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REVIEW ARTICLE

Progress in research on the relationships among tumor blood supply patterns

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Abstract

Tumor cell growth, invasion, and metastasis require a blood supply. The diversity of tumor blood supply patterns and the biological properties of tumor cells play important roles in these processes. The discovery of vascular mimicry (VM) has enhanced the understanding of the plasticity of tumor cells and angiogenesis. VM is only a supplemental form of tumor microcirculation. However, the extensive clinical significance and special formation of VM have generated new ideas regarding anti-vascular tumor therapy. Currently, the exploration of the relationship between VM and other blood supply patterns is in the early stages, and many questions remain unanswered. Further in-depth studies of the relationships among tumor blood supply patterns will identify novel anti-tumor therapeutics.

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The growth of a tumor requires a blood supply. Recent studies have suggested that the pattern diversity of the tumor blood supply and the biological properties of tumor cells play important roles. It is currently thought that the mode of tumor blood supply may be one of three types: endothelium-dependent vessels, mosaic vessels (MV), or vascular mimicry (VM). The relationships between the three modes of tumor blood supply are not clear and be a focus in numerous future studies.

Tumor blood supply patterns

Endothelium-dependent vessels

Classic angiogenic pathways include vasculogenesis and angiogenesis. Vasculogenesis refers to the differentiation of mesoderm-derived hemangioblastomas into endothelial cells, which line the capillaries and are involved in microcirculation. Angiogenesis refers to the process whereby new blood vessels form from pre-existing vessels and concerns the formation of endothelial cells through division, blastomycosis, expansion, and extension. Tumor angiogenesis involves a variety of cells and molecular interactions, including vascular endothelial basement quality degradation, endothelial cell migration, endothelial cell proliferation, formation of endothelial cell branch pipes, and formation of new vascular rings and basement membranes. Thus, tumor cells and endothelial cells interact throughout the entire process of tumor angiogenesis.

A number of studies have shown that active substances regulate tumor angiogenesis. These substances include a series of growth factors, cytokine polypeptides, low-molecular weight lipids, nucleotides, and vitamins, such as vascular endothelial growth factor (VEGF), fibroblast growth factors, interleukin-1, and interleukin-8 [1–9]. VEGF can directly stimulate endothelial cell migration, proliferation, and division, as well as increase microvascular permeability, which plays an important role in tumor angiogenesis [10–11]. Moreover, the coordination of angiogenesis inhibitors is involved in the process. Under normal conditions, equilibrium exists between excessive angiogenesis and inhibition of vascular degeneration [12–13].

Vascular mimicry

VM is the generation of microvascular channels without the participation of endothelial cells. In 1999, Maniotis *et al* [14] reported VM for the first time in their study of melanoma. The expression of VM was observed by immunohistochemical double staining of CD31 and by periodic acid-Schiff staining. Vascular endothelial cells stained by the endothelial cell marker CD31 were positive in tumor tissues, and the VM vessel wall was surrounded by tumor cells without vascular endothelial cells; thus, CD31 was marked as negative. The extracellular matrix stained

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using the periodic acid-Schiff reaction in the VM vessel wall, combined with hematoxylin and eosin staining, can detect the expression of the VM. Vascular mimicry can be described as follows: the vessel wall, which lacks endothelial cells, is arranged around the tumor cells; although blood flows through the vessel, there is no obvious inflammatory cell infiltration or surrounding necrosis. VM involves the interconnection of normal tumor blood vessels to provide a blood supply to the tumor tissue, indicating its functional role in microcirculation. The presence of VM in a variety of malignant tumors was subsequently confirmed [15–19]. In most studies, the expression of VM was an adverse factor in patient prognosis.

The mechanism for the formation and regulation of VM in blood vessels has been of great interest in tumor research in recent years. Based on a series of studies on melanoma, Hess *et al* [20] proposed a molecular signaling pathway for the regulation of VM formation. They considered a variety of factors associated with VM, such as epithelial cell kinase (EphA2), vascular endothelial cadherin, focal adhesion kinase (FAK), extracellular signal-regulated kinases 1 and 2, phosphoinositide 3-kinase (PI3K), and matrix metalloproteinase (MMP), all of which are associated with the mechanism of VM formation. Furthermore, Lu *et al* [21] reported that the formation of VM was increased in highly invasive gallbladder cancer cells via the PI3K/MMPs/Ln-5γ2 and/or the EphA2/FAK/Paxillin signaling pathways. This provides new targets for the treatment of human gallbladder cancer. However, studies of the mechanism of VM are problematic and researchers have reported a variety of factors that regulate VM formation. Comito *et al* [22] showed that the production of mitochondrial reactive oxygen species enhances hypoxia inducible factor-1α stability, leading to the activation of Met oncogenes. This in turn leads to the formation of metastatic melanoma cells and an increase in the ability to form VM. In a study of ovarian cancer, Millimaggi *et al* [23] found that the formation of CD147 and VM are correlated. CD147 is highly expressed in tumor cells in VM, and the expression of CD147 in ovarian cancer cell lines was found to be correlated with tumor invasiveness. The treatment of SKOV3 cells (a cancer cell line with high invasion activity) with small interfering RNA against CD147 significantly suppressed the ability of these cells to generate non-endothelial channels; however, transfection of CD147 cDNA into the CABA I cell line (a line with low invasion activity) resulted in increased tumor invasiveness and enabled the formation of vascular channels. Sun *et al* [24], in the detection of Twist1 expression in human hepatocellular carcinoma samples and cell lines, found overexpression of Twist1 in VM positive expression in hepatoma cells, and associated this result with the formation of VM. In summary, the formation of VM is induced by several factors functioning in concert and is the result of gene inversion, tumor cell plasticity, effect of protein molecular biology, and environment.

Mosaic vessels

The MV pattern is a special type of tumor blood supply that represents the transition mode between endothelial vascular dependence and vasculogenic mimicry. The vascular walls of MVs are composed of endothelial cells and tumor cells,which differ from the endothelium-dependent vascular system and vasculogenic mimicry.The mechanism of formation may be related to the formation of tumor vascular endothelial cells. Large gaps appear in the vessel wall by the shedding of endothelial cells; and these enable cancer cells exposed to the lumen and participated in blood vessel formation. Studies have shown that there is some loss of immune marker activity in endothelial cells during the tumor evolution process [26–28]. Zhou *et al* [29] showed that a large proportion of mosaic areas vary depending on their location, but most are areas of low collagen IV and laminin immunoreactivity. This suggests that the mechanism of MV formation involves extensive loss of the basement membrane. Given the lack or degradation of the basement membrane, which provides mechanical support to the vessel wall and acts as a physiological barrier, cancer cells can directly contact the vessel wall. This leads to the "mosaic" phenomenon between tumor cells and endothelial cells. Cao [30] showed that tissue present during early MV formation was disorganized and showed a lack of clear separation between arterioles and venules, lack of appropriate coating of mural cells, and high permeability. Therefore, further studies on MV will aid anti-angiogenic therapy.

Relationship between VM and other tumor blood supply patterns

The growth of solid tumors is inseparable from the blood supply. Folkman [31], known as the father of angiogenesis, proposed the classical theory of tumor angiogenesis. According to this theory, a tumor with a volume of less than 2–3 mm^3 can rely on diffusion to obtain adequate nutrition, but when the tumor mass exceeds 2–3 mm^3 endothelial cells are required to build blood vessels for blood supply, otherwise, the tumor will remain dormant or degrade. VM exists as a complement to the tumor blood supply in the form of vessels lined with endothelial cells; the two act together to provide an oxygen supply for tumor growth. A study by Hendrix *et al* [32] found three modes of tumor microcirculation; MV may represent an intermediate stage between VM and endothelium-dependent vessels. Sun *et al* [33–34] confirmed that different stages of tumor growth correspond to different stages in a three-stage process of blood supply patterns. In the early stage of tumor growth, blood is mainly supplied from vascular

mimicry; with increasing tumor volume, endothelial cells continue to proliferate and mosaic vessels appear between the VM and endothelium-dependent blood vessels. The first two are composed of endothelial cells, which gradually replace blood vessels and become the main form of tumor blood supply to provide sufficient blood and oxygen to support tumor growth, invasion, and metastasis. Xiang *et al* [35] also confirmed that VM was generated during the early stage in non-small cell lung carcinoma. As the disease progresses, VM may be replaced by vascular endothelial cells, and thus late-stage patients, particularly those with distant metastases, show fewer VM.

Tumor cells may express angiogenic factors, accumulate normal endothelial cells to form vascular channels, and support tumor growth and spread. However, VM and MV differ from the traditional angiogenesis model. The VM wall is composed of tumor cells and/or basement membrane lining without endothelial cells. In MV, the inner wall can be composed of endothelial cells and tumor cells. In a study examining the number of glioma polyploid giant cancer cells associated with vasculogenic mimicry formation and tumor grade in human glioma, Qu *et al* [36] found that there was more VM and MV in high-grade gliomas than in low-grade gliomas. Additionally, polyploid giant cancer cells generating erythrocytes contribute to the formation of VM and MV. Zhang *et al* [37], using C57 mouse melanoma B16 transplanted tumor tissue, attempted to identify the type of tumor blood supply vessels in different melanoma growth stages. They showed that in the early stage of rapid growth, VM is the dominant form of tumor blood supply. With increasing tumor volume, the number of vasculogenic mimicry channels decreased while the number of endothelium-dependent vessels increased, but the number of mosaic vessels was not associated with tumor size. Finally, endothelium-dependent vessels, which constitute the main pattern of blood supply, increased gradually.

Prospects

The discovery of VM has enriched the knowledge of the plasticity of tumor cells and angiogenesis. However, VM cannot replace endothelial-dependent angiogenesis in tumors, which is the dominant mode, and is only a supplemental form of tumor microcirculation. Nevertheless, the extensive clinical significance and special formation of VM have generated new avenues for anti-vascular tumor therapy. Currently, studies of the relationship between VM and other blood supply patterns are in the early stages. The use of anti-angiogenesis of endothelial vascular-targeted drugs alone have not got any outstanding effect. Anti-VM drugs can be used to compensate for the shortage. However, additional basic research studies are necessary to explore the VM formation mechanism further in order to identify the optimal target and inhibit the formation of VM as well as to develop clinical treatments. Large advances in the field of anti-tumor therapeutics are expected.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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