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Dynamic links between mechanical forces and metabolism shape the tumor milieu

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Abstract

Cell function relies on the spatiotemporal dynamics of metabolic reactions. In all physiopathological processes of tissues, mechanical forces impact the structure and function of membranes, enzymes, organelles and regulators of metabolic gene programs, thus regulating cell metabolism. In turn, metabolic pathways feedback impacts the physical properties of cell and tissues. Hence, metabolism and tissue mechanics are dynamically intertwined and continuously interact.

Cancer is akin to an ecosystem, comprising tumor cells and various subpopulations of stromal cells embedded in an altered extracellular matrix. The progression of cancer, from initiation to advanced stage and metastasis, is driven by genetic mutations and crucially influenced by physical and metabolic alterations in the tumor microenvironment. These alterations also play a pivotal role in cancer cells evasion from immune surveillance and in developing resistance to treatments.

Here, we highlight emerging evidence showing that mechano-metabolic circuits in cancer and stromal cells regulate multiple processes crucial for tumor progression and discuss potential approaches to improve therapeutic treatments by interfering with these circuits.

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Introduction

Animal organs consist of various types of cells, including parenchymal and stromal cells such as fibroblasts, endothelial cells, and immune cells. These cells secrete soluble factors (e.g., growth factors and cytokines) and macromolecules that form the extracellular matrix (ECM), such as collagen and fibronectin. The dynamic and spatiotemporal interplay among all these components governs the physiological and pathological processes of tissues, including growth, homeostasis, and regeneration [1].

All the cells of an organism are subjected to forces, including compressive, tensile, fluid shear stress and hydrostatic pressure, which play key roles in tissue physiological and pathological processes [2]. Mechanical stimuli from the ECM activate integrins in cell-ECM adhesions, while forces transmitted through cell-cell adhesions are sensed by cadherins. These adhesive structures are linked with the cytoskeleton, which in turn interacts with enzymes, organelles and, through the LINC protein complex, with the nucleus, thus modulating their organization and function [3]. Intra/extracellular forces also impact membranes tension, activating mechanosensitive ion channels (e.g., PIEZO1) [4]. Ultimately, mechanical inputs trigger gene programs controlled by cytoplasmic/nuclear localization of mechanosensitive transcription (co)factors. These include MRTF and YAP/TAZ, key regulators of tissue growth/regeneration, and a growing list of oncogenes (e.g., missense mutant p53) and metabolic sensors (e.g., HIF1α, SREBPs, NRF2) [5–8].

Through all these mechanisms, mechanical forces impact cell metabolic pathways, which in turn feedback, regulating the physical properties of cells and tissues. Therefore, cell metabolism is dynamically intertwined with tissue mechanics, establishing "mechano-metabolic" circuits, as highlighted in recent reviews [9–11]. Growing evidence suggests that metabolic and mechanical alterations perturbing this interplay are crucial in various pathologies, including metabolic, cardiovascular, and neurodegenerative diseases, and especially cancer.

Tumor evolution, along its multistep progression, is driven by genetic and epigenetic alterations, and is tightly controlled by physical and metabolic changes in the tumor microenvironment (TME) [12,13], which also contribute to evasion from immune surveillance, and resistance to treatments [14].

Here, we review emerging evidence showing that mechano-metabolic circuits, established in cancer and stromal cells, regulate multiple processes crucial for tumor progression and resistance to therapy. We also highlight approaches that, by interfering with these circuits, could improve therapeutic strategies.

Mechano-metabolic circuits regulate ECM physical properties in the TME

In the TME, cancer cells adaptively respond to a variety of stimuli, generated at the intracellular level and by changes in the extracellular compartment, including fluctuations of metabolites levels and modifications of physical traits. These comprise increased forces exerted by cells, ECM components (solid stress) and interstitial fluid, increased stiffness (up to tenfold that of normal tissues), and tissue disorganization (e.g., cell crowding/misplacement, altered porosity) [13,15–17]. Furthermore, cancer cells contribute to TME physical changes by overgrowing, invading surrounding tissues, and modifying ECM composition, organization, and stiffness. These modifications are induced by cancer cells both directly (e.g., secretion of ECM components and collagen crosslink) and indirectly by regulating the activity of stromal cells, such as cancer associated fibroblasts (CAFs) and macrophages [18]. Emerging evidence suggests that cell metabolism and mechanical stimuli interplay within the TME, and this interaction involves key oncogenic pathways, as discussed in Box 1.

Recent findings indicate that metabolic rewiring in response to microenvironmental cues plays a crucial role

Box 1. Role of oncogenic signaling in the interplay of mechanical cues with cancer cells metabolism.

Several studies have shown that, in response to intracellular and extracellular mechanical stimuli, activation of key oncogenic pathways, such as FAK/SRC, YAP/TAZ, RAS/RAF/ERK and PI3K/AKT/mTOR regulates, in cancer cells, multiple processes, including survival and proliferation, and dissemination and chemoresistance [16,60,61]. Furthermore, these oncogenic pathways have been shown to reprogram, in response to different stimuli (including physical cues) cancer cells metabolic pathways, such as energy, amino acids and lipids, thus supporting tumor progression (e.g., through biomass production during cell proliferation) [62].

For instance, in epithelia, adhesion to ECM is important for cell survival and proliferation, and cells detaching from ECM loose integrin-based cell survival signals and undergo metabolic changes leading to increased ROS, with consequent cell death and apical extrusion. Accumulating studies have shown that, in oncogene-expressing cells, detachment from the ECM is associated with induction of antioxidant response, which supports cell survival [63,64]. For example, in crowded RAS, SRC and ERBB2-transformed epithelia, extruded cells have been recently shown to evade ferroptosis and become able to grow as multilayer [65].

Also, ECM stiffness has been shown to play a key role in the activation of oncogenic pathways and consequent rewiring of cancer cell metabolism. YAP/TAZ activation by ECM stiffening was shown to foster the growth of glioblastoma cells through regulation of glucose metabolism, leading to production of intermediates for biomass production [66], and of BC cells, through induction of autophagy [67], and upregulation of dNTP biosynthetic enzymes [68].

Notably, studies of the mechanisms regulating the oncogenic activity of missense mutant forms of the p53 transcription factor (mutp53), which are highly prevalent in most cancers, unveiled a complex interplay of oncogenic signaling with mechanical cues and metabolism [69–71]. Once stabilized and activated in response to different stimuli (e.g., DNA damage, hypoxia, oncogenic stress), p53 controls a complex pathway that, by regulating multiple processes (e.g., cell cycle arrest, DNA repair, cell death, and metabolism) plays a pivotal role in the maintenance of genome integrity and tumor suppression [62,72]. p53 is encoded by the *TP53* gene, and mutp53 forms lose oncosuppressive functions and, upon stabilization and activation in response to different stressful stimuli, can also acquire properties that enable them to rewire cancer cell transcriptome, proteome, secretome and metabolism, thus fostering tumor progression [62,73]. Within tumors, mutp53 has been reported to accumulate mainly in fibrotic regions [74], which display altered physical traits. Interestingly, in BC cells, mutp53 was shown to sustain, at odds with wild-type p53 [75], the mevalonate pathway (MVP), and this promoted, through geranylgeranyl pyrophosphate (GGPP) production, the activation of RhoA and actomyosin-dependent mechanotransduction [71,76–78]. This in turn promoted, in response to ECM stiffening, HSP90 activation by the HDAC6 deacetylase, and thus mutp53 stabilization. These data suggest that mechanical stimuli from the TME play a key role in mutp53 accumulation. Furthermore, in BC models, mutp53 was recently shown to rewire the secretome, through HIF1α the induction of the microRNA miR-30d, thus promoting ECM stiffening and CAFs activation in both primary secondary tumor sites, which favored development of metastases. In turn, ECM stiffness increased miR30d expression and cancer cell secretion, thus establishing a pro-metastatic vicious cycle, which could be blocked by inhibiting miR30d [73].

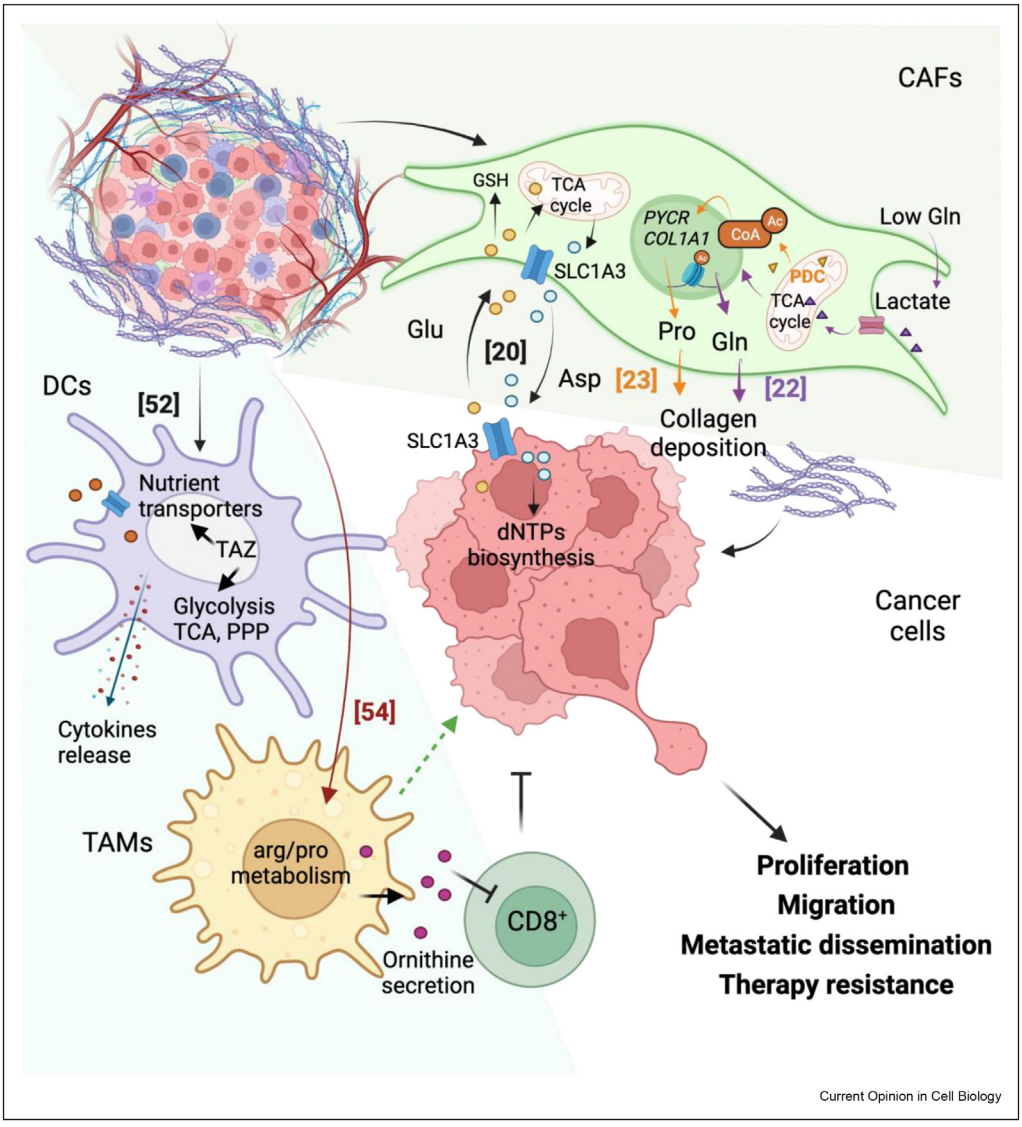
Importantly, further studies in BC models also demonstrated that metabolic rewiring in BC cells impacted the activity of YAP/TAZ. Recently, activation of the glucocorticoid receptor, a key regulator of metabolism, was shown to activate YAP/TAZ, leading to increased fibronectin deposition and consequent mechanosignaling, and this promoted BC cells stemness, growth and chemoresistance [79]. Also, the mutp53/MVP/RhoA axis was shown to activate YAP/TAZ, with consequent increased BC cells stemness and proliferation [69].

Collectively, these studies unveiled that oncogenic signaling plays a key role in the dynamic link between mechanical cues and metabolism, with important clinical implications. Analysis of patients' datasets displayed that, in BCs with *TP53* missense mutations, transcriptional signature of mutp53 activity positively correlated with signatures of MVP and YAP/TAZ activation [69,70]. Furthermore, inhibitors of the MVP rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA-reductase, such as statins, could block ECM mechanosignalling, providing a valuable approach to interfere with mutp53 stabilization and YAP/TAZ activation [70].

in modulating CAFs activity. Specifically, ECM stiffening was shown to promote pancreatic adenocarcinoma (PDAC) progression by inducing, in pancreatic stellate cells (PSCs), AMPK-dependent downregulation of lipid biosynthesis [19], a pathway crucial for cell fate determination [8].

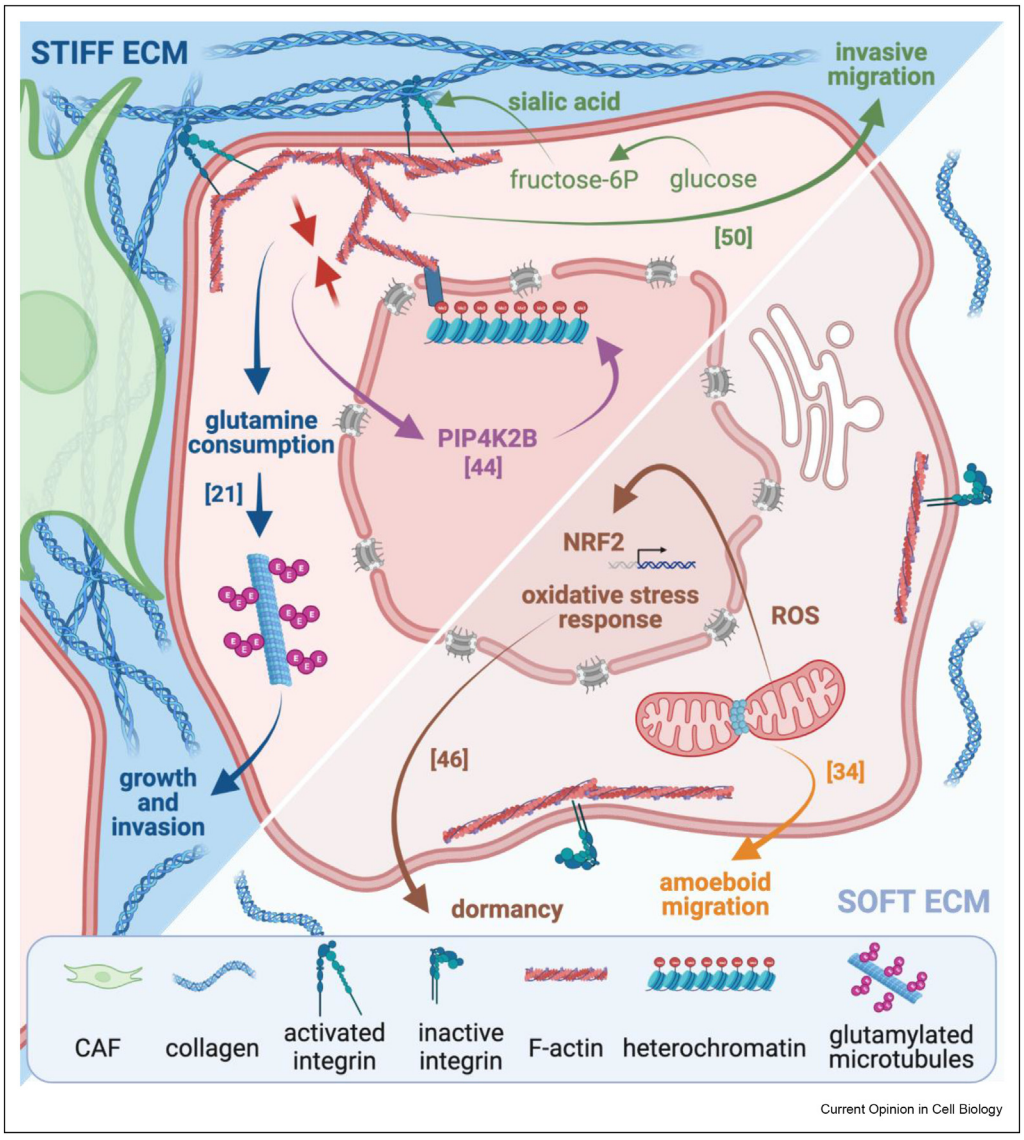
More recently, studies in breast, skin, and head/neck cancer models showed that high ECM stiffness promoted, in both CAFs and cancer cells, YAP/TAZ-dependent upregulation of aspartate/glutamate SLC1A3 antiporter and glutaminase 1 (GLS1) [20] (Figure 1). This led, in CAFs, to increased uptake and

Figure 1



Emerging mechanisms of the interplay between ECM mechanical stimuli and stromal cell metabolism. Upper right: in response to high ECM stiffness, SLC1A3 antiporter and GLS1 expression are upregulated in CAFs, resulting in increased uptake and production of glutamate, which was used to produce GSH, thus supporting redox homeostasis and ultimately ECM remodeling. Glutamate is also used to produce aspartate, which is released and uptaken by cancer cells. This, together with increased glutamine catabolism fuels nucleotide synthesis and subsequent cancer cell proliferation [20]. Also, in response to decrease of glutamine levels, the uptake of lactate is enhanced in CAFs, and this feeds TCA anaplerosis, with consequent increase of acetyl-CoA. This is then utilized for *COL1A1* promoter acetylation, with consequent increase of collagen deposition [22]. Acetyl-CoA is also used by the EP300 histone acetyltransferase, for H3K27 acetylation of the *PYCR1* gene promoter, with consequent upregulation of PYCR1 and thus production of proline, which is used for collagen biosynthesis [23]. This circuit supports tumor growth and metastasis. Lower left: in, dendritic cells (DCs), high ECM stiffness causes reprogramming of the flux of glycolysis, TCA cycle and pentose phosphate pathway, empowering DCs anti-tumor activity, as indicated by production of proinflammatory cytokines (e.g., IL1α and β, IL6, IL12, TNF) [52]. In macrophages, high ECM stiffness causes reprogramming of arginine/proline metabolism, leading to ornithine secretion, which impaired $CD8^+$ T cells anti-tumor activity [54]. Image created with BioRender.

Figure 2



Emerging mechanisms of the interplay between ECM mechanical stimuli and cancer cell metabolism. Upper left: high ECM stiffness promotes PIP4K2B-dependent chromatin compaction [44] and redirection of glucose metabolism towards production of sialic acid. This, in turn, modifies integrins structures, leading to their sustained activation and consequent increased metastatic migration of BC cells to the lung [50]. In addition, in BC cells, high ECM stiffness induces glutamine consumption, with consequent increase of glutamylation, and thus stabilization, of microtubules. This promotes with cell proliferation and invasive migration [21]. Lower right: low ECM stiffness promotes mitochondrial fission, with ROS production and induction of NRF2-dependent antioxidant response, promoting metastatic cell dormancy and chemoresistance [46]. In amoeboid cells, loose adhesion to ECM was associated with increased mitochondrial fission and decreased OXPHOS [34]. Image created with BioRender.

production of glutamate, which was used to produce GSH, thus supporting redox homeostasis and ultimately ECM remodeling. Glutamate was also used to produce aspartate, which was released and uptaken by cancer cells. This, together with increased glutamine catabolism, fueled nucleotide synthesis and subsequent cancer cell proliferation. In a follow-up study, the authors further showed that, in BC cells, ECM stiffening-induced glutamine consumption resulted in increased microtubule glutamylation and stabilization, promoting cell proliferation and invasive migration [21] (Figure 2). The mechanism by which glutamylated microtubules could impact cell function remains to be investigated. Nevertheless, in BC mouse models, pharmacological inhibition of GLS1 could impede tumor progression and metastasis, suggesting that mechano-metabolic circuits

involving glutaminolysis may represent a vulnerability in BC.

Moreover, recent evidence from PDAC and BC models has shown that, in the TME, low availability of glutamine, which is required for collagen biosynthesis, promoted CAFs metabolic reprogramming, leading to increased lactate uptake [22] (Figure 1). This triggered pyruvate carboxylase (PC) activation, feeding TCA anaplerosis, resulting in glutamine *de novo* synthesis, and elevated acetyl-CoA levels. This led to H3K27 acetylation and activation of the *Collagen-I* (*COL1A1*) promoter. The subsequent increase in collagen deposition promoted tumor progression, which could instead be mitigated by PC knockout in CAFs. Another study in BC models further demonstrated that, in CAFs, high activity of the pyruvate dehydrogenase complex (PDC) led to increased acetyl-CoA [23] (Figure 1). This was utilized by the EP300 histone acetyltransferase to acetylate H3K27 in the promoter of *COL1A1* and *Pyrroline-5-carboxylate reductase 1* (*PYCR1*), which encodes an enzyme required for biosynthesis of proline, an amino acid (AA) crucial for collagen synthesis. The upregulation of collagen production resulting from these changes supported tumor growth and metastasis, which could be both suppressed by knocking down PYCR1 in CAFs. Interestingly, in tumor cells, proline metabolism is also regulated by ECM rigidity, as recently demonstrated in lung cancer models [24]. In tumor cells, high ECM stiffness promoted the localization of the integrin activator Kindlin-2 at focal adhesions and in mitochondria. There, Kindlin-2 bound and increased stabilization and activity of PYCR1. These studies suggest that pharmacological inhibition EP300 and PYCR1 could disrupt mechano-metabolic circuits involved in reprograming of pyruvate and proline metabolism. Such approach holds promise as an effective therapeutic strategy.

Mechano-metabolic circuits regulate membrane and organelles' shape in migrating cancer cells

The lethal consequences of malignant tumors are primarily attributed to spreading to distant sites and formation of metastases, which often exhibit resistance to therapeutic interventions. This complex process involves the initial invasion of neighboring tissues, dissemination, and subsequent colonization of secondary sites. Each step necessitates cancer cells to adapt to physically and metabolically changing microenvironments [25,26].

For instance, high extracellular glucose levels have been demonstrated to increase, in BC cells glycolysis-dependent cAMP production, and thus cell stiffness and contractility, through RhoA-ROCK-Myosin-II activation [27]. In other studies, high ECM stiffness was shown to promote the invasive migration of BC cells by regulating glycolysis and OXPHOS [28–31]. Furthermore, upon mechanical stimulation, PDAC cells gain migratory ability, through upregulation of ATP production used for actomyosin contraction [32].

The type and magnitude of mechanical forces experienced during migration play a pivotal role in the regulation of cancer cell metabolism. Cancer cells can move either as adhering clusters (as seen in collective migration during tissue morphogenesis and wound healing processes) or individually, through mesenchymal or amoeboid migration. Leader cells driving collective migration and mesenchymal migrating cells exert substantial and energy-demanding traction forces [33]. Conversely, amoeboid cells adhere loosely to the ECM, and move via pseudopodia or lamellipodia. Interestingly, a recent study employing 3D cell culture models of melanoma and fibrosarcoma revealed that migration modality is controlled by mitochondrial and AMPK activity [34]. Cells performing mesenchymal migration displayed increased mitochondrial fusion and OXPHOS, with low AMPK activity, whereas amoeboid cells exhibited increased mitochondrial fission and decreased OXPHOS, coupled with high AMPK activity (Figure 2). This study suggests that, under stressful conditions, migrating cancer cells may adopt the low energy-demanding amoeboid modality, enabling dissemination and the formation of metastasis.

During migration, cancer cells adapt their structure and shape to physical constraints, a process influenced by membrane fluidity. This, in turn, depends on phospholipid fatty acyl chains saturation and cholesterol content [35]. Notably, a recent study showed that, in liver cancer cells, the fatty acid desaturase SCD1 was upregulated in response to high ECM stiffness. This led to increased plasma membrane fluidity, consequently promoting invasive migration [36].

Furthermore, migrating cells undergo dynamic changes in organelles structure and shape to cope with physical constraints. The nucleus is the stiffest organelle, and maintenance of its structure is critical to preserve genome function and integrity [37]. Accumulating evidence indicates that, in response to mechanical stimuli, the regulation of nuclear lamina structure plays a crucial role in the maintenance of nuclear integrity and chromatin organization [38–43]. Interestingly, a very recent study has provided evidence that, in BC cells, the metabolism of phosphatidylinositol (PI), key mediator of many signaling pathways, regulates nuclear mechanics, and this impact cell motility [44] (Figure 2). Specifically in response to ECM stiffening, the nuclear kinase PIP4K2B promoted heterochromatin compaction (a process previously demonstrated critical for nuclear stiffness [4]), cell mechanics and motility. However, further work will be required to validate this mechanism *in vivo*.

Table 1

Metabolic pathways and their interplay with physical traits in cancer.

Molecules	Function	Phenotype	Ref.
Amino acids			
Proline	Collagen synthesis in CAFs	BC growth and lung metastases	[23]
	Collagen catabolism and OXPHOS induction	PDAC growth	[80]
Glutamine	Collagen synthesis and ECM remodelling	Increased CAFs activity	[20]
Glutamate	Microtubule glutamylation	Enhanced invasive migration and metastasis	[21]
Lipids			
GGPP	Membrane localization and activation of small GTPases, i.e., RhoA, and increased mechanosignaling	YAP/TAZ and mutp53 activation, leading to tumor growth	[69,70]
Phosphatidylinositol	Chromatin compaction and nuclear envelope tension	BC cells cytoskeleton remodeling and motility	[44]
Glucose			
Fructose-6-phosphate	Increased sialylation of αVβ3 integrins	BC cells migration and dissemination in the lungs	[50]
Lactate	Collagen synthesis and deposition by CAFs	BC and PDAC growth	[22]
Pyruvate	Collagen hydroxylation and crosslinking in the lung	Outgrowth of BC metastases	[49]
α-ketoglutarate	Collagen hydroxylation and crosslinking in the lung	Outgrowth of BC metastases	[49]
D-2-hydroxyglutarate	Impaired collagen maturation and basement membrane alterations	Glioma progression	[81]
Glucose uptake and glycolysis	Increased energy and contractility	BC cells migration	[31]
Metabolic kinases and enzymes			
AMPK	Reduction of lipid biosynthesis and activation of PSCs	PDAC growth	[19]
	Decreased OXPHOS and increased mitochondrial fission	Increased amoeboid migration in melanoma	[34]
mTORC1	Loss of mTORC1 induces integrins and ECM internalization	PDAC invasive cell migration	[82]
SCD1	Increased membrane fluidity	Invasive migration of liver cancer cells	[36]
Others			
OXPHOS	Increased ATP production upon ECM stiffness	Invasion and metastasis	[32]
Creatine-phosphagen system	Increased ATP production upon ECM stiffening	Invasion and metastasis	[32]
Mitochondrial fission	Mitochondrial ROS production, NRF2 activation and GSH metabolism	Resistance to oxidative stress and chemotherapy in dormant BC cells	[46]
	Low energy state	Increased amoeboid migration	[34]

Interplay between mechanical cues and metabolism regulates metastatic cell dormancy and outgrowth

Cancer cells disseminated at secondary sites often enter in a dormant state, remaining quiescent and resistant to treatments, for even long time, before reawakening and giving rise to overt metastases [45]. A recent study explored the influence of ECM stiffness on disseminated BC cells, which tend to preferentially colonize soft tissues, such as the lung and the brain [46]. In the mouse lung, a low ECM stiffness environment promoted mitochondrial fission in dormant BC cells (Figure 2). This caused the production of reactive oxygen species (ROS) and concomitant activation of NRF2, thereby enhancing resistance to oxidative stress and chemotherapy. Similarly, in BC cells tha colonized the mouse brain, mitochondrial fission was recently demonstrated to maintain redox homeostasis [47]. These cells displayed increased uptake and oxidation of fatty acids released by astrocytes. Interestingly, a recent study revealed that the outgrowth of these cells was facilitated by the induction of *de novo* fatty acid biosynthesis [48], a pathway commonly activated in proliferating cells within a soft ECM environment [7,8]. However, determinants influencing the rewiring of fatty acid metabolism in these cells remain to be investigated.

Recent studies also provided evidence that rewiring of metabolic pathways could regulate metastatic cells growth by impacting the structure/function of ECM and integrins. For example, the growth of metastatic BC cells in the mouse lung was found to depend on pyruvate uptake, which increased α-ketoglutarate production [49]. This in turn led to activation of collagen prolyl-4-hydroxylase and thus deposition of hydroxylated collagen. Furthermore, in mouse models of BC, metastatic cells displayed heterogeneous levels of phosphoglycerate dehydrogenase (PHGDH). In cells with low PHGDH, fructose-6-phosphate was redirected from glycolysis to sialic acid synthesis. This metabolic shift resulted in sialylation and activation of αVβ3 integrins, thus promoting invasion and metastasis formation [50] (Figure 2). This mechanism might also involve interactions with stromal cells, as suggested by the observation that low PHGDH cells were predominantly localized in vascularized regions.

Interplay between mechanical cues and metabolism regulates immune cells function in the TME

The TME comprises a diverse array of resident and infiltrating immune cells populations, whose functions are modulated by different stimuli, including metabolic and physical changes [51]. These immune cells include antigen presenting dendritic cells (DCs), crucial for anti-tumor immune reactions, as well as B and T lymphocytes, and myeloid cells, with pro- or anti-tumor activities.

Notably, a recent work in lymphoma models has revealed that high ECM stiffness enhanced, the glycolytic flux, TCA cycle and pentose phosphate pathway in DCs, in a TAZ- and PIEZO1-dependent manner [52] (Figure 1). This, in turn, empowered DCs anti-tumor activity, as indicated by production of proinflammatory cytokines.

Another study recently demonstrated that, in melanoma cells, high membrane cholesterol content led to cortical softening, impairing the cytotoxic activity of T cells, which requires the generation of high forces during cell-cell interaction [53]. Conversely, treatment with methyl-β-cyclodextrin, which depletes cholesterol, increased cancer cell cortical stiffness, enhancing T cell killing activity and susceptibility to adoptive T cell therapy *in vivo*.

Furthermore, in a preprinted study in mouse BC models, collagen biosynthesis and ECM stiffening have been proposed to foster tumor progression by regulating arginine/proline metabolism in macrophages. This led to ornithine secretion, which impaired $CD8^+$ T cells anti-tumor activity [54] (Figure 1). These findings suggest that the mechanoreponsiveness of proline metabolism could play a key role not only in cancer cells and CAFs, as discussed above, but also in other cell types within the TME, such as myeloid cells.

Conclusions

Accumulating evidence has shown that, in the tumor ecosystem, cells experience varying levels of oxygen and nutrients in different phases of cancer development, progression and metastasis. Moreover, distinct activities of cancer and stromal cell subpopulations (e.g., CAFs and macrophages) contribute to the mechanical properties of TME. The studies highlighted above (and summarized in Table 1) suggest that complex and dynamic interconnections between mechanical cues and metabolism shape the TME in physically and metabolically heterogeneous subcompartments [55]. These subcompartments can act as specialized niches that impact tumor cell growth, escape from immune surveillance, and response to treatment. To understand this level of heterogeneity, it is essential to combine spatial multi-omics (transcriptomics, proteomics, metabolomics [56]) with advanced imaging techniques that assess physical traits (e.g., Brillouin microscopy and second harmonic generation [57,58]). Moreover, the development of *ex vivo* models that recapitulate the complexity of the human TME will be crucial [59]. All these approaches may uncover mechano-metabolic circuits with potential prognostic value. Elucidating the determinants of these circuits could unveil metabolic and mechano-targets, whose combined inhibition could improve current therapeutic strategies to effectively blunt tumor growth and metastasis.

Author contribution

R.B., F.N. and G.D.S. wrote the manuscript. R.B. and F.N. prepared the Figures.

Declaration of competing interest

Nothing declared.

Data availability

No data was used for the research described in the article.

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