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The Multistep Functions of EMMPRIN/CD147 in the Tumor Angiogenesis

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Abstract

CD147 is a member of the immunoglobulin family of receptors. Both clinical studies and basic research have indicated that elevated CD147 expression is correlated with tumor progression. It facilitates cancer invasion and angiogenesis. Targeting CD147 in cancer appears a promising future therapeutic strategy, but requires a better understanding of its mode of action and regulation. This review focuses on the most recent findings that addressing the role of CD147 in tumor angiogenesis and highlight the relational mechanisms. Supporting these findings are evidences that CD147 is an important modulator in tumor angiogenesis, thus, more attractive as a target for anti-tumor treatment.

Keywords: Tumor; Angiogenesis; Leukocytes

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Introduction

Tumor is one of the common diseases that seriously threaten human health. High invasion and metastasis are the principle reasons for the high mortality of cancer. Numerous studies have demonstrated that tumor vascularization is crucial in tumor progression [1-4]. EMMPRIN/CD147, a cell adhesion molecule highly expressed in a variety of tumors, is associated with poor prognosis in cancer patients. The results of our study and several other laboratories have confirmed that CD147 induces tumor angiogenesis and promotes tumor growth and metastasis. In the following pages, this review will summarize the mechanisms of CD147 induce tumor angiogenesis [5,6]. The present studies have shown that CD147 plays an important role in many aspects of the process of tumor angiogenesis.

Formation of Tumor Vessels: Vasculogenesis and Angiogenesis

The current concept was believed that, in tumors, new blood vessel formation has been thought to occur primarily via angiogenesis and vasculogenesis [2,7-15]. Angiogenesis is defined as the sprouting and growth of new capillaries from nearby existing blood vessels, however, postnatal vasculogenesisis defined as the endothelial precursor cells (EPCs) move to an angiogenic site and integrate into newly forming vessels [16-20]. In the angiogenic process, blood vessels grow through sprouting and intussusception, in which interstitial cellular columns are inserted into the lumen of pre-existing vessels and partition the vessel lumen [21]. In classical sprouting angiogenesis, the endothelial cells to form capillary walls secrete proteases which degrade the surrounding basement membrane, subsequently, invade the adjacent tissues and proliferate to generate new blood vessels.

Role of EMMPRIN/CD147 in Tumor Angiogenesis

Extracellular matrix metalloproteinase inducer (EMMPRIN), also known as CD147 and Basigin (Bsg) is a glycosylated transmembrane protein that belongs to the immunoglobulin (Ig) superfamily [22-25]. It is broadly expressed at varying levels on many cell types, including epithelial and endothelial cells, leukocytes [26-29], stromal fibroblasts [30], differentiated macrophage, activated T cells [31-34], dendritic cell [35], cardiac myocytes and platelets [36-38]. Interestingly, CD147 is highly enriched on the surface of malignant tumor cells. Indeed, CD147 has been greatly implicated

in malignancy as it is highly expressed in most tumor tissues and its expression often correlates with tumor progression [39-44]. Therefore, much attention has been focused on this molecule that plays a key role in tumor angiogenesis.

Enriched CD147 in tumor cells initiates the formation of an angiogenesis niche

Angiogenesis is the result of the combination of signaling molecules and tumor microenvironment [45-48]. The angiogenic switch is defined as an imbalance between pro- and anti-angiogenic molecules and is a key step in tumor angiogenesis [49-53]. The angiogenic molecules include: matrix metalloproteinases (MMPs), basic fibroblast growth factors (bFGF), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), insulin-like growth factor (IGF), epidermal growth factor (EGF), placental growth factor (PLGF) and so on [54-56]. All these molecules promote the formation of new blood vessels in tumor and stromal cells. Recently, various studies have demonstrated that CD147 regulates the cross-talk between tumors and endothelial cells (ECs), and may promote tumor angiogenesis via regulating the tumor-stromal microenvironment which contains pro-angiogenic molecules such as MMPs, HIF-1, IGF-I, VEGF and CD147 itself [57-62]. Among them, HIF-1, a key hypoxia response transcription factor, induces the expression of many target genes including VEGF and IGF. VEGF is expressed by alternative splicing as six different isoforms (VEGF121, VEGF145, VEGF165, VEGF183, VEGF189 and VEGF206). Faten Bougatef, et al. have observed that CD147 selectively increases the expression of VEGF121 and VEGF165 isoforms, but not the VEGF189 [60]. In addition, IGF-I strongly induces the expression of CD147 in HUVECs cells and multiple tumor cell lines, which shows that there is a positive feedback mechanism between CD147 and IGF-I.

Up-regulation of CD147 in HUVECs enhances the angiogenesis

Except for tumor cells, CD147 is also expressed at different levels in many other cell types, such as ECs. Mutin and colleagues demonstrated that CD147 is a surface molecular marker on HUVECs with a moderate expression level under resting condition [62]. Danilo Millimaggi showed that CD147 stimulates pro-angiogenic activities of human umbilical vein endothelial cells (HUVECs) in a CD147-dependent fashion [61]. Y. Chen reported that CD147 is significantly up-regulated in activated HUVECs and the up-regulation of this molecule strongly enhances the angiogenic phenotype of activated HUVECs. CD147 regulates angiogenesis of ECs by several mechanisms including proliferation, survival, migration, MMPs secretion and PI3K/Akt activation [29]. In addition, another study by Faten Bougatef reported that CD147 up-regulates the expression of VEGFR-2, which is a receptor of VEGF in endothelial cells. The increase in VEGFR-2 is responsible for CD147 stimulating of the migratory and tube formation capacity of ECs, thus directly regulating the angiogenic process.

CD147 recruits BMDCs and enhances tumor vasculogenesis andangiogenesis

The role of bone marrow-derived cells (BMDCs) in angiogenesis and vasculogenesis has been documented by multiple studies [16,62-66]. However, the contribution of bone marrow–derived circulating endothelial progenitor cells (CEPs) to tumor angiogenesis has been controversial, because of their low numbers in blood vessels of untreated tumors. These BMDCs appear to promote angiogenesis by the release of pro-angiogenic molecules at sites of neovascularization to stimulate expansion of local blood vessels [17,20]. In 2001, David Lyden showed that transplantation of wild-type bone marrow (BM) or VEGF-mobilized stem cells restore tumor angiogenesis and growth. This study demonstrated that recruitment of VEGF-responsive BM-derived precursors is necessary and sufficient for tumor angiogenes [16]. Brock A Peters demonstrated that bone marrow stem cells definitely contribute to tumor angiogenesis in diverse human tumor types, but this contribution is relatively small [63]. Recently, by studying GFP expressing BMDC donor cells in LLC tumor xenografts, Chen et al. noticed that CD147 regulates tumor growth and metastasis by recruitment of BMDCs, which contributes to tumor neovascularization [67]. This report revealed a novel mechanism that CD147 promotes tumor growth and metastasis by recruitment of BMDCs through controlling secretion and paracrine signaling of SDF-1 and VEGF. Until now several studies reveal a novel mechanism by which CD147 promotes tumor angiogenes via recruitment of BMDCs.

Conclusion

After reviewing the literature on this field is clear that CD147 plays a key role in tumor angiogenesis. It is highly expressed on the surface of tumor cells and facilitates to form a microenvironment induced angiogenesis. CD147 stimulates tumor cells, nearby fibroblasts and endothelial cells to produce and secrete MMP, VEGF, IGF-1, and SDF-1. They modulate the cross-talk between tumor cells and endothelial cells and BDMCs. On one hand, these growth factors activate endothelial cells and promote it proliferation, migration and neovascularization; on the other hand, these molecular signaling and recruitment of BMDCs contribute to tumor vasculogenesis and angiogenesis. In addition, IGF-1 strongly induces the expression of CD147 in HUVECs cells and tumor cells. It can feedback up-regulate production of pro-angiogenesis. In activated endothelial cells, increased CD147 expression also strongly enhances the angiogenic phenotype by activation of VEGFR2 and PI3K pathway **(Figure 1)**. These findings have made CD147 an important molecule in formation of tumor vessels. Consequently, the development of effective therapeutic interventions targeted to CD147 would provide a novel and potentially powerful alternative to current cancer treatments.

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2016
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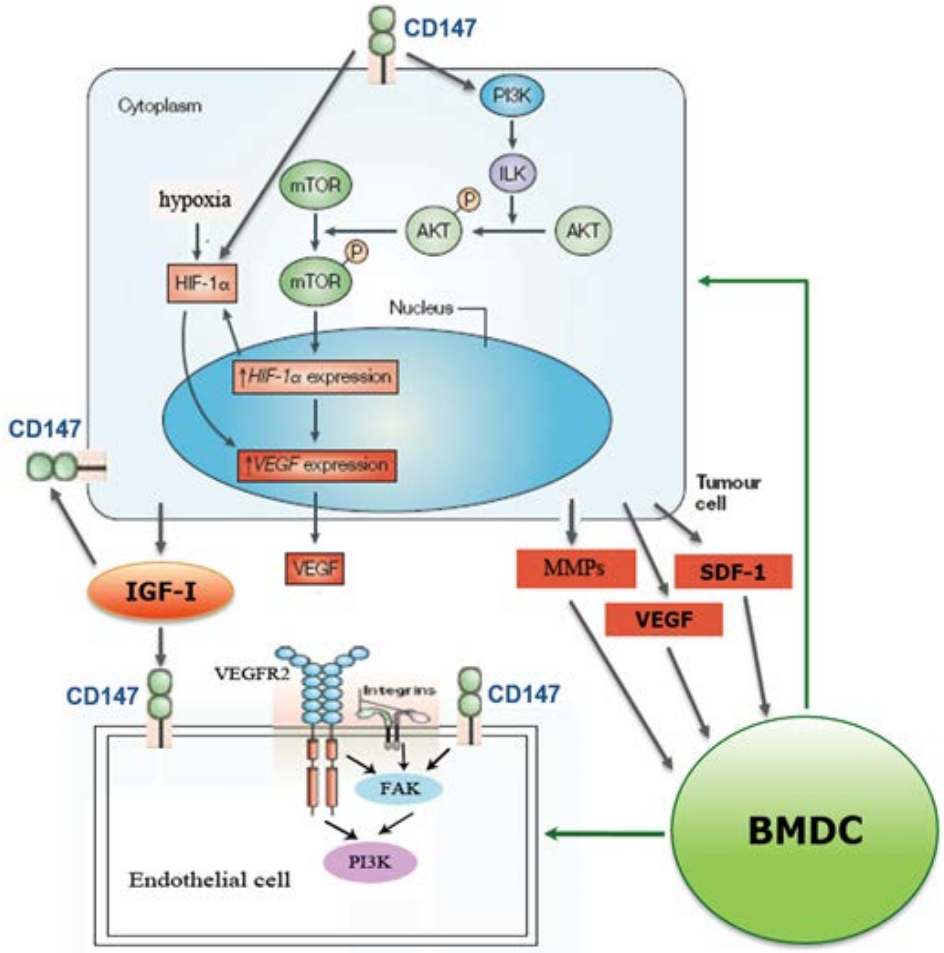

Figure 1 The multistep functions of CD147 in the tumor angiogenesis.

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