The Implication of Hypoxia and Cancer Stem Cells on Tumor Vasculogenesis

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Abstract

Tumors vasculature and lymphogenesis are crucial for growth and metastasis. Tumor vessels are characterized by irregular structure with higher permeability than normal vessels. This irregularity in shape results in micro-regional hypoxia due to inadequate oxygen supply to tumor cells. Triggered by hypoxia and mediated by Cancer Stem Cells (CSCs), both angiogenesis and Vasculogenic Mimicry (VM) were found in many solid tumors including breast cancer, melanoma, Head and Neck Squamous Cell Carcinoma (HNSCC).

Tumor Angiogenesis and Cancer Stem Cells (CSCs)

Tumor angiogenesis develops due to injury in the basement membrane in tissue and creation of hypoxia thus releasing angiogenic factors that activate endothelial cells to migrate, proliferate and stabilize [1]. The activation of the angiogenic factors such as Vascular Endothelial Growth Factor (VEGF), Basic Fibroblast Growth Factor (bFGF) and angiogenin and the down-regulation of the angiogenic inhibitors such as angiotatin, interferon, platelet factor 4 and endostatin together regulate tumor angiogenesis [2]. Tumor neovascularization is often linked to stemness through the differentiation of CSCs to endothelial cells. CSCs in melanoma differentiate into endothelial-like cells when cultured in specific endothelial cell growth medium [3,4]. Studies explained the implication of CSCs in angiogenesis [3-5].

The human melanoma cell line, WM115, expresses angiogenic factors including VEGF, VEGFR-2, Ang1/2 and Tie2 along with melanoma specific CSCs signaling proteins such as Notch [4,5]. Moreover, it was found that CSCs promote EGFR-Akt-Smad signalling resulting in ID3 regulated cytokine induction which drives tumor angiogenesis [3]. As in other tumors, the CSC marker, CD133, is also important for angiogenesis in melanoma. CD133+ melanoma specific CSCs play an important role in the formation of functional tubules and in the maintenance of endothelial cell alignment [4].

Rapid uncontrolled tumor growth leads to increased oxygen demand due to a surge in cellular metabolism, resulting in the eventual formation of hypoxic microenvironment [6]. Hypoxia is considered a key driving force of tumor progression, significantly impacting tumor cell differentiation [7]. In addition, hypoxia stimulates the activation of transcription factors and signaling pathways involved in angiogenesis and cell survival, which further promote tumor growth and metastasis [8,9].

Vasculogenic Mimicry is Triggered by Hypoxia

Anti-angiogenic cancer drugs that target tumor vasculature result in hypoxic stress within the tumor microenvironment [10]. Hypoxic conditions can trigger the formation of independent non-angiogenic vascular-like structure in a few solid tumors, a phenomenon is known as Vasculogenic Mimicry (VM) [11]. VM was first described in 1999 using an aggressive melanoma cell model that acquired endothelial-like properties by de-differentiating into multiple cellular phenotypes. The endothelial-like characteristics acquired by these cells resulted in the development of vascular-like structures described as vasculogenic-like matrix-embedded networks [12]. These vasculogenic-like networks contained plasma and red blood cells suggesting that this matrix could contribute to tumor blood circulation [12,13]. VM networks were found to be enriched in laminin and lined by tumor cells [12-14]. Importantly, there was no evidence for the presence of endothelial cells within these matrix-rich channels, identifying VM as a fully independent process from angiogenesis [12].
In aggressive tumors, an increased risk of metastasis is associated with an abundance of VM-associated matrix-rich networks in tumor tissue, consequently correlating with poor clinical outcomes in patients [12,15,16]. In hepatocellular carcinoma, hypoxia promoted VM through transcriptional co-activation of Bcl-2 and Twist1 where their nuclear co-expression is correlated to VE expression [17]. Also, the expression of hypoxia-inducible factor HIF-2α up-regulates VE-cadherin [18]. VE-cadherin expression triggers signaling pathways which in turn activates VM in melanoma [14]. Knockdown of VE-cadherin results in the inhibition of VM in aggressive melanomas [19].

**The Role of CSCs in Vasculogenic Mimicry**

Cell plasticity plays an important role in the neovascularization process, associated with extracellular matrix remodeling [20]. The de-differentiation of cancer cells to an embryonic or stem-like cell phenotype results in tumor plasticity resulting in VM forming tumor that express endothelial specific genes [21]. CSCs exhibit a plasticity that enables their trans-differentiation into cell types of variable lineage including endothelial-like and highly replicative tumor cells [22,23]. Furthermore, CSCs were observed in VM-forming tumors including melanoma, glioblastoma, OSCC and breast cancer [3,19,24,25].

Aggressive melanoma cells undergoing VM express genes relevant to stem cells as well as alternative cell phenotypes. The plasticity, multipotency and embryonic-like phenotype define these cells as Malignant Melanoma Stem Cells (MMSCs) [26]. In breast cancer cells, holoclones (CSC clones highly expressing CD133) were able to form a well-established VM tubular structure while meroclones and paraclines (well differentiated clones) failed to establish VM networks which highlights the important role CSCs play in the formation of VM [27].

**Conclusion**

Anti-angiogenic agents have been widely accepted as an effective anticancer therapy. However, conventional anti-angiogenic treatments exhibit limited efficacy in preventing tumor progression [28]. Common anti-angiogenic drugs like angiotatin and endostatin inhibit endothelial cell proliferation and enhance endothelial apoptosis resulting in a hypoxic microenvironment due to reduced vascular density [29]. Deficiencies in oxygen and nutrients contribute to VM formation as an alternative supply route, compensating for the loss of vasculature [30]. Tumors undergoing VM are typically highly aggressive, malignant and resistant to anti-angiogenic therapeutics [31,32]. Consequently, routine antiangiogenic therapies can, in part, contribute to disease progression. Therefore, it is crucial to develop new treatments capable of targeting different types of tumor vasculature; angiogenesis and VM, rather than conventional anti-angiogenics.

**References**


