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REVIEW

Role of endothelial cells in the regulation of mechanical microenvironment on tumor progression

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Abstract

Majority of cancer patients die from cancer metastases. The physical stimulation produced by microenvironment regulates invasive behavior of cancer cells. Blood vessel is one of the "pathways" for cancer to metastasize, in which tumor cells need to cross the endothelial barrier for intravasation and extravasation. Tumor vessels are arranged in untraditional hierarchies and characterized with rupture, bend, swell and high permeability that are beneficial to intravasation of cancer cell. Abnormal vessels are accompanied with uneven blood flow, increased compression and interstitial fluid pressure. Meanwhile, excessive proliferation of tumor leads to low oxygen pressure in solid tumor. The aberrant tumor mechanical microenvironment changes the biochemical and mechanical signal transduction of endothelial cells and participates in tumor progression. Many current researches focus on how chemical signals regulate endothelial cell function while the role of physical cues is unclear. In this review, the role of endothelial cells in the regulation of shear stress, intercellular force, extracellular matrix and pressure on tumor progression is summarized.

Keywords Endothelial cells · Cancer metastases · Mechanical microenvironment · Matrix stiffness · Shear stress

1 Introduction

Cancer is a major public health problem worldwide [1]. Metastasis of cancer cell is one of the main causes of death in cancer patients. When cancer cells migrate from the primary site to distant sites, they will undergo a series of biological and physical microenvironments. Although biochemical signals can guide all stages of the metastatic cascade, mounting evidences show that physical signals also guide the adhesion and migration even the growth and apoptosis of cancer cells. Over the past decade, there has been an almost exponential growth in mechanobiology research to study how physical stimuli alter cell biological behavior [2, 3]. For example, extracellular matrix (ECM) is constantly deposited, remolded and degraded during development that endows cancer cells with malignant phenotype due to the imbalance of it [4]. In mouse model, high matrix stiffness induces epithelial–mesenchymal transition of tumor cells to obtain aggressive phenotype by increasing the expression of invasion-associated proteins and the nuclear localization of Yes associated protein (YAP) and Tafazzin (TAZ) [5–7]. In addition, the expression of programmed death ligand 1 is regulated by high matrix stiffness to assist immune escape [8]. When tumor cells detach from the primary site, the cytoskeletal structures are destroyed and the expression of cyclooxygenase-2 is induced by suspended state, which endows stronger migration ability with cells [9]. Meanwhile, the reattachment and extravasation of cancer cell are strengthened by suspension state [10, 11]. Circulating tumor cells (CTCs) suffer from shear stress (SS) generated by blood [12], which induces apoptosis of CTCs. Consequently, less than 0.02% CTCs can survive [13]. Despite, SS also can promote migration and extravasation of cancer cells via activating extracellular signal-regulated kinases (ERK) and enhancing the level of reactive oxygen species (ROS)

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in cells [14]. Thus, physical signals are important factors in the progression of cancer [3].

Tumor metastasis is a key step in tumor progression. Cancer cells cannot complete metastasis process alone unless getting assistance of other cells in tumor microenvironment. Tumor microenvironment is composed of ECM including soluble secretory factors, stromal cells and blood vessels, which are essential for tumor growth and metastasis [15]. Tumor cannot grow more than a few millimeters without angiogenesis that will not threaten human life. Once the angiogenesis switch is turned on, tumor begins to grow and metastasize [16]. Tumor cells migrate via a natural transport network: the vascular system. However, entering and exiting circulation are not simple because tumor cells need to destroy the tight junctions between endothelial cells (ECs) to fulfill transendothelial migration, which is partly influenced by mechanical forces from the microenvironment [17]. Few cancer cells can migrate successfully due to the mechanical forces, thus crossing the endothelial barrier has become the rate-limiting step for tumor metastasis. The blood vessels in primary tumor are characterized with abnormal structure, such as curve, disorder and leakage, which facilitate cancer cells entering into the circulation and then throughout the body [18]. For extravasation, CTCs will slow down and stop moving in the capillary with the similar diameter of the cell then form stable attachment [19]. SS, mechanical force due to the friction between ECs and blood, not only regulates the adhesion of CTCs to the endothelium, but also fine-tunes the extravasation of cell by impairing the remodeling properties of ECs [20]. Moreover, the morphology, function and gene expression of ECs together with the differentiation of endothelial progenitor cells are regulated by SS [21]. ECs are exposed to different mechanical microenvironments including solid stress, pressure and mutual force with other cells. These mechanical signals have profound impact on the morphology and behavior of ECs, which will further affect the transendothelial migration of CTCs [22].

To understand the extravasation of CTCs, the interaction of ECs and other cells must be decoded firstly. Consequently, this study summarizes the role of ECs in the mechanical stimulation of tumor metastasis and spread. This review will focus on how physical stimulation from the tissue microenvironment to change the structure, biochemical and mechanical properties of the endothelium to promote cancer progression. The interactions among physical signals, cancer cells and ECs can be used as a target for anti-metastatic therapy.

2 Interaction between ECs and cancer cells

In tumor vessels, the wall has many holes with the diameter of 100 nm [23], characterized by widened cell–cell conjunction, irregular and defective basement membrane, which leads to high permeability [22]. The highly permeability of tumor vessels permits the macromolecules such as plasma proteins penetrate the vessel wall and enter into the tumor interstitium, resulting in increasing osmotic pressure, which is the basic condition for the intravasation of cancer cells [24]. Once cancer cells enter into the circulation, they will interact with various cells, such as leukocytes, erythrocytes and platelets. But the interaction with ECs is the most critical, because the adhesion between cancer cells and ECs is one of the key steps in extravasation.

The key steps of extravasation include the following processes: (1) blocking or adhering to ECs; (2) steadying the contact and increasing the local adhesion; (3) migrating through the endothelial layer; (4) forming colonization and new metastases [25]. During the interaction, both cancer cells and ECs will be out of shape. The elasticity and plasticity are the most common intracellular parameters and closely related to cell behavior [26]. The value of Young's modulus is always used to characterize cell elasticity, which is mainly determined by the cytoskeleton structure [27]. Elastic maps of ECs have revealed the heterogeneity that nuclear area is more elastic than the surrounding area [26]. When ECs are co-cultured with cancer cells, dynamic remodeling of cellular actin skeleton is enhanced and the stiffness is reduced because the deformability of ECs is enhanced by invasive cancer cells. As a result, the function of endothelial barrier is disrupted [28, 29]. The more aggressive cancer cells are characterized with lower elasticity, which may reflect the characteristics of cytoskeleton disorder. But this difference disappears when cancer cells adhere to the endothelial layer, following by an increase in adhesion especially in highly aggressive cancer cells [27]. When the compressive force produced by tumor cells is greater than the contractile force of ECs, an invasion hole is formed in the cell–cell junction, characterized by actin stretching and stress fiber breakage (Fig. 1). Meanwhile, myosin light chain kinase (MLCK) is activated and the myosin is recruited for transcellular circumferential invasion array to resist the compressive force of tumor cells. As a result, the size of invasion hole keeps relatively constant [30]. Then, the contraction of activated endothelial myosin tightens the actin cytoskeleton of tumor cells and facilitates them entering into the endothelial lumen [31]. ECs will not rupture because their skeleton is strong enough to withstand the external force exerted by cancer cells when they metastasize through endothelial layer [29]. However, when cancer cells are mechanically trapped in capillaries with smaller diameter than cells, cells are ruptured and release necrotic factor to destroy local vascular followed by extravasation [25].

Phillips et al. [32] proposed a hybrid mathematical method to describe tumor vessel changes and cell–cell interactions through agent-based models. The adhesion (φ) can be given by

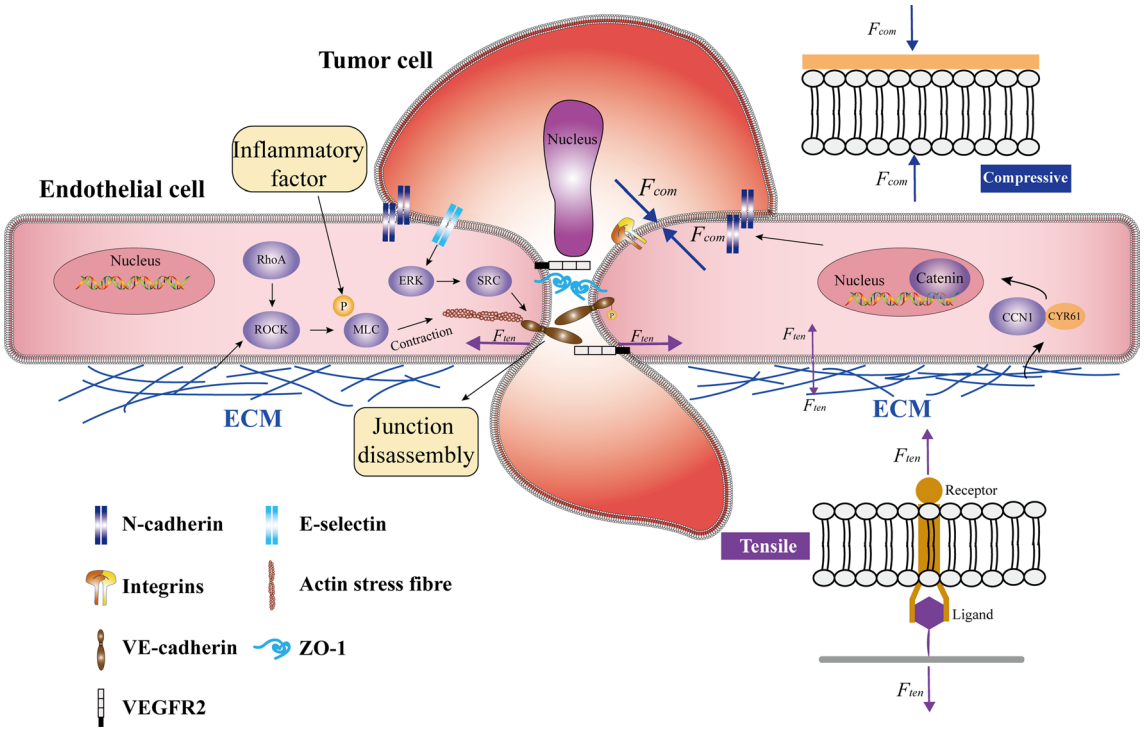

Fig. 1 Signal molecules and mechanical transmission in transendothelial migration of cancer cell. Endothelial monolayer maintains stable connections through vascular endothelial cadherin (VE-cadherin) and tension balance. The tight junctions are destroyed by compressive force produced from cancer cells, whose adhesion is relied on integrins and neural cadherin (N-cadherin). Meanwhile, myosin light chain (MLC) in ECs is activated to recruit myosin to maintain the size of invasive pore. Tumorigenesis is accompanied with an increase in matrix stiffness, which in turn enhances the contraction of endothelial cells (ECs) and adhesion with cancer cells. ZO-1 indicates the zonula occludens-1 and VEGFR2 vascular endothelial growth factor receptor-2

$$\nabla\varphi = \begin{cases} \left(\frac{|\mathbf{d}|}{R_A} - 1\right)^2 \frac{\mathbf{d}}{|\mathbf{d}|}, & 0 \le |\mathbf{d}| \le R_A, \\ 0, & \text{otherwise}, \end{cases} \tag{1}$$

where R_A is the action radius of cells and $\mathbf{d}$ is the distance from the center of the cell to the boundary of the region. The cell–cell adhesive forces ($\mathbf{F}_{cca}$) and compressive forces ($\mathbf{F}_{com}$) acting on the cells are proportional to the adhesion (φ) potentials. Based on Eq. (1), the $\mathbf{F}_{cca}$ and $\mathbf{F}_{com}$ of the i-th cell acting on the j-th cell or the boundary can be expressed as

$$\mathbf{F}^{ij}_{cca} = -c_{cca}\nabla\varphi\left(\mathbf{d}^{ij}; R^i_A + R^j_A\right), \tag{2}$$

$$\mathbf{F}^{i}_{com} = -c_{com}K\left(N_{out}, t\right)\nabla\varphi\left(\mathbf{d}^{i}_{n}; R^i_A\right), \tag{3}$$

where the positive constants c_{cca} and c_{com} are scaling parameters. N_{out} is the number of cells leaving the domain through the boundary. $K\left(N_{out}, t\right)$ simulates the stiffness of the boundary, which is among 0 to 1. The two limit values can be explained as: $K\left(N_{out}, t\right) = 0$, there is no stress accumulation and tumor cells can leave the area; $K\left(N_{out}, t\right) = 1$, the boundary is non-permeable and non-compressible so tumor cells are compressed.

ECs participate in the extravasation process of tumor cells directly or indirectly. Directly, when tumor cells adhere to the endothelial layer, the change in the morphology of ECs and the destruction of endothelial homeostasis are beneficial to the transendothelial migration of tumor cells. Indirectly, ECs enhance the invasiveness of cancer cells by secreting factors [33]. For example, cancer cells stimulate ECs to secrete C–C chemokine ligand 5, which in turn acts on cancer cells in a paracrine manner to promote migration, invasion and metastasis [34]. In conclusion, the endothelium plays a role in enhancing and promoting the invasion of tumor cells besides serving as a barrier.

3 Mechanical microenvironment of ECs

Intravascularly, SS and intercellular interaction directly affect the properties of ECs, such as deformed shape, increased adhesion molecules or induced apoptosis. Extravascularly, stiffen ECM and elevated interstitial fluid

pressure (IFP) increase the permeability of ECs. All these changes can favor to the metastasis of tumor cells.

3.1 SS

In the process of tumor metastasis, CTCs are exposed to the SS exerted by the flowing blood [35]. SS ranges from 0.01 to 4 Pa, which may cause damage to CTCs [36]. CTCs need to overcome the shear force and adhere to the endothelial layer to form a new site and eventually extravasate from the blood vessel [37, 38]. Extravasation involves the adhesion and transendothelial migration of tumor cells. The combination of adhesion molecules between ECs and tumor cells is essential for adhesion process. And transendothelial migration requires morphological changes of ECs. Studies have shown that SS can change the biological behavior of ECs, including cell morphology and protein expression [39]. For example, SS regulates the alignment and proliferation/apoptosis of ECs [40–42]. In addition, SS can also promote the sprouting of blood vessels to provide more adhesion sites for CTCs [43]. Consequently, extravasation of CTCs will be more likely to happen.

More researches have been done on SS sensing and signal transduction of ECs, and their molecular mechanisms has been gradually revealed. Before extravasation, the adhesion of CTCs to ECs is mediated by the interaction of adhesion molecules [44], and the adhesion molecules on ECs membrane are regulated by SS [45]. It has been suggested that SS regulates the arrest of CTCs by ECs. For example, colon cancer cells adhere to ECs through the interaction between E-selectin on ECs and sialyl Lewis a (SLe^a) on cancer cells [46] (Fig. 2). E-selectin expressed on ECs mediates rolling of human bone-metastatic prostate tumor cell [47]. Tumor cells can roll and tether on an E- and P-selectin matrix, while firmly adhesion is mainly mediated in E-selectin [48] (Fig. 2). Under physiological shear flow, prostate cancer cells can tether and roll on microvascular endothelium via E-selectin/E-selectin ligand interactions, which may contribute to the PCs extravasation and initiate metastasis [49]. These studies indicate that SS is implicated in the arrest of cancer cells by ECs.

Other than the molecules interaction, the morphologic change of ECs caused by SS also can promote the extravasation of cancer cells. In capillaries, tumor cells attached to the basement membrane causing a partial retraction of the ECs. With the proliferation of tumor cells, the cluster encompassed by ECs expanded in the vessel lumen. The tumor cells will extravasate from the vessel until the original endothelial layer is destroyed [50]. Al-Mehd et al. [51] proposed a novel metastasis model in which tumor cells attach to the ECs, proliferate intravascularly and produce metastatic foci without extravasation. Over time, the growth of the tumor colonies will exceed the blood vessels in which they are located and destroy the blood vessel walls [51]. In a zebrafish metastasis model, the endothelial-covered extravasation was damaged through inhibiting the vascular endothelial growth factor (VEGF) signaling pathway [52].

Interestingly, CTCs suffer from high SS (15–30 dyne/cm^2) that can induce cell necrosis by elevating the levels of ROS [53], while cell apoptosis also was induced by low SS [54]. Follain et al. [20] demonstrated that the adhesion of CTCs on ECs was favored by decreased flow velocity, which similar with the arteriovenous junction (AVJ) in zebrafish embryos. The flow force drives ECs to reconstruct around

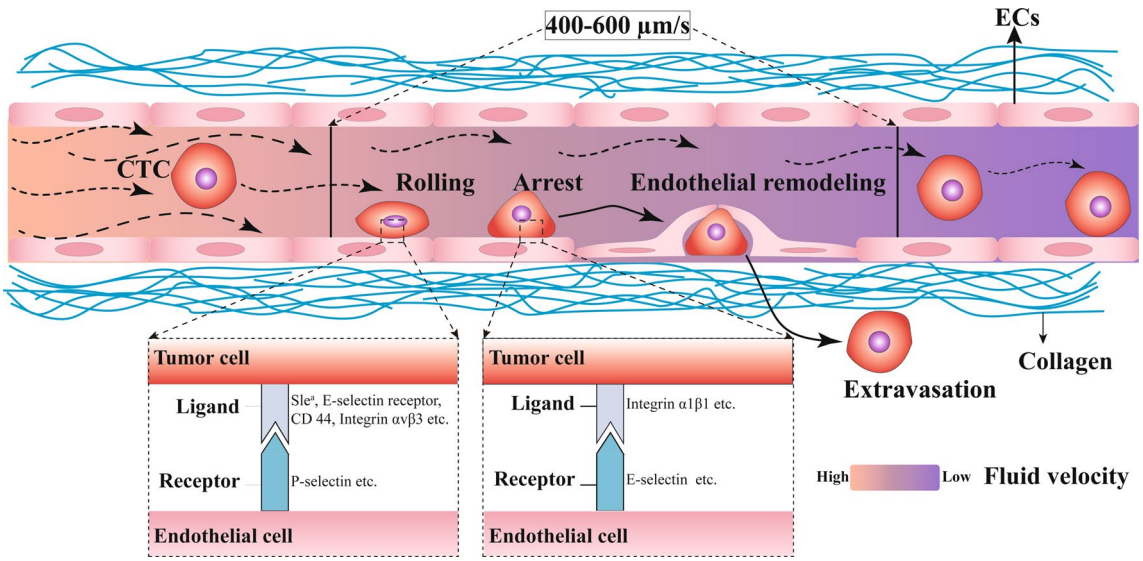

Fig. 2 Prerequisite for metastasis. Below flow velocities of 400–600 μm/s, CTCs can arrest or adhere to endothelial cell and extravagate from basement membrane. The different arrest capabilities of ECs are mediated by the energy of bind receptors on their membrane

the arrested tumor cells, which is conducive to extravasation before metastasis (Fig. 2). Follain et al. [20] also identified a threshold of homodynamic profiles (400–600 μm/s) which is a prerequisite for metastasis (Fig. 2). This suggests that appropriate SS generated by blood flow is beneficial for the cancer cells to be arrested by ECs [20]. Further study operated by Osmani et al. [55] suggested that the adhesion receptors contribute to the cell adhesion. They demonstrated that the early arrest is mediated by the low-binding-energy receptors (CD44 and integrin $\alpha_v\beta_3$), and the stabilization of the CTCs/endothelium bond and subsequent extravasation are mediated by high-energy receptor (such as integrin $\alpha_5\beta_1$) [55] (Fig. 2).

3.2 Intercellular force

The difficulty of extravasation is closely related to the permeability of the endothelial layer, which depends on the connections between ECs. The inner wall of the blood vessel is consisted of ECs that exposed to the interaction with different cells [56]. The interaction includes the connection of ECs and the adhesion of other cells in vessels to the endothelial layer, which can also induce mechanical transduction to change the biological behavior of ECs then participate in the extravasation of cancer cells.

Cell–cell connection creates tissue-scale tension via binding the contracted cytoskeleton together, which participates in tissue homeostasis and morphogenesis [57]. In the process of morphogenesis, traction is generated during cells adhere to neighboring cells that recruits vinculin into the vascular endothelial cadherin (VE-cadherin) complex to reconstruct the endothelial barrier [58, 59]. VE-cadherin, controlled by actomyosin cytoskeleton reorganization, mediates cell adhesion, whose phosphorylation dissociates and internalises cell–cell junction that further increase vascular permeability [60]. Once the tumor cells are in contact with ECs, the adhesive interaction between cells causes the redistribution of VE-cadherin [61] (Fig. 1). The interfered cadherin activates the force transmission signal and increases the integrin-dependent cell contractility, which destroys the endothelial junction [62]. Then tumor cells begin to penetrate the endothelial barrier. The presence of tumor cells can induce the rupture of connections, but unexpectedly, the cell–cell junction can dynamically break to form gap with a force-dependent manner in the absence of any extravasated cells. These gaps are preferentially formed at the vertices of the intersection among three or more ECs rather than the boundary between two cells. The adhesion of cancer cells on cell–cell junction is stronger than that on the edges or center of ECs due to the higher density of adhesion molecules in here [63]. Cancer cells are prior to extravasating at the vertex even if they initially attach to the boundary of two cells [64]. Escribano and his colleagues [64] have established equations about cell-generated forces and actin remodeling. Forces are generated in the cell due to cell movement and cytoskeleton remodeling. Myosin generated forces ($\mathbf{F}_i^{myo}$) act on the stress fibers in a contractive manner. Protrusive forces ($\mathbf{F}_i^{prot}$) generated by actin polymerization are directed to the outside of the cell:

$$\mathbf{F}_i^{gen} = \mathbf{F}_i^{myo} + \mathbf{F}_i^{prot}, \tag{4}$$

where cell generated forces ($\mathbf{F}_i^{gen}$) are the combination of aforesaid two forces due to contractive or protruding stress fibers or membrane elements. When external conditions remain approximately unchanged, rapid mechanical changes will not occur in cells. Once cells are exposed to external stimuli, such as changes in matrix stiffness or contact with cancer cells, myosin are activated and characterized by uneven force distribution result in the formation of intercellular spaces. The protrusions caused by actin polymerization may change the length of stress fibers. The stress fiber undergoes dynamic reconstruction by adapting rest length to current length at a certain speed:

$$\dot{\mathbf{L}}_s^0 = \boldsymbol{\upsilon}_s^{remodel} = K_{remodel} \cdot \left(L_s - \mathbf{L}_s^0\right), \tag{5}$$

where s is the index of the stress fiber, L_s is the current length of the stress fiber, $\mathbf{L}_s^0$ is the current balance rest length of the stress fiber, and $K_{remodel}$ is a constant describing the length adaptation rate.

The evidence suggests that tumor cells extravasate in a similar way of transendothelial migration of leukocytes [65]. Although there are some differences in these two processes, the extravasation of cancer cells may be assisted by leukocyte extravasation because cancer cells can use leukocyte or other hemocytes as bridge to adhere to the endothelial layer [66]. Leukocytes not only sense the adhesion force produced by ECs, but also induce the force to change mechanical transduction in ECs. The selectin aggregation induced by leukocyte promotes protein recruitment in the cytoplasmic region, including F-actin and the actin-binding proteins filamin and α-actinin, which control ECs rigidification and traction production [67]. When they are tightly combined, leukocytes generate force to disturb the connection tension of vascular endothelium, causing gap between the adjacent cells. Then leukocytes generate strong stress to push themselves through the gap. In addition, in the presence of pro-inflammatory signals, the tension fluctuation and contractility of the ECs monolayer are increased to facilitate diapedesis. Moreover, the traction force required to generate connection gap is greatly reduced during the inflammation process, which indicates that inflammation effectively softens the physical barrier for leukocytes migration [68]. Therefore, inflammation accompanied with tumor may accelerate the transendothelial migration of tumor cells.

3.3 ECM

ECM was once regarded as just a scaffold for cells, providing mechanical and structural support, but it can profoundly affect almost all the characteristics of cancer cell, such as restless proliferation, immortality, abnormal energy, resist death, invasion, immune escape and angiogenesis [69]. The physical properties of ECM mainly include stiffness, density and arrangement, among that density is a global parameter and affects other parameters such as stiffness, pore size and crosslinking [70]. Cells can sense the changes in the physical properties of ECM and make a series of responses. In turn, the changes of cell behavior remodel the ECM.

The integrins of ECs sense the stiffness of matrix and convert mechanical forces into intracellular signals to induce actin remodeling and myosin-based contraction. On the rigid matrix, the number of local adhesion and F-actin stress fibers are increased, which is manifested by enhanced adhesion and diffusion of ECs. Meanwhile, the rigid matrix induces RhoA-Rho-associated kinase (ROCK) myosin-based contractility (Fig. 1), which especially locates at the cell edge and junction, resulting in the fracture of the cell connection and the formation of intercellular space [67]. In addition, matrix rigidity activates focal adhesion kinase and ERK then determines the location of Src in the cell–cell junction, which in turn induces the increase of VE-cadherin phosphorylation in vivo and in vitro [71], leading to impaired vascular barrier function [72]. VE-cadherin mediates cell–cell adhesion through the transmembrane interactions formed by extracellular domain, while the cytoplasmic domain is anchored to the actin cytoskeleton through chain proteins, leading to the stability of VE-cadherin in the cell–cell connection [60] (Fig. 1). The specific signaling pathway of VE-cadherin increases focal adhesion remodeling and cell contractility, while maintaining the overall mesoscale mechanical balance. However, the increase of substrate stiffness exacerbates the destructive effect of the force transmission signal between cells due to heterogeneity of the stress distribution in monolayer, resulting in the destruction of the endothelial connection [62]. In the presence of the inflammatory cytokines, the phosphorylation of vinculin is activated by hard matrix to increase monolayer tension. Meanwhile, the co-localization of phosphorylated myosin light chain (MLC) and actin stress fibers is increased in ECs monolayer, accompanied by increased contractility (Fig. 1). As a result, ECs monolayer develops into focal adhesion junctions instead of reticular morphology, which induces more permeable [73]. Even more serious, the activated MLCK induces the formation of macropores in the endothelium for the transfer of other cells [74]. Compared to the stiff matrix, the cell–cell connections in endothelial monolayer are more mature on the soft matrix due to increased recruitment of vinculin and F-actin, accompanied by decreased paracellular transport events [75]. The increased stiffness of matrix breaks the connection between ECs not only via changing cytoskeleton, but also stimulating cells to express proteins to assist the extravasation of cancer cells. Matricellular protein CCN1/CYR61 of ECs is highly regulated by stiffness. CCN1 activates catenin nuclear translocation and signal transduction that contribute to the up-regulation of neural cadherin (N-cadherin) on the endothelial surface in vitro, which stabilizes N-cadherin-dependent interactions between cancer cells and ECs [76] (Fig. 1). The expression of vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 also correlated with the stiffen matrix, which induce chemotactic migration and adhesion of other cells [77, 78]. Meanwhile, the expression of matrix metalloproteinases (MMPs, such as MMP2, MMP3 and MMP7) increases as the stiffening of matrix, which is further conducive to the transendothelial metastasis of cancer cells [79]. Tumor is always accompanied with an increase of matrix stiffness, which will be bad for tight junctions of the endothelium. If the gap is utilized by cancer cells, the metastasis process will be accelerated.

It is known that tumor progression is accompanied by a coinstantaneous increase in matrix stiffness and density. Both of them are increased by the excessive deposition of collagen, which accounts for 90% of ECM [80]. The increase of ECM density significantly slows down the rate of angiogenesis [81] and reduces the length and branch points of the generated blood vessels, which severely affects the formation of vascular networks [82]. These phenomena explain the cause of the disordered vascular structure in solid tumors in another perspective. But if the density of the matrix is too low, the connection between cells and matrix is too weak to sprout [70]. The migration of cells is also affected by the arrangement of collagen fibers, which are pulled by cancer cells contractility via Rho/ROCK signal pathway to arrange radially. Then the cancer cells migrate along the arranged fibers [83, 84].

Tumor cells' behavior is affected by the changes of ECM, in turn, cell behavior reshapes ECM. For example, the traction of cancer cell increases with substrate stiffness, in turn traction-mediated cell contraction will pull the substrate [24]. Then the changes of substrate may induce the proliferation and invasion of cancer cells that represents a positive feedback loop [85]. Similarly, the deformation and remodeling of ECM promote angiogenesis, in which the traction force, proteolytic enzymes and new matrix are produced in turn to remodel the matrix. The traction force is a pretty important parameter to control matrix deformation [86]. ECs apply traction and deposit new matrix during the formation of capillary, both of them induce the increases of local ECM stiffness with the culture time [87].

Numerous researches have shown that the response of ECs to tumor stroma is one of the reasons that result

in abnormity of tumor vessels. Another point of view is that tumor-associated ECs lose the ability to perceive and respond to physical cues thus abnormal tumor vessels are formed. Compared with normal ECs, the ECs isolated from transgenic mice with prostate cancer fail to adjust their actin cytoskeleton when exposed to uniaxial cyclic strain. Meanwhile, they fail to show different shapes to response to ECM elastic changes and exert traction and contractility on the flexible ECM to reorganize into a tubular network in vitro. These behaviors are related to the high activity of small GTPase RhoA and its downstream effector ROCK. Tumor-associated ECs can be reprogrammed by inhibiting ROCK to redirect the response to uniaxial cyclic strain and the ability to form a tubular network [88].

3.4 Pressure

Tumor and the surrounding normal tissues are exposed to compressive stress due to the confined space [89] (Fig. 3). The growth of multicellular tumor spheroid in agarose matrices generated stress of 40–120 mmHg (1 mmHg = 133 Pa), causing blood vessel collapse and altering the expression of tumor vascular genes [90, 91]. Characteristically, most tumors exhibit an inhomogeneous internal environment during the tumor development, the gradients of oxygen (O_2), glucose, lactate and H^+ ions, and other critical metabolite [92], which may cause highly compressive stress or IFP [93, 94] (Fig. 3). In solid tumor, IFP ranges from 5 to 40 mmHg, and even to 75–130 mmHg in some cases [95]. The increased stress or IFP cause the collapse of blood vessels (Fig. 3). Solid stress [96] and IFP [97] generated during the tumor growth both can destroy the vascular system, thus affect the extravasation and metastasis of tumor cells [98].

The collapsed vessels system decreases the oxygen concentration in the tumor that further promotes tumorigenesis. Padera et al. [99] demonstrated that the intratumour vessels would collapse due to the proliferating tumor cell, especially those without supportive stromal structures. Re-expanding

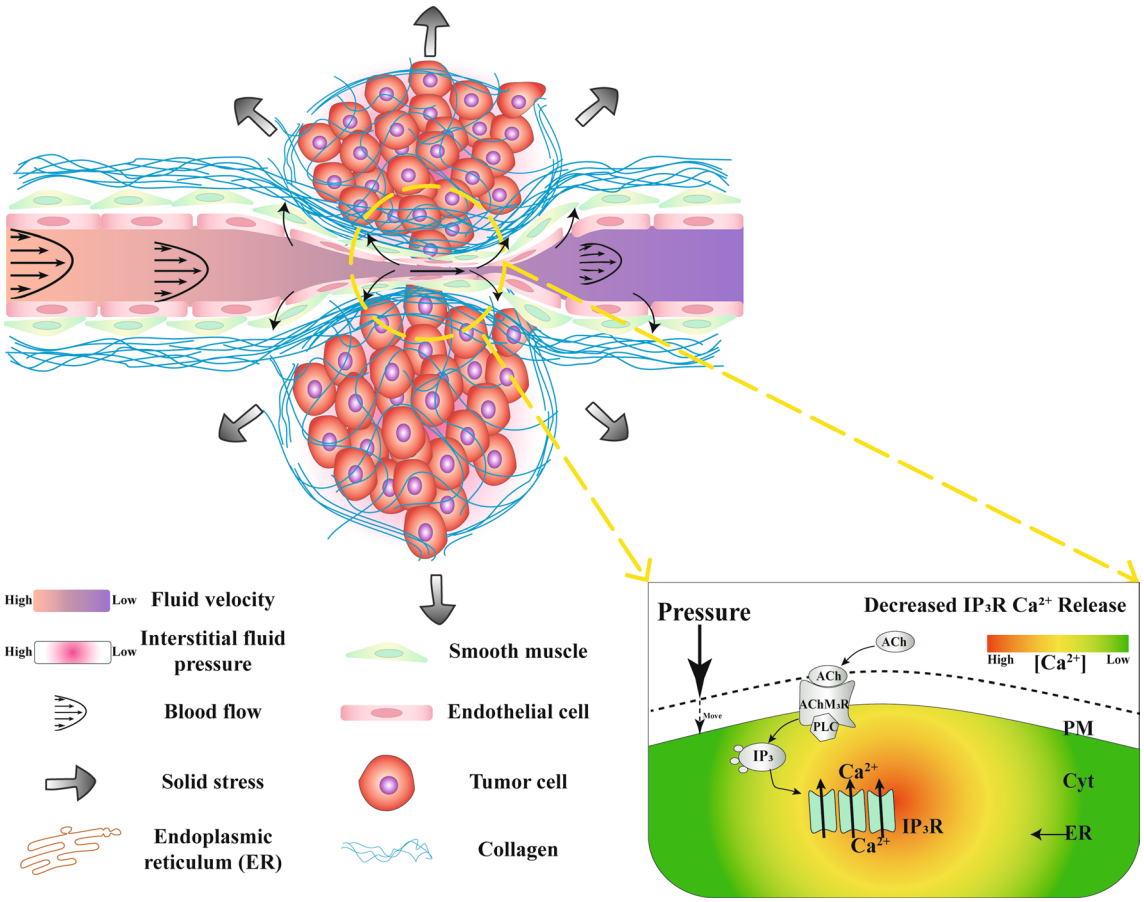

Fig. 3 Pressure on ECs in tumor microenvironment. The growth-induced solid stress from extracellular matrix (ECM) deposition and proliferating cancer cells cause tumor vessel compression, and the elevated interstitial fluid pressure (IFP) in tumor often causes limited perfusion. One possible mechanism about endothelium in sensing pressure is the Ca^{2+} release through IP_3. High-pressure squeezing of cells reduces cell height, reduces the distance between endoplasmic reticulum (ER) and plasma membrane (PM), restricts the diffusion of IP3 receptors (IP_3Rs) Ca^{2+}, and effectively increases local Ca^{2+} concentration

the microvasculature by normalizing the solid stress or IFP can improve the efficiency of chemotherapies [100]. For example, application of VEGF-C around the tumor induces lymphangiogenesis and reduces IFP, and the tumor exhibits delayed growth [101]. Pancreatic ductal adenocarcinoma (PDA) is a highly aggressive cancer characterized with a robust fibroinflammatory response, or desmoplastic, stromal reaction and degree of hypocascularity [94, 102]. PDA is hypoperfused in standard clinical imaging modalities and 75% of the vessels in PDA appear to be collapsed [100, 103]. The decrease of IFP can stimulate angiogenesis by inhibiting the hedgehog signaling in PDA, thus produce a salutary drug delivery [104]. The decreased vascular permeability induced by anti-VEGF monoclonal antibody can lower IFP [105]. N-3 polyunsaturated fatty acid can enhance the inhibitory effect of docetaxel, further reduce IFP, thereby improving the delivery of the drug and therapeutic effect [106]. Although releasing IFP can improve the effectiveness of therapy, the underlying mechanism is unknown.

Wilson et al. [107] demonstrated that ECs can respond to pressure by adjusting the concentration of Ca^{2+} (Fig. 3). Mechanical stimulation (such as hydrostatic pressure) of arteries can increase intraluminal pressure, flatten ECs, resulting in a decrease of the distance from the plasma membrane to the endoplasmic reticulum. Morphological changes of ECs limit the diffusion of Ca^{2+} from the inositol trisphosphate receptor (IP_3R) in the endoplasmic reticulum, effectively increasing the local Ca^{2+} concentration, thus inhibiting inositol trisphosphate (IP_3)-mediated Ca^{2+} signaling in the activated ECs [107] (Fig. 3). Ca^{2+} involves in the signal transduction mechanisms and network activities of ECs [108]. Increased intraluminal pressure changes the morphology of ECs by suppressing endothelial Ca^{2+} signals transduction, suggesting that solid stress and IFP may also can regulate the morphological changes of ECs through Ca^{2+} transduction pathway. For example, Yoshida et al. [109] demonstrated that ECs response to hypoxia through increasing the concentration of intracellular. Similarly, the transient receptor potential vanilloid 4 (TRPV4, one type of Ca^{2+} channels) can be activated under mechanical stress. Elimination of TRPV4 in the tumor model resulted in destruction of VE-cadherin on ECs [110]. Since ECs are considered as the key mediator between tumor progression and mechanical pressure, it is necessary to reveal the interaction between them.

4 Conclusion and prospect

In human diseases such as atherosclerosis, bone defect and heart disease, biomechanics plays an important role in the etiology and progression [111, 112]. Cancer is also affected by the biomechanical environment, which is comparable to any of the above diseases [113]. The mechanical changes of the tumor microenvironment not only affect the tumor, but also participate in tumor progression by regulating the surrounding stromal cells. Particularly, tumor vessels play a key role in the tumor growth, metastasis and therapy [69]. The rigid ECM promotes the abnormal branch and density of blood vessels with increased permeability, while the mechanical stress in tumor compresses the vessels and restricts perfusion. An increasing number of evidences have indicated that the tumor mechanical microenvironment induces changes in the phenotype and mechanical sensitivity of ECs. The abnormal mechanism sensitivity is related to the malfunction of the mechanism sensor in ECs [22]. Although it is known that ECs are involved in the tumor progression regulated by mechanical microenvironment, there is still much work to be done to fully understand how ECs respond to mechanical stimuli and participate in tumor metastasis. Similarly, many drugs have targeted tumor vessels, but drug delivery will be affected by the stress in tumor, abnormal vascular structure, interstitial high pressure and dense interstitial matrix. As a result, the penetration distance of the drug is short and the drug can only concentrate locally in the peripheral area of vessels [24, 114]. Therefore, it is necessary to fully describe the interaction among mechanical stimulation, ECs and tumor cells to understand the underlying mechanisms for achieving treatment benefit. Understanding the role of ECs in mechanical regulation of tumor progression may provide new therapeutic targets for tumor therapy.

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