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Mini-review

Positive feedback loop between cancer stem cells and angiogenesis in hepatocellular carcinoma

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ABSTRACT

Anti-angiogenesis-related therapies have become the standard care for patients with advanced hepatocellular carcinoma (HCC), as HCC is a highly vascularized solid tumor. Unfortunately, only modest and limited efficacies are observed. Emerging evidence have attributed to the limited efficacy to the presence of cancer stem cells (CSCs) in the tumor. CSCs predominantly drives angiogenesis via releasing proangiogenic factors and exosomes. They have the ability to resistant intratumoral hypoxia via autophagy or by directly forming the tubular structure to obtain blood. On the other hand, the vascular niche in tumor microenvironment also releases growth factors via juxtacrine and paracrine mechanisms to support the growth of CSCs and maintain its stemness features. This positive feedback loop between angiogenesis and CSCs exists in liver tumor microenvironment that is responsible for the development and poor prognosis of HCC. In this review, we summarize recent advances in our understanding of the crosstalks between angiogenesis and CSCs, and their interactions in liver tumor microenvironment and their purpose that an effective anti-angiogenic therapy should also target CSCs for HCC treatment.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of death from cancer worldwide, as 748,300 new cases are diagnosed yearly. The incidence of HCC differs greatly depending on the geographic area and gender, with the highest prevalence of HCC occuring in East and Southeast Asia, as well as in Middle and West Africa. In addition, the incidence of HCC in men is approximately four times higher than that in women. Hepatitis B or C virus infection and alcohol-related liver damage are the major risk factors for HCC [1,2].

HCC is a highly vascularized solid tumor with rapid growth rate and poor prognosis. At present, liver resection or transplantation is the first-line treatment for patients with HCC, however, they showed only a 50% 5-year survival rate and a 70% recurrence rate [3]. Transcatheter arterial chemoembolization (TACE), a treatment referring to injection of anticancer drugs and iodized oil into the hepatic artery and followed by the administration of embolic agents, is more effective than systemic chemotherapy or conservative treatment [4]. For recurrent and un-resectable HCC, anti-angiogenesis therapies are the clinical standard cares, and Sorafenib, a multi-kinase inhibitor of angiogenesis, has been approved for advanced HCC [5]. While the antiangiogenesis treatments definitely showed modest efficacies and provide alternative therapies for patients with HCC, the recurrence rate and mortality have not been significantly improved [6,7]. Recent studies have attributed these problems to the existence of cancer stem cells (CSCs) in the HCC tumor mass [8–10]. CSCs or tumor-initiating cells are a rare population of cells that drives tumor initiation and growth. They play critical roles in tumor metastasis/recurrence, and the resistance to chemotherapy/radiotherapy in various malignancies [11].

Emerging evidence in particular from breast and brain cancer studies have documented the presence of crosstalks between CSCs and angiogenesis in tumor microenvironment, and they are directly associated with cancer development, progression and metastasis [12,13]. As one of the most vascular solid tumors, the role of angiogenesis in hepatocarcinogenesis has been investigated extensively. Because targeting against CSCs is a very promising approach for the development of curative treatments to cancer, the field of CSCs research is flourishing in recent years. Plenty of studies have also explained the biological features, functions and clinical significance of CSCs in HCC. More recently, researchers are interested in understanding the communications between CSCs and their microenvironment in HCC. However, tumor microenvironment is composed of various components and involves very complex mechanisms. As two most important pathological events in tumor microenvironment, the interactions between angiogenesis and CSCs in HCC remain elusive.

We summarized here the recent advances in these fields and proposed the presence of a feedback loop between angiogenesis and

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CSCs in tumor microenvironment that should play critical roles in tumor development and therapeutic resistance for HCC.

Angiogenesis and CSCs in HCC

Tumor angiogenesis is essential for tumor growth and metastasis in solid tumor. Angiogenesis is a multistep process that is tightly regulated by various factors in tumor microenvironment [14,15]. There are plenty of reviews on this topic. Generally, in their early stage, the growing tumor cells can obtain nutrients from the surrounding tissue via permeation process. If a tumor lesion exceeds a few millimeters in diameter, of which the permeation process is no longer sufficient to the oxygen/nutrient requirements of tumor growth, the 'angiogenic switch' will be triggered that means to tilt the balance between pro- and anti-angiogenic factors towards to pro-angiogneic priority. Endothelial cells (ECs) from the around vessels are proliferated by the stimulation of these pro-angiogneic factors, which further sprout and liberate enzymes to interrupt the basement membrane. Finally, ECs migrate to the final location where they assemble to form a new vessel together with the extracellular matrix (ECM). The formation of neovascular in tumor will greatly promote tumor progress.

The angioarchitecture and hemodynamic of angiogenesis in HCC have distinct pathophysiological characterizations that are changed with tumor progression [16]. HCC is one of the most vascular solid tumors with characteristic vascular abnormalities [17]. The blood of normal liver parenchyma, regenerative and dysplastic nodules are mainly supplied by the portal vein. In contrast, HCC predominantly develops blood supply from the arterial system according to its high requirement of oxygen during progression. It has been shown that new unpaired arteries without accompanied bile duct are a characteristic morphology that differentiates neoplastic nodules from regenerative cirrhotic nodules. From cirrhotic nodules (lowest) to low- and high-grade dysplastic nodules, the number of unpaired arteries is gradually increased and HCC has the greatest numbers of unpaired arteries, particularly in HCC with a size smaller than 3 cm in diameter. By use of hepatic arteriography and the contrast-enhanced computed tomography (CT), the minimal enhancement on contrast-enhanced CT imaging appears in small and well-differentiated HCC lesions that usually had isovascular or hypovascular. The greater enhancement on the CT imaging of the lesion was shown in HCC with increased microvessel density (MVD) [15,18]. These observations suggest that the main drainage vessels of hepatocellular nodules are transformed from hepatic veins to hepatic sinusoids, and then to portal veins during HCC development. These deregulated architectures should contribute to intra-tumoral hypoxia/or necrosis, and further injures the liver and induces the tumor cells and matrix cells to release pro-angiogenic factors to initiate angiogenesis.

In HCC, many factors have been identified to regulate angiogenesis with VEGF being the most important cytokine [19]. VEGF can bind with VEGFR1 and VEGFR2 in ECs to activate several signaling pathways that are responsible for the proliferation, migration, and invasion of ECs. In addition, VEGF can also directly affect the functions of hepatic stellate cells, Kupffer cells and hepatocytes, stimulate the dissolution of the vascular basement membrane and the interstitial matrix, and promote the aggressiveness of HCC [15]. Angiopoietin 2 and Tie-2 receptor have been identified as the other two important angiogenic factors that can boost the effect of VEGF on ECs; FGF, a member of the heparin-binding growth factors, acts synergistically with VEGF to induce angiogenesis, whereas PDGF is involved in cell migration and new vessel maturation. PDGF secreted by cancer cells acts as an activator to ECs and fibroblasts that correlates with cancer progression. In addition, integrins and cadherins have also been shown to associate with the tumor neoangiogenesis in HCC. Integrins can mediate cell-matrix interactions and cadherins is responsible for the cell–cell interactions during the new vascular tube formation. These regulation pathways emphasize the existence of complex orchestration for angiogenesis in tumor microenvironment of HCC.

Cancer stem cells in HCC

The cancer stem cells paradigm hypothesizes that tumors are frequently composed of heterogeneous cell types, in which a rare population of CSCs or tumor-initiating cells drives tumor initiation and growth, as well as tumor metastasis, recurrence, and chemotherapy/radiotherapy resistance. Therefore, therapies targeting CSCs could have major impact on cancer patient survival [11,20,21]. A large number of studies related to CSCs of HCC have been published in the last ten years. Many reviews have discussed this topic.

Early-phase studies are associated with the identification of CSC biomarkers in HCC. Multiple cell surface proteins have been identified as the biomarkers of CSCs that include CD133, the epithelial cell adhesion molecule (EpCAM), CD90, CD44, CD24, CD13, OV6, intercellular adhesion mole-cule 1 (ICAM-1) and calcium channel α2δ1 isoform5 [22–31]. In addition, the selected side population (SP) cells in Hoechst dye-staining also possess stemness properties of CSCs [29,32]. Among them, the stemness properties of calcium channel α2δ1 isoform5, EpCAM, CD90, and CD133-enriched cells were characterized in primary HCCs [32,33]. Recent studies showed that EpCAM+ and CD90+ cells were two independent subpopulations and had different tumorigenic/metastatic capacities [33]; EpCAM+ cells were associated with a high tumorigenic capacity and hepatic epithelial stem cell features, while CD90+ cells had a metastatic propensity with mesenchymal vascular endothelial cell features; moreover, CD90+ CSCs could enhance the motility of EpCAM+ CSCs via the activation of TGF-β signaling pathway. More recently, the biological functions of a few CSCs biomarkers have been explained [30]. For example: CD133 can activate neurotensin/IL-8/CXCL1 signaling to support the stemness properties [34]; EpCAM up-regulates Wnt signaling in ES cells and cancer [35,36]; CD44 regulates the redox status [37]; CD13 can prevent cell damage from genotoxic reagents-induced oxidative stress [24]. Calcium channel α2δ1 isoform5 regulates calcium influx and ERK signaling [38]. 1B50-1 is a monoclonal antibody of calcium channel α2δ1 isoform5 that can inhibit CSCs via block calcium influx and ERK signaling. These results suggest that the cell surface markers of CSCs may also be the therapeutic targets.

Tumorigenesis often mimics the progress of embryogenesis and shares similar signaling pathways. It has been shown that the signal transduction pathways regulating fetal liver development are also responsible for the regulation of the stemness and malignant phenotypes of hepatic cancer stem cells. During liver organogenesis, a few of liver specification signals are activated, including fibroblast growth factor (FGF), bone morphogenic protein (BMP), and Wnt [39–41]. Among them, the Wnt/β-catenin signaling pathway is very important for the self-renewal and maintenance of the stemness properties [10]. Mokkapati et al. showed that Wnt/β-catenin signaling pathway plays a tumor initiating role in HCC by the use of β-catenin overexpressing transgenic mice specifically targeting liver stem/progenitor cells [42]. As an evolutionarily conserved signaling module, notch participates in embryonic cell fate decisions and regulates stem/progenitor cell states [43,44]. Notch1 and Notch2 are key regulators for liver development, and they have been documented to play critical roles for the initiation of HCC [45]. The role of TGF-β signaling in HCC development remains controversial. Wu et al. showed that the TGF-β expression is positively correlated to CD90, CD133 and EpCAM stem cell markers; it also confers the rat liver progenitor cells with tumor-initiating cells properties in a DEN-induced hepatocarcinogenesis rat model [46]. However, on the contrary, Morris et al. showed that the loss of TGF-β signaling in liver restricted Pten and Tgfbr2 double knockout mice promoted HCC