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Mechanical regulation of mitochondrial morphodynamics in cancer cells by extracellular microenvironment

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ABSTRACT

Recently, it has been recognized that physical abnormalities (e.g. elevated solid stress, elevated interstitial fluid pressure, increased stiffness) are associated with tumor progression and development. Additionally, these mechanical forces originating from tumor cell environment through mechanotransduction pathways can affect metabolism. On the other hand, mitochondria are well-known as bioenergetic, biosynthetic, and signaling organelles crucial for sensing stress and facilitating cellular adaptation to the environment and physical stimuli. Disruptions in mitochondrial dynamics and function have been found to play a role in the initiation and advancement of cancer. Consequently, it is logical to hypothesize that mitochondria dynamics subjected to physical cues may play a pivotal role in mediating tumorigenesis. Recently mitochondrial biogenesis and turnover, fission and fusion dynamics was linked to mechanotransduction in cancer. However, how cancer cell mechanics and mitochondria functions are connected, still remain poorly understood. Here, we discuss recent studies that link mechanical stimuli exerted by the tumor cell environment and mitochondria dynamics and functions. This interplay between mechanics and mitochondria functions may shed light on how mitochondria regulate tumorigenesis.

1. Introduction

In a last decade, a number of research has demonstrated that mechanical forces play a pervasive role in living organisms and exert a direct influence on cell functions [1–4]. Importantly, it is evident now that mechanical forces regulate plenty of biological phenomena, spanning from cell growth and specialization to maintaining tissue equilibrium and orchestrating inflammatory reactions [2,5-8].

In the past, cancer was predominantly viewed as a cellular disease, driven by genetic mutations regulating cell growth, specialization, and apoptosis [9]. Recently, it has become clear that the microenvironment of cancer cells plays a significant role in tumor development, migration, metastasis, metabolic activity, evasion of the immune system, and response to treatments [5-7,9-11]. It has been postulated that main four physical factors largely contribute to tumor progression and resistance to chemotherapy, namely elevated solid stresses (compression and tension), elevated interstitial fluid pressure, altered material properties (e.g., increased tissue stiffness), and altered physical microarchitecture [9]. During expiation of tumors, tumor cells distort nearby tissues both physically and biochemically. Such distortion leads to structural and functional alterations of the tumor surrounding. Thus, mechanotransduction plays a crucial role in shaping tumors and altering their functionality [5-7,9-11]. Importantly, mechanics of the tumor surrounding regulates metabolic reprogramming of cancer cells. Metabolic reprogramming is integrated into the adaptive processes of cancer progression, influencing and, in turn, altering the extracellular matrix (ECM) and its mechanical environment [6,12].

Cellular metabolism undergoes critical reprogramming in cancer, representing a fundamental hallmark necessary for sustaining elevated growth and proliferation of cancerous cells [6,12,13]. It has become evident that cancer's metabolic reprogramming encompasses a diverse array of metabolic pathways [6,12,13]. This complex metabolic shift supports rapidly proliferating cancer cells with energy and essential building blocks for macromolecular biosynthesis, concurrently supporting altered redox homeostasis [6,12,13]. In addition to its role in energy production and biosynthesis, metabolic reprogramming in cancer plays a role in signaling by accumulating certain metabolites that act as oncometabolites [14]. Current research highlights that it is very

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challenging to identify a unified metabolic landscape across cancers [6,12,13]. It is clear that tumors originating from different tissues exhibit distinct metabolic features/profiles. Furthermore, these metabolic profiles dynamically evolve during the progression of the tumor [6,12,13].

Mitochondria is a crucial regulator of metabolism. In fact, it was proposed that there are strong interconnections between mitochondrial morphodynamics, mechanics, and metabolism [15,16]. Additionally, mitochondria are highly dynamic organelles. Generally, mitochondria are capable of sensing and integrating of variety of mechanical, physical, and metabolic signals [15–18]. Intracellular transmission of such physical cues results in changes in mitochondria dynamic and metabolic functions [15–18]. The process of mitochondria fission and fusion impacts mitochondrial function and regulates the equilibrium between mitochondrial energy production and execution of different cell death programs [15–18]. Under normal physiological conditions, the processes governing mitochondrial dynamics are strictly regulated but often become deregulated in various tumors. Factors such as mitochondrial protein homeostasis, transcriptional regulation, and posttranslational modification contribute to the control of mitochondrial dynamics [15–18]. Importantly, mounting evidence suggests that dysregulated mitochondrial dynamics significantly affects tumor cell proliferation, metastasis, resistance to therapeutic interventions and tumor microenvironment (TME) modulation [15–18]. It is not surprising that recently, cell metabolism regulated by mitochondria dynamics has come into focus as a process influenced by mechanical signals during tumorigenesis. Although the general structure of metabolic pathways within a cell is well-established, the regulation of metabolic rewiring in this context remains elusive. Specifically, our understanding of interconnections between cell mechanics and mitochondria regulated metabolism is still rather fragmented. This review focuses on the evolving interplay between cellular mechanics and mitochondria dynamics during tumor development and progression. Our objective is to introduce innovative ideas and concepts that contribute to uncovering novel intersections between tissue mechanics, mechanotransduction, metabolism and cancer.

2. Overview of mechanical alterations and metabolic reprogramming during cancer progression

Before analyzing impact of mechanics on mitochondria functions during cancer progression, we need to briefly discuss main mechanical alterations and metabolic changes in cancer. It is widely accepted that metabolism is switched to glycolysis followed by pyruvate conversion to lactate over pyruvate oxidation and oxidative phosphorylation (OXPHOS) in many tumors [19]. This metabolic switch, even in the presence of oxygen, named “the Warburg effect”, is originated from elevated uptake of glucose and upregulation of glucose transporters in the vast majority of cancer types [19,20]. Although substrate phosphorylation is energetically unfavorable over OXPHOS, its inefficiency is compensated or even overcompensated by elevated glycolysis which, on the other hand, does not predispose deprivation of OXPHOS [19,20]. The primary reason for elevated glycolysis in cancer cells may be metabolic support (serine and glycine synthesis, production of NADPH and nucleotides) and cell signaling (maintaining the balance of reactive oxygen species (ROS)), which is essential for growth, proliferation, survival of tumor cell and invasive tumor growth [13,19]. For example, it was found that for active migration of prostate and breast cancer cells ATP production by mitochondria alone is not enough. Thus, cancer cells actively use glycolysis to support migration [21]. Further, plasminogen activator inhibitor 1 (PAI1), is known to be upregulated in migratory cancer cells, and has been shown to enhance glycolysis in triple-negative breast cancer cells [22].

Interestingly, it was recently noted that there is significant metabolic heterogeneity in tumors [23]. Differences in metabolic activity among cancer cells within a primary tumor play a pivotal role in governing both the overall efficiency of metastasis and the specific targeting of organs [13]. Overall, one can clearly see that cancer cells modify their metabolism in response to changing surrounding factors and cues within the tumor.

It is well known that the ECM during cancer progression undergoes reorganization, becoming deregulated and disorganized comparing to normal tissues [24]. Generally, such ECM reorganization results into tissues stiffening [24]. In fact, increased tissue stiffness has been well recognized as major mechanical alteration in tumors [9]. Stiffness is utilized in clinical routine as a diagnostic marker and a prognostic factor of tumor development [25–28]. Moreover, cell stiffness of numerous malignant cancer types has been shown to be significantly higher in comparison with the stiffness of benign tumors, e.g. in the breast, pancreatic, liver and prostate [29–32]. A mounting body of evidence suggests that stiffness of the microenvironment plays a crucial role in regulating various functions and traits of cancer cells, e.g. proliferation, angiogenesis, metabolism, invasion, and migration and metastasis (for review see [9] and references therein).

During cancer progression perturbations in physical cues are associated not only with stiffness. These include solid stresses (e.g. compressive, tensile, and shear) are also elevated in a number of tumors [9]. The proliferation of cancer leads to the accumulation of cells within the tissue. This in turn gives rise to a natural competition amongst the cell populations for both nutrients and available space [9]. In the context of tumorigenesis, this phenomenon becomes crucial as cancer cells invade new areas by causing damage and death to the normal surrounding cells [33]. The mechanical forces of compressive and tensile stress, arising from the dysregulated growth of cell layers, are proposed as a potential driver of cell competition [9].

Further, cancer progression is accompanied with significant changes in osmolytes and vasculature, that in turn lead to elevated interstitial fluid pressure [9]. In normal tissues blood income and release is maintained by balanced vasculature (e.g. arteries, veins, lymphatic vessels) leading to near zero interstitial fluid pressure in most organs [9]. During tumor progression this balance is dysregulated by leaky vessels and a compromised drainage system of lymphatic vessels. These factors can lead to high interstitial fluid pressure [9].

Overall, altered tumor microenvironment and mechanical constraints, force cancer cells to adapt both mechanically and metabolically to survive, migrate and proliferate. A crucial part of such adaptation is metabolic reprogramming of cancer cells that also reciprocally changes the ECM and the mechanical environment [9]. For example, the stiff tumor ECM of pancreatic cancer was found to induce yes-associated protein (YAP)-mediated upregulation of cytoplasmic creatine kinase B (CKB) resulting in increased phosphocreatine production [34]. In turn, increased phosphocreatine production leads to elevation of ATP via creatine-phosphagen ATP recycling, providing a source of energy for cancer cells distinct from mitochondria [34]. Ultimately, the phosphagen system and CKB promoted directed migration of cells, which in turn resulted in increased pancreatic cancer cell ECM invasion and chemotaxis [34]. Further, the same study found that during pancreatic ductal adenocarcinoma progression CKB is overexpressed, promoting metastasis [34]. Increased stiffness of ECM in non-small-cell lung carcinoma has been associated with elevated proline metabolism and cell proliferation [35]. Interestingly, kindlin-2 (a focal adhesion component) was shown to increase proline synthesis by upregulating pyrroline-5-carboxylate reductase 1 (PYCR1) [35]. Further, it was found that elimination of kindlin-2 in lung adenocarcinoma significantly decreased PYCR1 and proline levels, leading to a notable reduction in fibrosis [35]. Importantly, elimination of kindlin-2 also promoted substantial inhibition of tumor growth and a decrease in the mortality rate [35]. Further, uptake of pyruvate in breast cancer was found to affect the tricarboxylic acid (TCA) cycle increasing the production of α-ketoglutarate [36]. In turn, α-ketoglutarate leads to activation of the enzymatic activity of collagen prolyl-4-hydroxylase resulting in ECM remodeling [36]. Blocking pyruvate metabolism proved effective in hampering collagen hydroxylation, thereby impeding the growth of lung metastases

derived from breast cancer in various mouse models [36]. Those examples illustrate that tissue stiffness dramatically rewires the metabolism of cancer cells. Concomitantly, rewired metabolism leads to changes in tissue mechanics.

Summarizing, physical cues play an important role in tumorigenesis and have been found to drive major hallmarks of cancer [9,19]. ECM in tumors displays disorganized and aberrant structure resulting in the exertion of distinct mechanical cues compared with normal ECM [9,19,24]. Emerging evidence suggest that mechanical forces modulate metabolism of cancer cells resulting in control of crucial functions, e.g. proliferation, survival, migration and metastasis [6,8,10-12]. In fact, cancer cells display significant metabolic reprogramming because of adaptation to aberrant mechanical forces compared to normal cells (Fig. 1) [6,8,10-12].

3. Mitochondrial dynamics in cancer

Mitochondria exhibit remarkable plasticity and dynamism, playing a crucial role in cellular metabolism, stress responses, and the maintenance of homeostasis. These organelles serve as a central intracellular point for essential biochemical activities like ATP production, fatty acid synthesis, the generation of intracellular reactive oxygen species (ROS), OXPHOS, thermogenesis, and calcium homeostasis [18,37,38]. During metabolic processes mitochondria produce signal intermediates playing a crucial role in regulating cellular function and phenotype [39]. Specifically, mitochondrial reactive oxygen species (mt-ROS) are essential for the regulation of intracellular signal transduction pathway of inflammatory responses [39]. Importantly, dysfunctional mitochondria are intricately linked to various diseases and pathologies, such as neurodegenerative conditions, metabolic disorders, and cancers. These conditions are broadly characterized by compromised mitochondrial function [18,40,41].

It is well established that mitochondria constantly change their morphology and activity undergoing the processes of fission, fusion, mitophagy and transport cycles [18,40,41]. These processes regulate and control morphology, quality, quantity and distribution of mitochondria and function (Fig. 2) [18,40,41]. Recently, a novel mechanism of mitochondria quality control (mitocytosis) during cellular migration was described [42]. Migrating cells utilize specific organelles, migrasomes, to excrete damaged mitochondria and this clearance mechanism

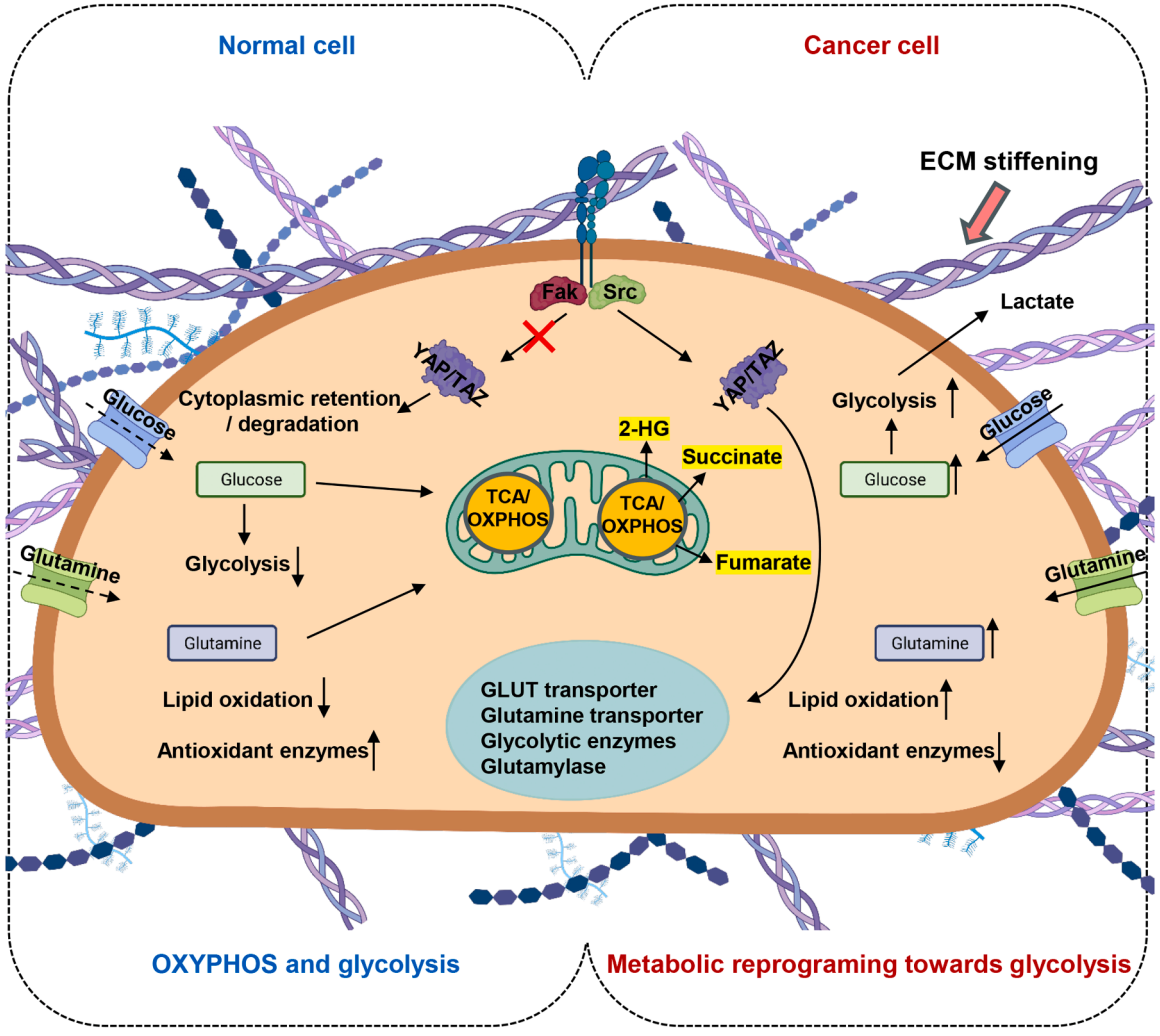

Fig. 1. Metabolic reprogramming in cancer cells. In normal tissues ECM suppresses activity of YAP and TAZ protein, resulting into their cytosol retention and/or proteolytic degradation. Normal cells predominantly metabolize glucose to pyruvate, followed by oxidation through the TCA and the OXPHOS process in mitochondria. In cancer aberrant ECM stiffness leads to YAP/TAZ activation leading to metabolic reprogramming, that includes altered glucose and glutamine metabolization. The metabolism is shifted towards conversion of glucose to lactate. The TCA cycle is biased by glutamine and glucose metabolic products, which in turn leads to the enhanced accumulation of the oncometabolites, such as fumarate, succinate and 2-HG. ECM: extracellular matrix; OXPHOS: oxidative phosphorylation; YAP: yes associated transcriptional regulator; TAZ: tafazzin, phospholipid-lysophospholipid transacylase; TCA: tricarboxylic acid cycle; 2-HG: 2-hydroxyglutarate; Fak: protein tyrosine kinase 2; Src: SRC proto-oncogene, non-receptor tyrosine kinase. Created with BioRender.com.

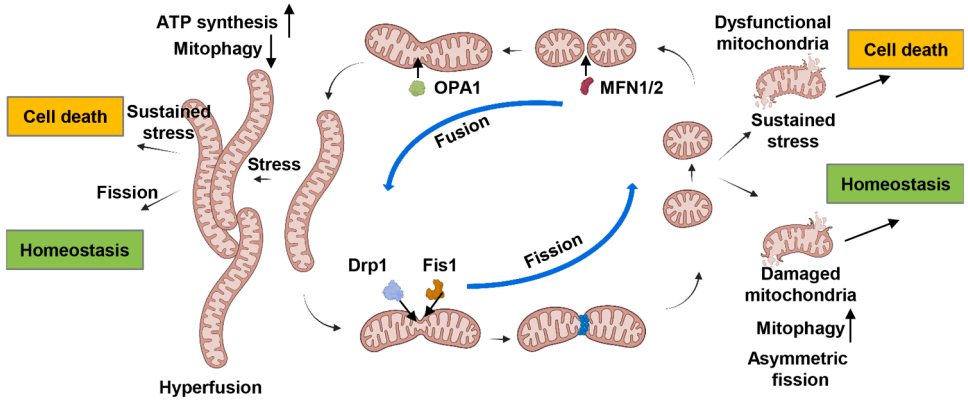

Fig. 2. Scheme of mitochondrial fission and fusion. The main fusion factors, that interact with the inner and outer membranes of mitochondria, are Opa1, MFN1, and MFN2. Drp1 is a major regulator of fission. Drp1 interacts with the outer membranes of mitochondria, promoting their division. Drp1: dynamin-related protein 1; MFN1/2: mitofusin 1/2; Opa1: optic atrophy protein 1; Fis1: protein fission 1. Created with BioRender.com.

has an impact on cell viability [42]. Damaged components of mitochondria can be cleared away via the process of mitochondrial dynamics. Seriously damaged dysfunctional mitochondria are typically eliminated through mitophagy, preventing potential cellular harm [18,43]. Optimal mitochondria function in healthy cells requires well balanced mitochondrial dynamics [44]. In summary, fission plays a key role in maintaining mitochondrial quality by eliminating damaged or dysfunctional mitochondria, particularly during intense cellular stress that may lead to apoptosis. Conversely, fusion supports the mixing and exchange of intramitochondrial contents between mitochondria, contributing to the preservation of mitochondrial function [18,43].

Recent studies suggest that mitochondrial fission and fusion processes are deregulated in cancer [18,45]. We summarized major regulators of mitochondria dynamics and their association with cancer progression in Table 1. From this table it is clear that mitochondrial dynamics regulators play a critical role in tumorigenesis and cancer progression in different cancer types since aberrant expression of key regulators of mitochondrial dynamics associated with cancer leads to dramatic functional consequences often connected with increased proliferation, migration, invasion and survival of cancer cells (Table 1). During tumorigenesis and cancer progression mitochondria actively play a crucial role in bioenergetic functions, calcium homeostasis, cancer anabolism, redox regulation, gene transcription, and regulation of essential cell functions [18,45]. Furthermore, the optimal functioning of immune processes relies on the efficient metabolism of mitochondria within immune cells, suggesting that targeting mitochondrial dynamics holds promise as a potential therapeutic approach for combating cancer [46].

Cellular dysfunction is characterized by uncontrolled cell growth, disrupted cell cycle regulation, and abnormalities in programmed cell death are widely recognized distinctive features of cancer [47]. Mitochondrial dynamics play a crucial role in these processes. In various types of cancer, such as lung cancer, metastatic breast cancer, glioblastoma, neuroblastoma, colorectal cancer, pancreatic cancers, and melanoma, cancer cells often display fragmented mitochondria (for review see [15] and references therein). This phenotype is commonly associated with either heightened expression or increased activation of dynamin 1 like protein (Drp1) and/or the downregulation of mitofusin 2 (MFN2) [15]. The correlation between elevated fission or reduced fusion has been associated cancer progression. Inhibition of Drp1 or overexpression of MFN2 reverses cancer progression, leading to cell cycle arrest and elevated spontaneous apoptosis [15]. It was found that survivin overexpression induces mitochondrial fragmentation, accompanied by a reduction in complex I activity [48]. This alteration promotes glycolysis, curbs the accumulation of ROS, and increases chemotherapeutic drug resistance [48]. On the other hand glycolysis inhibition by glucose analog 2-deoxy-D-glucose, sensitized survivin-overexpressing neuroblastoma cells to chemotherapeutic agents [48].

Altered mitochondrial dynamics can impact the signaling during tumorigenesis and cancer progression. Phosphorylation of Drp1 at Ser616, induced by active mitogen-activated protein kinase 1 (MAPK1), results in mitochondrial fragmentation associated with tumor growth [49]. Furthermore, reduced Drp1 expression hampers the growth of tumors resulting from MAPK-mediated malignancies [49]. In hepatocellular carcinoma (HCC), the extracellular matrix-associated protein, collagen and calcium binding EGF domains 1 (CCBE1), plays a significant role in increasing mitochondrial fusion and inhibiting HCC progression through suppressing HCC cell proliferation and metastasis [50]. Importantly, decreased CCBE1 expression as found to be associated with poor prognosis and outcomes in HCC [50]. Mechanistically, CCBE1 blocks mitochondrial fission by preventing the localization of Drp1 to mitochondria through the inhibition of Drp1 phosphorylation at Ser616 [50]. It was shown that MFN2 suppresses proliferation and cell-cycle progression of cervical carcinoma Hela cells via inhibition of the expression of crucial proteins, such as NF-κB p65, Myc, and mechanistic targets of rapamycin kinase (mTOR) [51]. Additionally, mitochondrial fission is tightly related to progression of tumor metastasis. For example, elevated levels of active Drp1 and decreased mitofusin 1 (MFN1) expression contribute to increased mitochondrial fragmentation in metastatic breast cancer cells [52]. In fact, mitochondrial fission was found to be crucial for breast cancer cell migration and invasion [52]. By contrast, mitochondrial elongation or clustering has the potential to significantly diminish the metastatic capabilities of breast cancer cells. This effect can be achieved through either Drp1 deficiency or overexpression of MFN1. Conversely, silencing the MFN1 gene induces mitochondrial fragmentation in breast cancer cells, consequently enhancing their metastatic potential [52].

Additionally, altered dynamics of mitochondria have been identified as pivotal in the development of drug resistance in cancer cells [53]. For instance, chemotherapy resistance and recurrence in breast cancer is predominantly governed by breast cancer stem cells (BCSCs) [18,53]. Recently, it was demonstrated that BCSCs show significantly elevated levels of fission mitochondrial 1 (Fis1) and MFN1 proteins [54]. Treatment with AZD5363 (Capivasertib) was found to influence mitochondrial dynamics in BCSCs by suppressing MFN1 expression, thereby increasing chemotherapeutic sensitivity of BCSCs to doxorubicin [54]. Additionally, breast carcinoma cells have been observed to metastasize to organs with a more favorable microenvironment. Such metastasis is associated with increased mitochondrial fission driven by Drp1 and mitochondrial elongation factor 1/2 (MIEF1/2) [55]. Drp1 inhibition was restored sensitivity to chemotherapy with cisplatin [55]. These findings provide the basis for potential therapeutic strategies to prevent

Table 1
Alterations in mitochondrial fission/fusion regulators and their association with cancer progression in patients.

Type of cancer	Alterations in mitochondria dynamics regulator gene/ protein	Signaling pathway affected	Clinical outcome	References
Bladder cancer	MFN2 downregulated compared with normal tissues.	Wnt/ β-catenin ↑	Shorter overall survival time; increased proliferation, migration and invasion.	[70]
Breast cancer	Low MFN2 expression were associated with poor prognosis as compared to patients with high expression of MFN2.	mTORC2/ Akt ↓	Promotes cell viability, colony formation, and invasion of cancer cells.	[71]
Lung cancer	Low MFN2 expression were associated with poor prognosis as compared to patients with high expression of MFN2.	mTORC2/ Akt ↓	Promotes cell viability, colony formation, and invasion of cancer cells.	[71]
Breast cancer	Drp1 was elevated while MFN1 was downregulated compared with normal tissues.	Notch ↑	Promoted the survival, proliferation and apoptotic resistance of cancer cells.	[72]
Pancreatic cancer	MFN2 was downregulated in cancer tissues.	VEGFR2 ↑	Promoted the survival and proliferation of cancer cells.	[73]
Thyroid cancer	MFN2 downregulated compared with normal tissues.	PI3K/Akt ↑	Enhanced cancer cell migration and invasion.	[74]
Cutaneous squamous cell carcinoma	Drp1 was elevated compared with normal tissues.	MAPK ↑	Promoted proliferation of cancer cells.	[75]
Glioblastoma	Increased expression of phospho-Drp1 (Ser616).	AMPK ↓	Supports tumor growth and apoptotic resistance of cancer cells.	[76]
Glioma	Increased expression of Drp1.	RHOA/ ROCK1 ↑	Supports proliferation and invasion of cancer cells.	[77]
Hepatocellular carcinoma	Increased expression of Drp1 and decreased expression of MFN1.	TP53 ↓ and NFKB ↑	Promoted the survival of cancer cells and inhibited mitochondria-dependent apoptosis.	[78]

MFN1/2: Mitofusin 1/2; Drp1: Dynamin 1 like; mTORC2: Mechanistic target of rapamycin kinase 2; Akt: AKT serine/threonine kinase; VEGFR2: Vascular endothelial growth factor receptor 2; PI3K: Phosphoinositide 3-kinase; MAPK: Mitogen-activated protein kinases; AMPK: AMP-activated protein kinase; RHOA: Ras homolog family member A; ROCK1: Rho associated coiled-coil containing protein kinase 1; TP53: Tumor protein p53; NFKB: Nuclear factor kappa B.

chemotherapy resistance during metastasis, utilizing controlled modulation of mitochondrial dynamics [55].

In general, proteins that stimulate mitochondrial fission are often found at elevated levels in different tumors compared to normal tissue (Fig. 3). The elevated expression of these proteins is frequently linked to unfavorable clinical outcomes, impacting tumor growth, migration, invasion, and resistance to chemotherapy [18]. The distinguishing features of cancer cells include an excessive proliferation and an elevated resistance to apoptosis execution [47]. These characteristics, to a certain extent, should be supported energetically. Therefore, it is logical that cancer cells acquire irregularities in mitochondrial function, particularly a transition from oxidative metabolism to aerobic glycolysis [56]. The involvement of mitochondrial dynamics in cancer is associated with the necessity for mitochondrial division during the process of mitosis (Fig. 3). This synchronized action, known as mitotic fission, mitigates an even distribution of mitochondria to the resulting daughter cells [56]. Thus, mitochondrial fragmentation plays an important role in shaping the cancer phenotype acting via multiple mechanisms. Specifically, it can enhance mitotic fission and disrupt intramitochondrial calcium waves, thereby hindering apoptosis mediated by calcium signaling [56].

4. Mechanical cues regulate mitochondrial functions in cancer

ECM stiffness is one of the main physical factors that provides a universal signal regulating cell proliferation, differentiation and death [57–60]. As we saw in section 2, aberrant ECM stiffness is associated with tumor progression and contributes to the regulation of the cancer cell fate. Specifically, mechanical forces originated from stiffer tumor ECM significantly promote tumor growth and invasiveness [61]. Not surprisingly, it has become evident that physical cues of tumor ECM mechanically regulate metabolism of different tumor lineages [6,12,19]. Additionally, mitochondria, a major control hub of intracellular metabolism, are also dramatically altered in tumors [18,45,56]. These facts combined lead to the logical assumption that mechanical cues originated from aberrant tumor microenvironments could drive mitochondrial dynamics and ultimately functions in cancer cells.

Recent studies report that physical stimuli originating for substate stiffness can affect the function and dynamics of mitochondria in cancer cells [34,55]. Elevated substrate stiffness promotes mitochondria elongation [34,55]. Specifically, pancreatic tumor cells showed elongated and fused mitochondria when cultured on 2-4 GPa (glass) and 38 kPa (stiff) in comparison with 0.7 kPa (soft) substrates [34]. Metastatic breast cancer cells subjected to soft ECM exhibited Drp1-mediated mitochondrial fission [55]. Breast cancer cells cultured on soft (0.5 kPa) fibronectin-coated acrylamide hydrogels displayed fragmented mitochondria contrary to the cells grown on stiff (15 kPa) substrates [55]. Mechanistically this elevated fission was modulated by peri-mitochondrial F-actin, which formation in turn was regulated by Spire1C and Arp2/3 [55]. Increasing ECM rigidity associated with pancreas tumor cells promoted the appearance of more elongated and fused mitochondria[34]. Interestingly, these changes in mitochondria dynamics were accompanied with changes in arginine metabolism and creatine biosynthesis [34]. Creatinine levels were found to be enriched on soft matrix, whereas a stiff matrix promoted high levels of creatine and phosphocreatine [34]. Overall, in response to changes in matrix stiffness, pancreas tumor cells adjusted their metabolic processes, redirecting L-arginine metabolism towards the biosynthesis pathway of creatine [34]. Further, ECM stiffening (Young's moduli increase from 0.35 kPa to 40 kPa) induced mitochondrial elongation by both promoting fusion and inhibiting fission in lung adenocarcinoma A549 cells and fibrosarcoma HT1080 cells [62]. It was found that kindlin-2 is responsible for fusion upregulation. Suppression of Drp1 expression was driven by PINCH-1, that resulted in inhibition of fission [62]. It is worth noting that some other studies indicate that stiff (not soft) substrates may promote mitochondrial fragmentation [63–65]. For instance, mammary epithelial cells cultured on surfaces with stiffness of 400 Pa displayed elongated mitochondria, whereas cells grown on soft substrates (6-60 kPa) exhibited marked mitochondria fragmentation [63]. Further, mesenchymal stem cells grown on soft (1 kPa) substrates possessed filamentous structure of mitochondria. Contrary mitochondrial morphology was found to be fragmented on stiff (20 kPa)

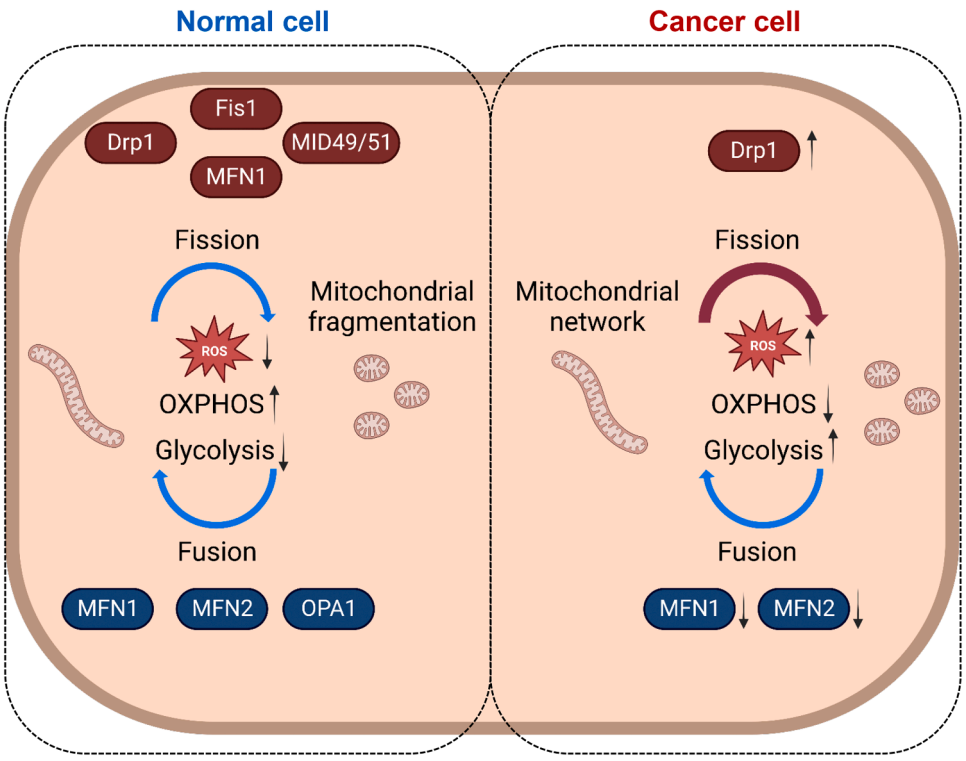

Fig. 3. Comparison of mitochondrial dynamics in normal and cancer cells. Many current studies reveal that main regulators of mitochondria dynamics, like Drp1, MFN1, and MFN2, show altered activity and/or expression levels. Dysregulated fission/fusion of mitochondria in cancer cells results into metabolic switch. Drp1: dynamin-related protein 1; MFN1/2: mitofusin 1/2; Opa1: optic atrophy protein 1; Fis1: protein fission 1; MID49: mitochondrial elongation factor 2; MID51: mitochondrial elongation factor 1. Created with BioRender.com.

substrates [64]. Next, human lung fibroblasts were found to sense increasing matrix stiffness (i.e. from soft 1 kPa to stiff 20 kPa) adopting mitochondrial dynamics in favor of mitochondrial fission and increased production of ATP [65]. Although those studies tried to link mitochondria dynamics to cancer, they utilized non-cancerous cell models, which could be an explanation for conflicting results obtained in [55, 62]. Additionally, stiffness values are inconsistent in different studies adding variability to the outcomes.

Adhesion-mediated mechano-signaling transduces physical cues from altered ECM that result in changes in mitochondrial dynamics, which in turn leads to metabolic rewiring of cancer cells [6,34,55]. Emerging evidence suggests that during cancer progression ECM stiffening activates integrin- and cadherin-mediated adhesions that lead to cytoskeleton remodeling and focal adhesions. Cytoskeleton remodeling changes in turn impinge on expression and the activity of metabolic enzymes and mitochondrial fission/fusion resulting in reprograming of cancer cell metabolism [6,34,55,66]. For example, throughout the metastatic process, cells undergo variations in stiffness as they transition from the rigid milieu of primary tumors to the often more pliable environments of secondary metastatic sites [6,34,55,66]. In the case of MDA-MB-231 metastatic breast cancer cells, alterations in both collagen matrix density and fiber orientation play a crucial role in shaping the intracellular ATP:ADP ratio [67]. When confined within denser collagen matrices that hinder cell migration, there is an observed elevation in the ATP:ADP ratio compared to less dense gels. Furthermore, in aligned collagen matrices, enhanced cell migration is accompanied by a concurrent reduction in the ATP:ADP ratio [67]. Finally, treatment with contractility and migratory inhibitors resulted into decrease of intracellular ATP:ADP levels. Those data imply that the local ECM may actively regulate three-dimensional cancer cell metastatic invasion via intracellular energy rewiring [67]. ECM stiffening triggers metabolic rewiring of pancreatic cancer cells in order to strengthen cell invasion and migration [34]. It has been shown that soft substrate promotes glycolysis, with stiffer substrates supporting ATP production through the TCA-cycle and OXPHOS [34]. Indeed, cancer cell invasion was reduced upon pharmacological inhibition of mitochondrial ATP synthase and OXPHOS by oligomycin A [34]. Further, metastatic breast cancer cells cultured on soft ECM increased cytoplasmic, mitochondrial and membrane lipid ROS production [55]. Increased ROS resulted in upregulation of the transcriptional factor nuclear factor erythroid 2-related factor (NRF2). Additionally, soft ECM promoted activation of Drp1, that subsequently participated in the regulation of ROS levels and oxidative stress mitigation [55]. Further, such ECM-driven mechanotransduction plays an important role in chemotherapy resistance. In fact, cells grown on a soft ECM showed significantly increased resistance to cisplatin and As_2O_3 [55]. However, situation in 3D tumor environments might be more complex than in 2D ECM substrates. A recent study showed that soft 3D collagen scaffolds may upregulate glycolysis in liver cancer cells [68]. Cell growth in the soft 3D collagen scaffolds interestingly resulted in mitochondrial depolarization, accompanied by the downregulation of mitochondrially encoded cytochrome c oxidase I [68]. This mitochondrial activity and function adaptation led to slow proliferation rate and dormancy of liver cancer cells [68]. This study postulated that in 3D tumor microenvironment there might be several physical cues that affect mitochondria function [68]. It was proposed that during cell culturing using 3D collagen scaffolds cells may experience competing mechanical cues, i.e., adhesion and pressure that regulate cell function via mitochondria dynamics [68]. Collagen fibers offered sites of adhesion, whereas porous structure of collagen scaffold supported cell-cell interaction and elevated pressure on neighboring cells [68].

5. Conclusions and future perspectives

It becomes evident that mitochondria exhibit dynamic characteristics, adapting their responses to both mechanical and chemical signals.

Current evidence suggests a connection between cancer and alterations in mitochondrial dynamics. Specifically, cancer cells frequently exhibit an imbalance in the dynamics of mitochondrial fission and fusion, resulting in a fragmented mitochondrial network [15,16,45]. A number of avenues of evidence suggest that mechanical cues originating from the tumor microenvironment (e.g. solid stresses, interstitial fluid pressure, tissue material properties and shear stress in the vasculature) drive crucial cancer cell functions, such as tumorigenesis, metastasis, proliferation, invasion, metabolic activity, chemotherapeutic resistance [6, 12,15,16,19,45,61].

This review explores the features and mechanisms underlying mitochondrial dynamics related to the cancer progression. We highlighted the influence of mitochondrial dynamics on both mitochondrial and cellular function and discussed changes in mitochondrial dynamics within the context of health and cancer development. One can see that mechanical stress, originating from aberrant ECM remodeling, drives progression of various cancers thorough stimulating proliferation, migration, and invasion. In fact, it was found that mechanical load can directly induce recruitment of the mitochondrial fission machinery, and subsequently stimulate mitochondria fission [69]. Therefore, it is not surprising that mitochondrial dynamics in cancer is modulated by mechanical forces. It seems that stiffening of tumor ECM leads to mitochondrial elongation via elevated fusion [34,55,62]. Of note, there are some conflicting studies postulating that enhanced stiffness stimulates mitochondrial fragmentation [63–65]. Overall, elevated mitochondrial dynamics has pathophysiological consequences such as stimulation of cancer progression, promotion of mitochondria redistribution during cell division and metabolic support of growing and invading cancer cells.

Yet, the molecular mechanisms through which physical interactions between cancer cells and their surroundings influence the morphodynamics, metabolic functions, and mechanics of mitochondria still remain unclear and require further investigation. There are several unanswered questions. Is mitochondrial fission a prerequisite for migration in all cancer cells? Is increased mitochondrial fission a reliable clinical diagnostic marker for metastasis? Mechanical properties of mitochondria seem to influence mitochondria dynamics and function. In this regard, is there any generalized mechanophenotype for mitochondria from cancer cells? Answers to these questions will bring fundamental knowledge crucial for the development of effective therapeutic interventions in mitochondrial dynamics. There is currently a lack of a systematic investigation into the direct reciprocal connections between mitochondrial morphodynamics, mechanics, and metabolism. Specifically, the demonstration of how changes in mitochondrial morphology affect their mechanical or mechanosensing properties is yet to be established. Although it is recognized that disrupting mitochondrial morphodynamics has profound effects on cell metabolism, the reciprocal regulation of mitochondrial mechanics by these morphological alterations has not been fully demonstrated. Additionally, there is a lack of systematization in cell models and mechanical properties of systems utilized to generate mechanical stress. An intriguing approach would involve comparing the mitochondrial response to a specific mechanical and/or metabolic stimulus across different cell types using the same methodology. It should be noted, that considering the nature and intensity of the ECM-driven mechanical stress represents a crucial factor in the metabolic and mechanical characteristics of the cells. Finally, investigating the molecular mechanisms regulating mitochondrial responses to mechanical and metabolic signals poses a technical challenge, whether conducted *in vitro* or within live cells. To address this issue effectively, there is a need for the development of non-invasive, and preferably high-throughput, intracellular mechano-stimulators and probes for use in live cell studies.

It is essential to conduct additional research to pinpoint the optimal molecular targets. Moreover, defining safe and effective doses of fission and fusion modulators that specifically target the relevant cellular populations is imperative.

CRediT authorship contribution statement

Mariia Lunova: Writing – review & editing, Validation, Methodology, Investigation, Data curation, Conceptualization. **Milan Jirsa:** Writing – review & editing, Validation, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation. **Alexandr Dejneka:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Data curation. **Gareth John Sullivan:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Oleg Lunov:** Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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