

The origins of vascularization in tumors

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1. ABSTRACT

Vascularization is crucial for tumor growth and metastasis. Angiogenesis and vasculogenesis are widely accepted processes of tumor vascularization, particularly for endothelium-dependent vessels. In both these processes, the tumor vascular endothelial cells are derived from the host cells, including cells in normal tissues around the tumor or endothelial progenitor cells. In addition, the mosaic vessels occur as a transitional pattern between endothelium-dependent vessels and vasculogenic mimicry (VM), wherein both host endothelium and tumor cells participate in tumor vascularization. VM provides a special passage not involving endothelial cells and is conspicuously different from angiogenesis and vasculogenesis. The biological features of the tumor cells that form VM remain unknown. Tumor stem cells may participate in VM. In this review, we discuss the patterns involved in the origin of vascularization in tumors.

2. INTRODUCTION

Vascularization is crucial for the growth and metastasis of tumors. Cancer progression is largely dependent on tumor vascularity, whereby new vessel formation ensures an adequate supply of nutrients, oxygen, and growth factors to the growing tumor and facilitates tumor dissemination (1).

The blood supply to tumors is proposed to involve 3 patterns, including vasculogenic mimicry (VM), mosaic vessels, and endothelium-dependent vessels (2). All 3 patterns provide blood supply to the tumor. According to the current model, VM is the main source of blood supply in the early stage of tumor growth, whereas endothelium-dependent vessels replace VM and mosaic vessels to become the dominant blood supply pattern at the late stage of tumor growth; thus, mosaic vessels appear as a transitional pattern.

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However, the occurrence of tumor vascularization remains an area of intense debate and tremendous interest. This paper focuses on the discoveries in this field and intends to summarize the current view of vascularization origins in cancer with respect to the blood supply patterns.

3. ORIGIN OF ENDOTHELIUM-DEPENDENT VESSELS

Presently, angiogenesis and vasculogenesis are the widely accepted processes of vascularization in tumor microcirculation. Angiogenesis is the formation of new microvessels from an established vascular network, and was first proposed in 1971 by Folkman as a therapeutic target for cancer (3). More recently, vasculogenesis has been suggested to be involved in the neovascularization of tumors from bone marrow-derived endothelial progenitor cells (4).

3.1. Current understanding of the angiogenic process in tumors

Blood vessels are remodeled through growth, migration, sprouting, and pruning to form a functional circulatory system by a process called angiogenesis. Angiogenesis is the process of vessel growth in which vessels sprout from pre-existing ones.

The first observation that angiogenesis occurs around tumors was reported approximately 100 years ago (5-7). In 1968, Greenblatt, et al (8) and Ehrmann, et al (9) proposed that tumors produce a diffusible “angiogenic” substance. Folkman subsequently proposed that tumor growth and metastasis are angiogenesis-dependent, and thus, blocking angiogenesis could be a strategy to arrest tumor growth (3). This prompted researchers to search for pro- and anti-angiogenic molecules. In 1976, Gullino observed that angiogenesis is essential for the transformation of precancerous tissue to cancerous tissue (10). Therefore, he suggested that angiogenesis could be a target in strategies to prevent cancer (7), which was later confirmed by genetic approaches (11). Vascular endothelial growth factor (VEGF), which is one of the key factors in angiogenesis, was then identified (12, 13). Due to these and subsequent discoveries of molecular determinants of vascular growth, angiogenesis research has assumed great importance (14). The process of angiogenesis is governed by a balance between multiple endogenous pro- and anti-angiogenic factors. An imbalance in these factors can lead to cancer progression.

It is now widely accepted that the imbalance of pro- and anti-angiogenic factors switch on an “angiogenic switch,” whereas these factors are balanced when the switch is “off” (15, 16). Various signals that trigger this switch have been identified, including metabolic stress, mechanical stress, immune/inflammatory response, and genetic mutations (17, 18). Moreover, the angiogenic process involves multiple cell types, including endothelial cells (EC), vascular smooth muscle cells, stromal cells, and parenchymal cells. The interactions among these cells

occur through secreting factors such as VEGF, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and angiopoietins, as well as through cell-extracellular matrix (ECM) interactions (19-21). If the tumors are able to switch the mechanisms of vascular growth and certain mechanisms relied less on VEGF, then the tumors would possess the means to escape treatment with VEGF receptor inhibitors. Thus, identifying the molecular basis of these alternative modes of vessel growth will be critical to improve the efficacy of anti-angiogenic treatment.

Recent studies provided insights into angiogenesis that lead to vessel branching (22-25). At first, the basement membrane of venules near tumor tissues changes with loss of electron density and gel-sol transition, which may be mediated by matrix metalloproteinases or plasminogen activators from tumor cells. During this process, angiogenesis factors such as FGF or VEGF, which are secreted by the tumor cells or host cells, can be liberated from the endothelial basement membrane. This process may be involved in the initiation of endothelial cell division and migration. Only the tips of the emigrating endothelial cells are free of basement membrane. These tip cells spearhead new sprouts and probe the environment for guidance cues. The stalk cells then extend filopodia, establish a lumen, and proliferate to support sprout elongation. The tip cells anastomose with cells from neighboring sprouts to build vessel loops. The new vessels become stable when blood flow becomes smooth, the basement membrane has been established, and mural cells congregate in the vessels (Figure 1). The sprouting process ceases when the pro-angiogenic signals abate, although it will restart once the signals are present. Moreover, studies have reported that the growth of the new capillary sprouts is not oriented towards the tumor, but leads to a high density anastomosing network of capillaries in the surroundings of tumor cell islands, resulting in a higher vessel density around the tumor than within.

In summary, an important concept in tumor angiogenesis is that tumor blood vessels contain genetically normal and stable ECs unlike tumor cells, which typically display genetic instability.

3.2. Current understanding of the vasculogenic process in tumors

Besides sprouting, tumors utilize other modes of vessel growth. Research has suggested alternative means of vessel formation by postnatal vasculogenesis or by differentiation of primitive/progenitor EC into mature EC (26). The initial assembly of progenitor cells (angioblasts) into a primary network of small blood vessels and into the dorsal aorta and cardinal veins of the very young embryo is called vasculogenesis. It has been observed that vasculogenesis can also occur in adults, particularly during tumor vascularization (27, 28). Vasculogenesis may occur when circulating endothelial precursor cells or bone marrow-derived hematopoietic cells are recruited in response to factors secreted from tumor cells, resulting in the generation of new vessels in the tumor.

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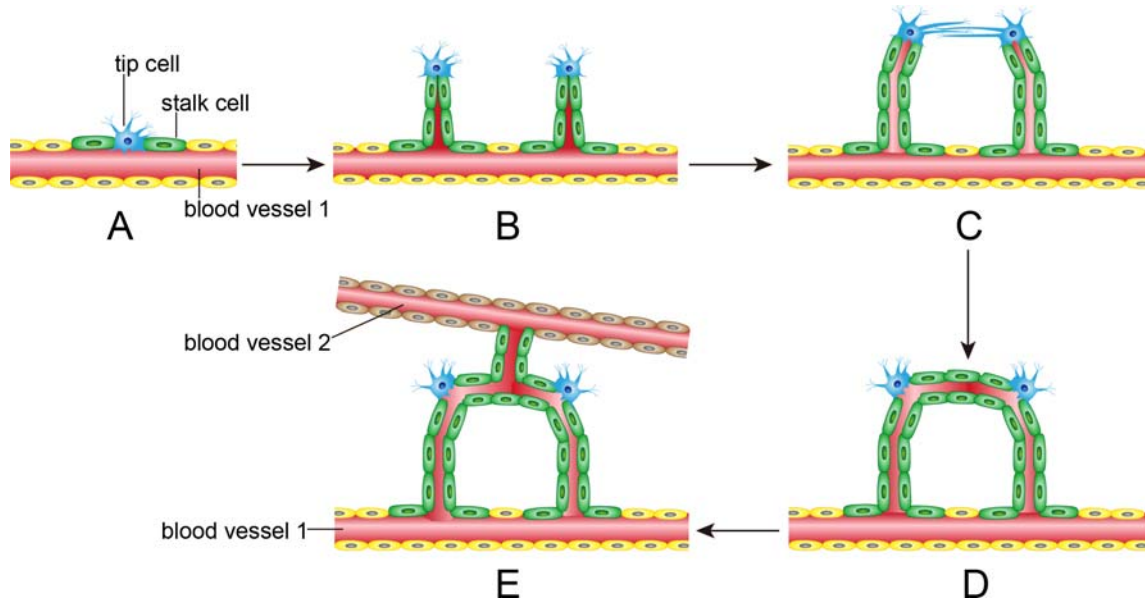


Figure 1. Angiogenesis process in tumor. (A) The basement membrane of venules near tumor tissues changes. The tips of the emigrating endothelial cells are free of basement membrane and spearhead new sprouts and probe the environment for guidance cues. (B) Stalk cells extend filopodia and establish a lumen and proliferate to support sprout elongation. (C) Tip cells anastomose with cells from neighboring sprouts to build vessel loops. (D) The new vessel has formed. (E) The new lumen connects with other vessel.

In the process of vasculogenesis, bone marrow-derived cells play a central role, and consist of many different cell types including endothelial progenitor cells, myeloid cells, and mesenchymal cells. Endothelial progenitor cells (EPCs) have the ability to differentiate into mature endothelial cells when recruited to angiogenic sites. In addition, EPCs can pro-angiogenically secrete many angiogenic cytokines including VEGF (29, 30), stromal-derived factor-1 (SDF-1) (29), angiopoietin-1 (31), angiopoietin-2 (32), and erythropoietin (30). A clinical study indicated the presence of EPC incorporated into the tumor vasculature of cancer patients, who had received gender-mismatched bone marrow transplantation (33). Genetic mouse models have indicated that impaired EPC mobilization inhibits growth of certain tumor models (34, 35). However, myeloid cells and mesenchymal cells can support the vasculogenic process. Myeloid cells have been reported to possess the capability to promote tumor angiogenesis (36) and progression (37, 38). In myeloid cells, many of the pro-angiogenic factors that promote vasculogenesis have also been identified, including matrix metalloprotease-9 (MMP-9) (39, 40), cathepsin cysteine protease (41), Bv8, and prokineticin 2 (42). As for bone marrow-derived mesenchymal cells, these factors can promote tumor vasculogenesis by providing carcinoma-associated fibroblasts (43, 44) or perivascular mural cells (45), and by secreting angiogenic cytokines such as SDF-1 (44) and VEGF (46).

These bone marrow-derived progenitor cells are highly orchestrated under the specific tumor microenvironment, which varies depending on the tumor type, thereby tightly regulating neovascularization in the tumors. Although these factors can promote tumor

vascularization during metastasis, their specific role in tumor vasculogenesis is still debated and context-dependent (47).

In summary, vasculogenesis is believed to arise from the recruitment of circulating cells, largely derived from the bone marrow, and de novo clonal formation of blood vessels from these cells.

4. ORIGIN OF MOSAIC VESSELS

Though angiogenesis and vasculogenesis are widely accepted patterns of tumor vascularization, these classical patterns have been challenged by the observation that tumor vasculature can also be formed by tumor cells or tumor stem cells (48, 49). The mosaic vessel is a pattern between endothelium-dependent vessel and VM, in which both host endothelium and tumor cells participate in tumor vascularization.

The mosaic vessel is a blood supply pattern for malignant tumor growth with endothelial and tumor cells randomly lining the vascular wall. However, the mechanism of mosaic vessel formation is still unclear. In recent years, some theories on this mechanism were proposed as follows: 1) Endothelial cells could drop from the vessel wall, and tumor cells are directly exposed to the blood tube (50); 2) some endothelial cells that lose immunological marker activation in tumor progression cannot be stained and become recessive cells; and 3) endothelial cells form the blood vessel structures, whereas tumor cells invade and are located in the blood vessel wall (51). These theories suggest that the vascularization origin of mosaic vessels is from both host epithelial cells and tumor cells.

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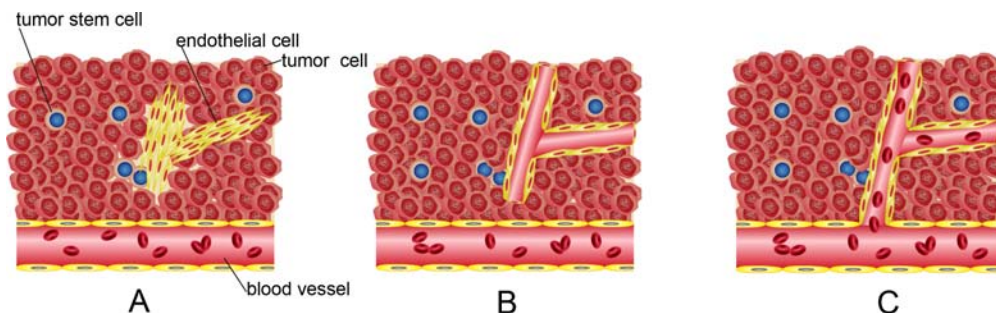


Figure 2. Tumor stem cells participation in vascular mimicry. (A) Tumor stem cells differentiate into endothelial cells. (B) Those endothelial cells line up to form lumen. (C) The new lumen connects with other vessels, and the new vessels become stable when blood flow becomes smooth.

5. ORIGIN OF VASCULOGENIC MIMICRY

In both angiogenesis and vasculogenesis patterns, the vascular endothelial cells in tumors are derived from the host cells, including cells in normal tissues around the tumor or endothelial progenitor cells. However, recently there has been published evidence of a novel occurrence of tumor vascularity, which suggests that tumor cells themselves organize in channels because their structures are lined by cells lacking the endothelial phenotype and markers (52-54). This observed pattern of tumor vascularization appears to be VM.

The VM pattern involves vessels lined exclusively with tumor cells mimicking the presence and function of endothelial cells (55, 56), in which the vascularization origin is from tumor cells only. One study has indicated that VM is clinically important because it represents an important survival mechanism contributing to the failure of current anti-angiogenic therapy that aims to completely deprive tumors of their blood supply (57). However, the cellular and molecular events underlying the formation of VM are not well understood. The origin of VM may provide a novel target for tumor therapy.

The discovery of tumor stem cells, with the capability of self-renewal and multipotency of differentiation, has stimulated great interest in redefining tumor vascularization (58). Recent studies have observed that tumor stem cells could be an origin of tumor vascularization in VM (59, 60). The plasticity of tumor stem cells could explain the expression of genes associated with vascular cells in tumor cells (59, 61), and the organization of tubular structures by tumor cells (62). A human renal cell carcinoma study observed that a subset of tumor-initiating cells, which express the mesenchymal stem cell marker CD105 and display stem cell properties but lack of differentiative epithelial markers, can generate epithelial and endothelial cells in vitro (63). An in vivo study also showed that tumor stem cells can differentiate into both tumor epithelial and endothelial cells (64). More recently, the ability to differentiate into endothelial cells has been reported for cancer stem cells present in neuroblastomas (49, 65). Further studies have shown that tumor stem cells coexpressing CD133 and CD144 (65), or Oct4 and tenascin C (66) had the potential to become tumor

vasculature. Selective targeting of tumor-derived endothelium in mouse xenografts resulted in tumor reduction and degeneration, indicating a relevant role of tumor stem cell-derived vasculogenesis (49). Therefore, we suggest that tumor stem cells differentiate into endothelial cells, the endothelial cells then line up to form a lumen, the new lumen connects with mosaic vessels or endothelium-dependent vessels, and the new vessels become stable when blood flow becomes smooth (Figure 2).

6. CONCLUSIONS

Through examination of the patterns of angiogenesis, vasculogenesis, and VM involving tumor stem cells in tumor vascularization, we conclude that tumor vascularization is a complex scenario due to the concomitant activity of different mechanisms, which may in turn vary according to the tumor type, grade, and therapeutic response, and may be unique to each patient.

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Abbreviations: VM: vasculogenic mimicry; FGF: EC: fibroblast growth factor; endothelial cells; PDGF: platelet-derived growth factor; ECM: extracellular matrix; EPCs: Endothelial progenitor cells; SDF-1: stromal-derived factor-1; MMP-9: matrix metalloprotease-9

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