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Mini-review

Vascular permeability changes involved in tumor metastasis

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ABSTRACT

Cancer cell extravasation resembles the leukocyte recruitment during inflammation. Evidence suggests that cancer cells need to weaken the interendothelial junctions in order to cross the endothelial barrier. Several tumor-derived vasoactive compounds have been pointed out to drive this increase in vascular permeability: VEGF, Angptl4, CCL2, SDF-1, etc. Therefore, tumor cells have a wide repertoire of soluble factors to increase vascular permeability in order to colonize new tissues. Tumor soluble factors activate different signaling pathways to induce interendothelial junction disassembly, one common element is Src kinase. Here we summarize the relevant current knowledge about vascular permeability changes involved in tumor metastasis.

1. Introduction

Despite the local damage caused by primary tumors, they are only responsible for 10% of all cancer-related deaths; the remaining 90% persons die because of metastasis. Since Stephen Paget postulated his "seed and soil" hypothesis in 1889, a significant amount of data regarding the metastatic process have accumulated [1]. However, metastasis remains one of the lesser understood events in cancer biology. Tumor cell dissemination is the product of several biological events such as the following: (i) local invasion; (ii) intravasation; (iii) survival in the circulation; (iv) adhesion to the vascular bed; (v) extravasation and (vi) colonization [2]. To obtain the aforementioned metastatic properties, it is well established that tumor cells are required to undergo epithelial to mesenchymal transition (EMT); for example, tumor cells deriving from an epithelial origin that become metastatic must obtain a mesenchymal phenotype [3]. How metastatic cells achieve EMT comprises a currently intensive research field. Several reports have shown that cancer stem cells (CSCs) in many ways resembles cancer cells that have just undergone EMT [4,5]. CSC represent a subpopulation of tumor cells endowed with, as are normal stem cells, self-renewal and multi-linage differentiation capacities [4]. Moreover, it was hypothesized that metastatic cells are a subpopulation of the CSC compartment, denominated migrating CSC [4–6]. The molecular mechanisms underlying each of these metastatic processes remain poorly understood. More general discussions that review the metastatic process are recommended [2,7–9]. On the other hand, despite the lack of sufficient data on metastatic biology, several experimental evidences highlight the critical importance of the increase in vascular permeability associated with the extravasation of tumor cells. The present review is focused on summarizing current data on the vascular permeability changes involved in metastasis.

2. Mechanism controlling vascular permeability

We begin by discussing the general mechanism that regulates vessel permeability. In general, there are two pathways controlling the flux of solutes through the endothelium, known as the transcellular and the paracellular pathways [10]. The first, also known as transcytosis, is defined as a vesicle-mediated transport of macromolecules and cells through the endothelial cell body [10]. The second one is formed by a minute intercellular space between contacting endothelial cells, and restricts the diffusion of macromolecules more than 3 nm in size [10].

We summarize the general characteristics of the intercellular junctions, which are the determining structures for changes in endothelial permeability.

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2.1. Endothelial junctions

In endothelial cell architecture, there are three types of junctions: the Tight junctions (TJs); the Adherent junctions (AJs), and the gap junctions [11]. Because there is no evidence that gap junctions participate in vascular permeability, they are not further considered in this review.

According to Martin and Jiang, TJ functions are the following [12]: TJ serve as a diffusion barrier to plasma membrane lipids and proteins, thus helping to polarize cells defining apical and basolateral membrane domains; TJ molecules act as intermediaries and transducers in cell signaling, thus playing a role in the processes of polarity, cell differentiation, cell growth and proliferation; also, TJ proteins act as cell–cell adhesion molecules, and finally, they represent a barrier that regulates cell migration. On the other hand, AJ functions include maintenance of the physical association between cells in the epithelia, providing the structural framework to aid to defining an endothelial cell apical-basal axis acting as a reference for cell polarity coordination, and finally, they also contribute to the control of vascular permeability [11,13,14].

The molecular components of TJ can be classified as follows: (i) integral transmembrane proteins such as claudins, occludins and Junctional adhesion molecules (JAMs), with these molecules binding to homologous proteins in contiguous cells; (ii) peripheral- or plaque-anchoring proteins, such as the membrane-associated guanylate kinase (MAGUK) family proteins ZO-1, ZO-2, and ZO-3. The cytoplasmic domains of the transmembrane molecules are fixated to the cell through their interaction with the ZO proteins [10,15–18]. The ZO family binds to the C-terminus of claudins and other TJ transmembrane proteins, acting as a bridge that links these to the F-acting cytoskeleton [15,16,18]; (iii) TJ-associated/regulatory proteins such as PKC and Src, these are bound to MAGUK proteins, which they regulate, and also to the transmembrane proteins, examples of which are the αPKC-Par3-Par6 complex, heterotrimeric G-proteins, and kinases such as Src and Yes, among others. Even the transcription factor ZONAB can be found associated with TJ in resting epithelia [15–17].

With regard to TJ, general constituents of AJ can be grouped to include (1) transmembrane proteins such as VE-cadherin and nectins, which bind to a homologous partner present on the membrane of the neighboring cell [10,13,14]; (2) anchoring proteins such as catenins α, β, γ, and p120-catenin. VE-cadherin is bound to β-catenin and the latter to α-catenin, which serve to interconnect the transmembrane protein to the actin cytoskeleton [13,19], and finally, (3) regulatory proteins such as the Src kinase and several phosphatases such as VE-PTP, Shp2, Dep-1, and PTP-μ, proteins which modulate the AJ response [11,13,19].

Permeability of the endothelium is controlled by a variety of physiological signals. Treatment of endothelial cells with VEGF leads to a significant increase in permeability that is also known as hyperpermeability. One key component in the TJ disassembly mechanism are conventional novel and atypical PKC, activated by a variety of physiological stimuli, such as HGF, VEGF, vasopressin, TNF and INFγ [17]. VEGF increases permeability, inducing the production of NO, which raises the levels of cGMP leading to the subsequent activation of PKG. Another mechanism of VEGF-induced hyperpermeability is the sequential activation of Src, ERK, JNK, and PI3K/Akt leading to ZO-1 and occludin phosphorylation [17,20]. Pro-inflammatory cytokines promote the GTP-associated form of RhoA that leads to the activation of ROCK kinase, which in turn phosphorylates several TJ proteins such as occludin, claudin-5, ZO-1, and ZO-2. All of these molecular changes lead to the opening of the TJ [17,20]. TNF and IFNγ induce the increase in vascular permeability activating myosin light chain kinase (MLCK) that in turn phosphorylate myosin light chain (MLC), leading to the contraction of the acto-myosin belt [17]. Another important element in the hyperpermeability response is NF-κB. Activation of this transcription factor in endothelial cells alters the distribution of TJ proteins [10]. Oxidative stress also modifies the TJ inducing its disassembly. This process is dependent on the activation of Src, which phosphorylates occluding, promoting its separation from ZO proteins; this occludin phosphorylation impairs its ability to bind ZO proteins [17].

Our current understanding of the regulation of AJ has developed from studies that have analyzed the effect of vasoactive compounds on the structural proteins of AJ. Several protein kinases have been identified as regulatory elements of the AJ, such as MLCK and different forms of PKC. The calcium–calmodulin-dependent activation of MLCK by activators such as histamine and thrombin leads to the MLC phosphorylation which in turn promotes actin–myosin cellular contraction; this event pulls VE-cadherin and disassembles their homotypic interactions [10,21–24]. Permeability agonists induce the PKC-dependent phosphorylation of p115RhoGEF and/or RhoGDI-1, with both events generating the activation of Rho to form actin stress fibers [10]. Thrombin binding to its PAR-1 receptor activates G_q leading to an increase in intracellular calcium and promoting VE-cadherin phosphorylation through a PKC-dependent mechanism [10]. Other mediators such as histamine, PDGF, TNF and VEGF alter AJ through the phosphorylation of the intracellular components of AJ, namely VE-cadherin, β-catenin, and p120-catenin [11]. Moreover, VEGF activates two alternative mechanisms leading to the phosphorylation of VE-cadherin, which that converge on the activation of Src. In one of these pathways, Src itself phosphorylates VE-cadherin and in the other, phosphorylation results from the sequential activation of Src, Vav2, Rac, and finally, PAK. This second mechanism is related with the internalization of VE-cadherin through β-arrestin and clathrin-coated pits [10,19,20,25].

3. Leukocyte diapedesis: model for cancer extravasation

Tumor cells spread from a primary tumor to distant organs through the lymphatic and arteriovenous systems [26–28]. Once cancer cells become trapped or specifically reach their target organs, they adhere to the luminal vascular membrane [29] and slide over it in such a way as to acquire a convenient site for crossing the endothelial monolayer and invading the target organs interstitial space [29–31]. This sequence of events resembles the fate of neutrophils during the inflammatory response, characterized by endothelial activation in response to pro-inflammatory cytokines secreted by resident monocytes that respond to PAMPs such as lipopolysaccharides [32,33]. Activated endothelial cells express cell adhesion molecules that bind circulating neutrophils that, after firm adhesion to the luminal vascular wall, slide to find suitable sites in order to extravasate by crossing the endothelial monolayer following a gradient of chemokines [32,33]. Thus, leukocyte diapedesis and extravasation are the paradigms of transendothelial migration.

3.1. Cell adhesion to the luminal endothelial cell membrane

Circulating leukocytes adhere to the activated endothelium through PSGL-1, which binds the P- and E-selectin expressed in the luminal membrane of the endothelial cells. In addition, ESL-1 and CD44 expressed on neutrophils bind the E-selectin present on the endothelial membrane and, finally, the L-selectin on neutrophils binds to endothelial GlyCAM-1 [34–36]. P- and E-selectins are not constitutively expressed in endothelial cells, but are rapidly transcribed and synthesized in response to pro-inflammatory cytokines such as TNF or IL-1β [20,34]. During the following step, neutrophils pass from slight to firm adhesion, and this process is