Angiogenesis and de novo Arteriogenesis

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Arteriogenesis supply oxygen and nutrients in tumor microenvironment (TME), which may play an important role in tumor growth and metastasis. Current anti-angiogenetic targeted treatments have not shown substantial clinical benefits and they are poorly tolerated, and even lead to more malignant relapse. The heterogeneity of tumor-associated endothelial cells (TAECs) and tumor vasculature may be important and should be appreciated in therapeutic targeting the TME. In this regard, the de novo arteriogenesis within the TME may be associated with tumor progression, stemness of cancer stem-like cells (CSCs) and therapeutic resistance and relapse. Targeting tumor arteriogenesis may thus be a potential novel therapeutic target. Specifically, targeting the FoxO1-CD36-Notch pathway could show the clinical potential by acting on arteriolar niche and CSCs at the same time in a variety of cancers including neuroendocrine cancers, breast cancers, lung cancers and malignant melanoma.

Basic Concept of Angiogenesis

Angiogenesis is considered one of the hallmarks in tumor growth and metastasis[1] , in which the heterogeneity of vascular endothelial cells (ECs) and de novo arteriogenesis may play important roles and serve as new therapeutic targets, especially in highly angiogenic tumors such as neuroendocrine tumors. John Hunter, a British surgeon, was the first to coin the term angiogenesis by describing blood vessels that grow in reindeer antlers in 1787 [2]. Two centuries later, Dr. Judah Folkman, a surgeon at Harvard Medical School further developed the concept of angiogenesis, which was defined as the development of new blood vessels from preexisting vessels via sprouting[3] . Mechanistically, angiogenesis is growth and remodeling process of primitive networks into a complex network[4] .

Broadly speaking, the growth of new blood vessels includes vasculogenesis, angiogenesis, and arteriogenesis. Vasculogenesis is defined as the generation of blood vessels from hemangioblasts (endothelial precursors) during embryonic development of the cardiovascular system[5] , including the initial formation of blood islands and tubes. This is followed by the development of vascular trees with the myriad of blood vessels to nourish all tissues and organs. Vasculogenesis can also occur during tumor progression, which may lead to the formation of immature and poorly functioning vascular networks[4] .

Angiogenesis is a more generic concept referring to the formation of new microvessels[6] . This process is also known as neoangiogenesis under both ischemic and neoplastic conditions[7] , where new capillaries are formed by sprouting or longitudinally splitting of preexisting blood vessels[8][9] . The capillary networks are fed by the arterioles, the terminal components of the arterial system via arteriogenesis.

Arteriogenesis refers to a process in which smooth muscle cells (SMCs) cover ECs during vascular myogenesis, accompanied by vascular stabilization. A typical change seen in arteriogenesis is the enlargement of preexisting arterioles [4]. However, an adult arteriogenesis can be a de novo process that occurs by the blood vessels expansion and capillary arterialization[10][11][12] . Previous studies suggested that de novo arteriogenesis in adult organisms under ischemic and oncogenic conditions[13][14][15] could be associated with CD36 expression. CD36 is a key regulator in angiogenesis and fatty acid metabolism[16][17] , and is a potential driver in metastatic cancer stem cells (CSCs)[18][19][20] .

Venogenesis is used to define the formation of new venous vessels[21] . Similar to the ECs in the arteriogenesis, the venous ECs may generate different batches or concentrations of similar factors to complete the recruitment and differentiation of venous SMCs, and formation of new venules during angiogenic processes. The venules is the first ramifications of the venous system that can drain blood and components in the microcirculation away from the capillary networks.

As for the tumor vasculature, it is highly heterogeneous with regard to their organization, function and structure.

Six distinct types of tumor-associated blood vessels have been identified in several types of human cancers and replicated in an animal model. These vessels develop into neoangiogenesis by three distinct but parallel interrelated processes: angiogenesis, arteriogenesis and venogenesis[14][21][22] , as well as vasculogenesis by the formation of capillaries via endothelial progenitor cells or CSCs[23][24] .

De novo Arteriogenesis, an Emerging Concept of Formation of New Vascular Networks

Angiogenesis as a hallmark of cancer supplies oxygen and nutrients, and disposes wastes, which is critical for tumor growth and metastatic spreading[3] [25][26]. Tumor angiogenesis originally referred to new capillary growth by regeneration of a population of capillary ECs within a neoplasm[25] . Tumor cells cannot grow more than 2-3 millimeters in diameter without angiogenesis[27] . Tumor angiogenesis is regulated by VEGF prominently via VEGF receptor 2 (VEGFR-2) signaling in vascular ECs[28] . This signaling pathway is also required for angiogenic remodeling[29] , an important process of vascular maturation and arteriogenesis. The anti-VEGF monoclonal antibody bevacizumab has shown certain clinical significance in multiple tumor types with limited efficacy, which probably results from its targeting mainly at the newly formed capillaries but not at matured tumor-associated vessels and newly formed tumor-associated arterioles[21] that we call de novo arteriogenesis.

There is a general belief that arteriogenesis refers to the remodeling process of pre-existing arteries or the increase in the lumen volume and size of the vessel wall, in which smooth muscle cell (SMC) proliferation may play an essential role[4][30][31] . However, de novo arteriogenesis represents the formation of new arteriolar networks via capillary arterialization, in which the proliferation and arteriolar differentiation of ECs, particularly MVECs, may be critical[11][12][13][15][32][33][34][35] .

EphrinB2 represents the earliest specific marker for arterial ECs[36] . In Zebrafish, the gridlock gene, an HLH gene required for assembly of the aorta, specifies arterial fate[37][38] and regulates Notch signaling pathway[39][40] . Inhibition of the Notch pathway in ECs by gridlock determines an arterial fate. While VEGF can upregulate the expression of ephrinB2 and stimulates the arterial fate of ECs[41][42][43] . Angiopoietins, a multifaceted cytokine that functions in angiogenesis, also regulates an arterial fate of ECs via modifying VEGF functions [43]. The small chemical molecule GS4898 can rescue the gridlock function in a Zebrafish model with gridlock mutant phenotype[44][45] . This small chemical molecule promotes arterial differentiation via stimulating MAPK/Erk pathway during postnatal angiogenesis in a mouse hindlimb ischemia model[13] . These studies suggest a role of de novo arteriogenesis during development and under ischemic conditions. The micro-CT imaging actually documented the occurrence of the newly formed arterioles under ischemic conditions [13].

Recent studies have shown that lysophosphatidic acid (LPA), a lipid signaling mediator, may facilitate the formation of functional arterioles in corporation with VEGF in vivo[15] . This biological effect may be associated with FoxO-1 regulation of VEGF expression and crosstalk between VEGF signaling and CD36 pathway[46] . Studies suggest that MVECs may be converted to arteriolar ECs. This process is likely to be involved in the CD36-mediated priming of VEGF signaling and capillary arterialization[16][47][48][49][50] . In fact, the crosstalk between angiogenic and antiangiogenic signaling could be critical to the specification of arterial ECs[46][47] .

Venous ECs can be converted to arterial ECs by VEGF both in vitro and in vivo[42][43] , further exemplifying the plasticity of vascular EC phenotypes. This phenomenon is supported by the fact that shear stress in circulation may determine the phenotypes of ECs[51] , leading to the formation of either arterioles or venules through differentiation of two distinct types of ECs.

Vascular ECs are indeed critical for the regulation of arteriogenesis. In response to VEGF and other cytokines, ECs can be activated to increase the expression of FGF-2, platelet-derived growth factor PDGF-B and TGF-β1, thereby inducing the regrowth of SMCs and vessel enlargement[4][52] . Moreover, VEGF-mediated arteriogenic gene expression and Notch signaling may be essential for arterial differentiation and arteriolar remodeling in tumor microenvironment (TME)[13][15][29][49] , and may determine arterial fate and stimulate *de novo* arteriogenesis via preferential activation of downstream MAPK/Erk rather than PI3Kinase/Akt signaling as shown in animal models[13][44] . We propose that during adult angiogenesis, arteriolar ECs can signal recruitment and appropriate differentiation of

arteriolar SMCs, thus leading to the development of arterioles, particularly under ischemic and oncological conditions. Furthermore, arteriolar ECs will generate a variety of factors including PDGF-B, TGF-β1, FGF-2, and thrombospondin 1 (TSP-1) to facilitate the recruitment and proliferation of arteriolar SMCs to form arterioles. This is accompanied by a corresponding formation of extracellular matrix, leading to the development of a mature arteriolar network.

The arterioles that feed into a capillary network in TME[53] represent a long-term structural adaptation to altered metabolic demand[54] , likely occurring via de *novo* arteriolar remodeling of capillaries into arterioles[11][13][15][33][55][56] . The significant increase in intratumoral capillaries during tumor progression[57][58] reasonably requires concurrent expansion of upstream arterioles[14][53][57][59]. Analysis of tumor angiogenesis based on TAEC proliferation and pericyte recruitment demonstrated that there is an active angiogenesis in several types of human tumors[60] . The results actually implicate the formation of feeding arterioles or de novo arteriogenesis[14][21][22] since the staining for the tumor vessels was not confirmed with other specific markers other than α-SMA, a key marker for SMCs [60]. Dr. Harold Dvorak group elegantly documented the appearance of arteries and arterioles in TME[21] .

Most tumors continue to generate significant amount of VEGF over long periods of time, thus, continually inducing the formation of new blood vessels[21] . In collaboration with LPA and/or FGF-2, the VEGF might concurrently lead to previously formed vessels to develop into more stable forms of arteriolar vasculature[15][52][61] within TME. In response to VEGF overexpression capillaries are enlarged and transformed toward an arterial phenotype in a process that is known as capillary arterialization[62] or arteriogenesis. Similarly, Dvorak group showed that in TME VEGF-secreting tumors and Ad-VEGF-A164 stimulates abnormal arteriogenesis and venogenesis via remodeling of pre-existing arteries and veins to feed and drain the angiogenic vascular bed in animal models[21] .

In fact, extensive studies show that arteriogenesis may likely occur within TME in animal models and in patients with cancer[15][21][22][53][56][57][59][63][64][65] , possibly within TME of pNETs. NETs including pNETs classically are most easily apparent on the early arterial phase of a computed tomography (CT) scan. For decades, it has been clinically appreciated that many primary gastrointestinal NETs and metastatic sites have a pattern of early arterial enhancement on cross-sectional imaging. Consequently, contrasted multiphase CT or magnetic resonance imaging is an important component in the evaluation of a patient with a suspected primary or recurrent NETs[66][67] . Compared with normal pancreatic islets, pNETs have increased expression of nestin, probably contributing to vascular remodeling within TME of pNETs[21][22][53][68] . Though the vessels in grade 3 NETs display the highest EC angiogenic activity, they have regained pericyte coverage[69] . These studies suggest an increase in the formation of matured blood vessels and possibly development into arterioles within the TME of pNETs. The development of arteriogenesis is supported by studies showing the high levels of pro-arteriogenic factors VEGF, VEGF receptors and FGF-2 in NETs, but not in normal islet cells. Moreover, recent studies suggest that MVEC transdifferentiation into arteriolar ECs is likely an approach to facilitating the formation of arterioles under physiological or pathological conditions[14][15] . Intriguingly, during development different types of blood vessels may be generated from different origins. Pulmonary capillaries are developed by angiogenesis while pulmonary arteries are developed by vasculogenesis[70] , which further supports the concept that *de novo* arteriogenesis exists under physiological and pathological conditions[13][14] .

Maturation of the endothelial networks within TME involves remodeling and 'pruning' capillary-like vessels with uniform size, and irregular organization into a structured network of branching vessels. Blood flow in tumor vessels is often chaotic, slow, and not efficient in meeting metabolic demands in some tumors[71] . However, blood vessels in tumor beds should be functional enough to allow oxygen and nutrients to be supplied and metabolic wastes to be removed. De novo arteriogenesis may be the case in highly angiogenic tumors such as in pancreatic neuroendocrine tumors, in which the antiangiogenic drug sunitinib is partially effective as a targeted therapy against tumor vessels[72] .

Tumor Arteriogenesis: Potential Target in Cancers

Tumor angiogenesis has been extensively studied since Folkman coined this concept more than three decades ago[25] whereas the role of de novo arteriogenesis within TME is important but under- appreciated, and the mechanisms remain largely unknown. The arterioles to supply the vascular beds of tumors[53] might be generated by de novo arteriogenesis. The arteriolar differentiation of TAECs (a key component of the CSC niche[73]) and arteriolar remodeling within the TME might serve as a unique vascular niche for CSC maintenance and self-renewal in malignant progression of pNETs and other types of cancers including breast and lung cancers, and malignant

melanoma.

Actually, not only do ECs serve as gatekeepers of organ homeostasis[74], but they are also essential to maintain the function of arterioles in providing nutrients to cancer cells[13][14][75] including CSCs. EC differentiation likely plays a key role in tumor arteriogenesis[14][21][53][59][76] in that arteriolar ECs may recruit SMCs to form arterioles and promote tumor progression by serving as an arteriolar niche for CSC maintenance and self-renewal. Prior studies have shown that the LPA/PKD-1-CD36 signaling axis switches MVECs to an “arteriolar phenotype” [15][34][77]. We postulated that TAECs also possess plasticity and may be reprogrammed for arteriolar differentiation toward arteriolar remodeling in response to microenvironmental factors within TME for the progression of cancers.

Future potential therapeutic strategies may include combinations of antiangiogenic therapy with anti-CSC strategy by targeting both FoxO-1-CD36 signaling axis and Notch pathways. This combination might significantly limit the growth of cancers including neuroendocrine tumors and breast cancers and inhibit their metastasis by targeting both arteriolar niche and CSCs despite the caveats that CSC plasticity evokes toward the design of anti-CSC therapies. Additionally, venous components could be involved in regulation of CSC behavior via venogenesis, the functional role of which needs to be further investigated in a variety of cancers. It will also be worthy of better understanding of the mechanisms by which vascular niche within TME specify the CSC state and plasticity in the setting of malignant tumors. Moreover, developing clinically relevant cancer models with robust angiogenesis, matured vasculature, and arteriogenesis in animals should facilitate the understanding of mechanisms and early diagnosis.

The transdifferentiation of TAECs and CSCs may be explored and targeted since TAEC heterogeneity may respond to anti-angiogenic drugs differently and CSC plasticity concept represents the capacity of CSCs undergoing both differentiation and transdifferentiation. Because targeting vascular niche may reactivate and sensitize quiescent CSCs to anti-cancer therapy, an approach to targeting both vascular niche and CSC compartment may present an attractive strategy via the identification of key regulators of arteriolar differentiation and CSC metabolism and differentiation in cancers. In this regard, the PKD-1/CD36-FoxO1 signaling axis is likely to be a promising and potential candidate target. Dissecting this pathway will facilitate the identification of key and targetable regulators because of its close association with both tumor neoangiogenesis (de novo arteriogenesis) and stemness and plasticity of CSCs.

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