Hu, Z.B. Grodzinski, A. Rekechenetskiy, V. Falahatian, A.V. Lyubimov, Y.L. Chen, L.S. Leoh, T.R. Daniels-Wells, M.L. Penichet, E. Holler, A.V. Ljubimov, K.L. Black, J.Y. Ljubimova, Blockade of a laminin-411-notch Axis with CRISPR/Cas9 or a nanobioconjugate inhibits glioblastoma growth through tumor-microenvironment cross-talk, Cancer Res. 79 (2019) 1239–1251.
[128] T. Szoke, K. Kayser, J.D. Baumhakel, I. Trojan, J. Furak, L. Tiszlavicz, J. Eller, K. Boda, Prognostic significance of microvascularization in cases of operated lung cancer, Eur. J. Cardiothorac. Surg. : Off. J. Eur. Assoc. Cardio-thorac. Surg. 27 (2005) 1106–1111.
[129] D.P. Tabassum, K. Polyak, Tumorigenesis: it takes a village, Nature reviews, Cancer 15 (2015) 473–483.
[130] I. Tadeo, A.P. Berbegall, V. Castel, P. Garcia-Miguel, R. Callaghan, S. Pahlman, S. Navarro, R. Noguera, Extracellular matrix composition defines an ultra-high-risk group of neuroblastoma within the high-risk patient cohort, Br. J. Canc. 115 (2016) 480–489.
[131] I. Tadeo, A.P. Berbegall, L.M. Escudero, T. Alvaro, R. Noguera, Biotensegrity of the extracellular matrix: physiology, dynamic mechanical balance, and implications in oncology and mechanotherapy, Front Oncol. 4 (2014) 39.
[132] I. Tadeo, A.P. Berbegall, S. Navarro, V. Castel, R. Noguera, A stiff extracellular matrix is associated with malignancy in peripheral neuroblastic tumors, Pediatr. Blood Cancer 64 (2017) e26449.
[133] I. Tadeo, G. Bueno, A.P. Berbegall, M.M. Fernandez-Carrobles, V. Castel, M. Garcia-Rojo, S. Navarro, R. Noguera, Vascular patterns provide therapeutic targets in aggressive neuroblastic tumors, Oncotarget 7 (2016) 19935–19947.
[134] I. Tadeo, E. Gamero-Sandemetrio, A.P. Berbegall, M. Gironella, F. Ritort, A. Canete, G. Bueno, S. Navarro, R. Noguera, Lymph microvascularization as a prognostic indicator in neuroblastoma, Oncotarget 9 (2018) 26157–26170.
[135] I. Tadeo, M. Piqueras, D. Montaner, E. Villamon, A.P. Berbegall, A. Canete, S. Navarro, R. Noguera, Quantitative modeling of clinical, cellular, and extracellular matrix variables suggest prognostic indicators in cancer: a model in neuroblastoma, Pediatr. Res. 75 (2014) 302–314.
[136] J.R. Todd, K.A. Ryall, S. Vyse, J.P. Wong, R.C. Natrajan, Y. Yuan, A.C. Tan, P.H. Huang, Systematic analysis of tumour cell-extracellular matrix adhesion identifies independent prognostic factors in breast cancer, Oncotarget 7 (2016) 62939–62953.
[137] H.F. Tsai, A. Trubelja, A.Q. Shen, G. Bao, Tumour-on-a-chip: microfluidic models of tumour morphology, growth and microenvironment, J. R. Soc. Interface 14 (2017) 20170137.
[138] T. Ushiki, Collagen fibers, reticular fibers and elastic fibers. A comprehensive understanding from a morphological viewpoint, Arch. Histol. Cytol. 65 (2002) 109–126.
[139] M.G. Vander Heiden, R.J. DeBerardinis, Understanding the intersections between metabolism and cancer biology, Cell 168 (2017) 657–669.
[140] L. Vona-Davis, L.F. Gibson, Adipocytes as a critical component of the tumor microenvironment, Leuk. Res. 37 (2013) 483–484.
[141] B. Waclaw, I. Bozic, M.E. Pittman, R.H. Hruban, B. Vogelstein, M.A. Nowak, A spatial model predicts that dispersal and cell turnover limit intratumour heterogeneity, Nature 525 (2015) 261–264.
[142] J.C. Walrath, J.J. Hawes, T. Van Dyke, K.M. Reilly, Genetically engineered mouse models in cancer research, Adv. Cancer Res. 106 (2010) 113–164.
[143] C. Wei, C. Yang, S. Wang, D. Shi, C. Zhang, X. Lin, Q. Liu, R. Dou, B. Xiong, Crosstalk between cancer cells and tumor associated macrophages is required for mesenchymal circulating tumor cell-mediated colorectal cancer metastasis, Mol. Cancer 18 (2019) 64.
[144] Z. Werb, P. Lu, The role of stroma in tumor development, Cancer J. 21 (2015) 250–253.
[145] L. Wilde, M. Roche, M. Domingo-Vidal, K. Tanson, N. Philp, J. Curry, U. Martinez-

Outschoorn, Metabolic coupling and the Reverse Warburg Effect in cancer: implications for novel biomarker and anticancer agent development, Semin. Oncol. 44 (2017) 198–203.
[146] P.P. Wong, F. Demircioglu, E. Ghazaly, W. Alrawashdeh, M.R. Stratford, C.L. Scudamore, B. Cereser, T. Crnogorac-Jurcevic, S. McDonald, G. Elia, T. Hagemann, H.M. Kocher, K.M. Hodivala-Dilke, Dual-action combination therapy enhances angiogenesis while reducing tumor growth and spread, Cancer Cell 27 (2015) 123–137.
[147] L. Wullkopf, A.V. West, N. Leijnse, T.R. Cox, C.D. Madsen, L.B. Oddershede, J.T. Erler, Cancer cells' ability to mechanically adjust to extracellular matrix stiffness correlates with their invasive potential, Mol. Biol. Cell 29 (2018) 2378–2385.
[148] D. Yang, Y. Li, L. Xing, Y. Tan, J. Sun, B. Zeng, T. Xiang, J. Tan, G. Ren, Y. Wang, Utilization of adipocyte-derived lipids and enhanced intracellular trafficking of fatty acids contribute to breast cancer progression, Cell Commun. Signal. : CCS 16 (2018) 32.
[149] L. Yang, Y. Zhang, Tumor-associated macrophages: from basic research to clinical application, J. Hematol. Oncol. 10 (2017) 58.
[150] M. Yang, W.J. Brackenbury, Membrane potential and cancer progression, Front. Physiol. 4 (2013) 185.
[151] H. Ye, B. Adane, N. Khan, T. Sullivan, M. Minhajuddin, M. Gasparetto, B. Stevens, S. Pei, M. Balys, J.M. Ashton, D.J. Klemm, C.M. Woolthuis, A.W. Stranahan, C.Y. Park, C.T. Jordan, Leukemic stem cells evade chemotherapy by metabolic adaptation to an adipose tissue niche, Cell Stem Cell 19 (2016) 23–37.
[152] E.J. Yeo, Y.S. Chun, Y.S. Cho, J. Kim, J.C. Lee, M.S. Kim, J.W. Park, YC-1: a potential anticancer drug targeting hypoxia-inducible factor 1, J. Natl. Cancer Inst. 95 (2003) 516–525.
[153] M. Yin, S. Tan, Y. Bao, Z. Zhang, Enhanced tumor therapy via drug co-delivery and in situ vascular-promoting strategy, J. Control. Release : Off. J. Control. Release Soc. 258 (2017) 108–120.
[154] J. Yu, J. Li, Y. Chen, W. Cao, Y. Lu, J. Yang, E. Xing, Snail enhances glycolysis in the epithelial-mesenchymal transition process by targeting FBP1 in gastric cancer, Cell. Physiol. Biochem. : Int. J. Exp. Cell. Physiol. Biochem. Pharmacol. 43 (2017) 31–38.
[155] M. Zhang, J.S. Di Martino, R.L. Bowman, N.R. Campbell, S.C. Baksh, T. Simon-Vermot, I.S. Kim, P. Haldeman, C. Mondal, V. Yong-Gonzales, M. Abu-Akeel, T. Merghoub, D.R. Jones, X.G. Zhu, A. Arora, C.E. Ariyan, K. Birsoy, J.D. Wolchok, K.S. Panageas, T. Hollmann, J.J. Bravo-Cordero, R.M. White, Adipocyte-derived lipids mediate melanoma progression via FATP proteins, Cancer Discov. 8 (2018) 1006–1025.
[156] S. Zhang, X. Yang, L. Wang, C. Zhang, Interplay between inflammatory tumor microenvironment and cancer stem cells, Oncology Lett. 16 (2018) 679–686.
[157] Y. Zhang, M. Dang, Y. Tian, Y. Zhu, W. Liu, W. Tian, Y. Su, Q. Ni, C. Xu, N. Lu, J. Tao, Y. Li, S. Zhao, Y. Zhao, Z. Yang, L. Sun, Z. Teng, G. Lu, Tumor acidic microenvironment targeted drug delivery based on pHLIP-modified mesoporous organosilica nanoparticles, ACS Appl. Mater. Interfaces 9 (2017) 30543–30552.
[158] H. Zhao, Q. Duan, Z. Zhang, H. Li, H. Wu, Q. Shen, C. Wang, T. Yin, Up-regulation of glycolysis promotes the stemness and EMT phenotypes in gemcitabine-resistant pancreatic cancer cells, J. Cell Mol. Med. 21 (2017) 2055–2067.
[159] X.L. Zu, M. Guppy, Cancer metabolism: facts, fantasy, and fiction, Biochem. Biophys. Res. Commun. 313 (2004) 459–465.