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Cancer stem cells and their vascular niche: Do they benefit from each other?

Yi-Fang Ping [a,b,*], Xia Zhang [a,b], Xiu-Wu Bian [a,b,**]

[a] Institute of Pathology and Southwest Cancer Center, Southwest Hospital, Third Military Medical University, Chongqing 400038, China
[b] Key Laboratory of Tumor Immunopathology, Ministry of Education of China, Chongqing 400038, China

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ABSTRACT

Cancer stem cells (CSCs) locate in and interact with particular vascular niches to maintain their stemness. CSCs induce, remodel and participate in the formation of microenvironmental niches to facilitate survival, stemness and escape from radio-/chemo-/bio-therapies. Neovasculature in tumor is often basement membrane-deficient and enriched with CSC-derived endothelial cells (ECs) and other mural cells, which may promote tumor invasion and metastasis. The aim of this review is to summarize recent findings about the crosstalk between CSCs and their vascular niches and discuss the potential therapeutic significance.

Introduction

Cancer stem cells (CSCs) represent a special subpopulation of cancer cells with the exclusive capacity of self-renewal, multilineage differentiation and tumor initiation [1,2]. Although there remain controversies and discordances about the frequency of CSCs, the results from at least three independent groups support the existence and therapeutic importance of CSCs by using genetic techniques to track normal adult stem cells during tumorigenesis in the brain, the gut and the skin [3–5]. Due to the lack of specific markers, CSCs have been enriched by a variety of methods followed by confirmation of their stemness via combined evaluation of their self-renewal, multi-differentiation potential, and especially tumor initiating ability [6]. Therefore, the term "CSC" is only a functional definition and "CSCs" have recently been described as "a subclass of neoplastic stem cells that propagate malignant clones indefinitely and produce an overt cancer" (*The Year 2011 Working Conference on CSCs)* [2]. CSCs are relatively resistant to conventional radio- and chemo-therapies because they usually remain quiescent in cell cycle, rich in ABC drug transporters, with active DNA repair machinery and resistant to apoptosis [7,8]. Moreover, CSCs are highly migratory and invasive [9]. Recently, it has been reported that CSCs interact with tumor macrophages to promote tumor invasion and escape from killing by natural killer cells [10–12]. Therefore, CSCs are considered as the seeds of metastasis and recurrence after therapies including surgery and radio-/chemo-therapies as well as biotherapy.

CSCs reside in special vascular niches to maintain an undifferentiated state during tumorigenesis and progression. Meanwhile, CSCs induce extensive changes in vascular niches to exhibit heterogeneity [13–21]. Newly formed tumor microvessels are not only different from those formed during development and wound healing, but also vary among different tumors, with different stages or grades of a same tumor, and even in different patients with the same tumor. Therefore, better understanding of the interaction between CSCs and their vascular niches in tumor is of great importance for understanding the mechanisms underlying cancer development and progression as well as for development of novel therapeutic strategies.

Vascular niches for CSCs

Normal vasculature is composed of endothelial cells (ECs), basement membrane, and mural cells. ECs are in contact with blood and form the inner (luminal) surface of the vessels. Mural cells surrounding ECs are composed of pericytes in capillaries and smooth muscle cells in large vessels [22]. Vascular niches are important for maintenance of the stemness of normal adult stem cells, including self-renewal, undifferentiated status, and dormancy [23]. In the central nervous system, neural stem cells (NSCs) reside in vascular niches mainly at subventricular and subgranular zones. When co-cultured, ECs promote NSCs to show increased self-renewal capability but delayed differentiation through direct cell–cell contact and paracrine signaling. The paracrine signals include Notch receptor ligand Dll4, the Notch effectors Hes1 and Hes3, as well as the pro-angiogenic factors angiopoietin 2 and the chemokine axis CXCL12/CXCR4 [24–27]. Vascular niche also regulates adult stem cells in other organs. For example, vascular niches influence hair cycling by regulating the activity of hair follicular stem cells (HFSC) [28].

* Corresponding author. Tel.: +86 023 68754431; fax: +86 023 68754431.
E-mail address: pingyifang@126.com (Y.-F. Ping).
** Corresponding author. Tel.: +86 023 68754431; fax: +86 023 68754431.
E-mail address: bianxiuwu@263.net (X.-W. Bian).

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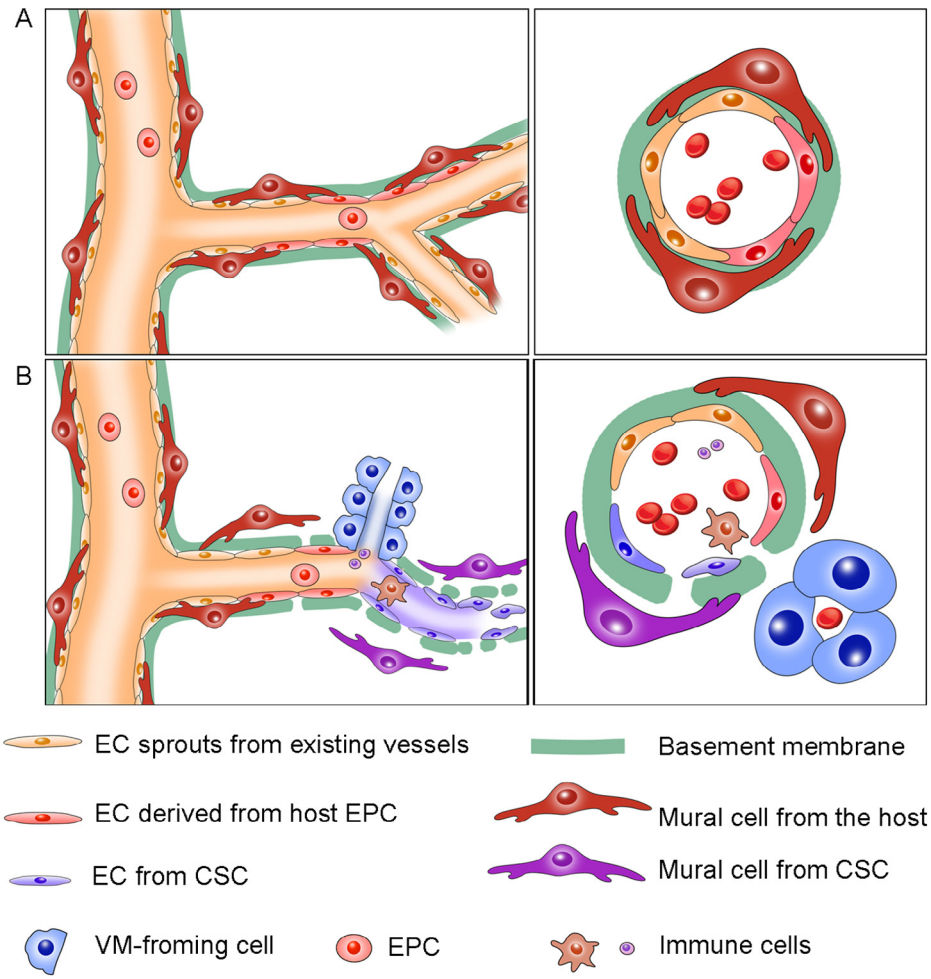

Fig. 1. Diagram of adult stem cells and CSC vascular niches. (A) Adult stem cell vascular niches are composed of ECs, basement membrane, and pericytes. ECs generated by either angiogenesis (ECs sprouting from existing vessels) or vasculogenesis (ECs derived from endothelial progenitor cells through recruitment and differentiation). (B) CSC vascular niches consist of ECs, pericytes, VM, basement membrane and immune cells trafficking to tumor via microvessels. In addition to angiogenesis and vasculogenesis, CSC transdifferention is another origin of ECs in CSC vascular niches. Pericytes can also be derived from both the host and CSCs. Morphologically, tumor microvessels are irregular, leaky and lacking of basement membrane and pericyte coverage. The left panel is a longitudinal section of vessels and the right panel represents the cross section. Abbreviations: EC, endothelial cell; CSC, cancer stem cells; EPC, endothelial progenitor cells; VM, vasculogenic mimicry.

During tissue regeneration, vascular niches orchestrate the balance between quiescence and proliferation of adult stem cells [29]. After injury, bone marrow-derived ECs are able to promote HSC proliferation through the adhesion molecule E-selectin and several pro-angiogenic factors [30–33].

CSCs are also preferentially located in vascular niches, therefore they are rich in perivascular microenvironment. Tumor blood vessels are abundant, leaky and poorly organized with a tortuous, dilated morphology, and are connected with each other in a haphazard pattern, which are different from normal vessels in number, structure and function [34]. These newly-formed immature microvessels in solid tumor tissues usually lack basement membrane and pericyte coverage [35,36]. Tumor-associated ECs are actively proliferative, hypertrophic in morphology, and form thickened vessels. These ECs genetically differ from normal ECs, being aneuploid and having complex abnormal karyotypes, such as loss of chromosomes, and double minute chromosomes and abnormal multiple centrosomes [37]. Some tumor EC cells even contain the same genetic abnormality as malignant cells. Their neoplastic origin has been supported by the findings of CSC transdifferentiation into ECs [13,14,38]. Furthermore, vasculogenic mimicry (VM), a channel formed by aggressive tumor cells without EC-lined inner surface, has also been shown to function as blood vessels to nourish tumor cells [39,40]. Based on the complicated components of neoplastic vasculature, we propose that vascular niches for CSCs consist at least of ECs (generated by angiogenesis, vasculogenesis and transdifferention of CSCs), basement membrane, pericytes (derived either from the host or from CSCs), VM and immune cells recruited to tumor via microvessels (Fig. 1).

The impact of vascular niches on CSCs: nourisher and protector

Vascular niches enhance the stem-like properties of CSCs

The adjacent localization of CSCs to vascularized areas indicates the importance of vascular niches to CSCs [41–45]. Calabrese et al. demonstrated that brain CSCs (identified by nestin) directly contact tumor microvessels (marked by CD34) through three-dimensional reconstruction and measurement of the distance between nestin-positive and CD34-positive cells. In co-culture, CSCs are prone to physical contact with ECs as compared to differentiated tumor cells [41]. CSCs have also been detected near ECs in other tumors, such as skin papilloma and colorectal cancer [42,45].

In transwell system experiments, ECs have been shown to regulate CSC phenotype by secreting soluble factors [41]. As compared

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