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Heterogeneity of hepatocellular carcinoma contributes to cancer progression

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Contents

Abbreviations: HCC, hepatocellular carcinoma; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; TSP1, thrombospondin-1; HIF-1α, hypoxia-induced factor-1a; bFGF, basic fibroblast growth factor; TNF-α, tumor necrosis factor alpha; IL-8, interleukin-8; PEDF, Pigment epithelial derived factor; PDGFR, platelet-derived growth factor receptor; ECM, extracellular matrix; LOX, lysyl oxidase; MCPs, matricellular proteins; MMPs, matrix metalloproteinases; MMP1, metalloproteinase 1; CTGF, connective tissue growth factor; EMT, epithelial mesenchymal transition; TGFβ1, transforming growth factor-β1; NK, natural killer; NKT, natural killer T cells; Treg, regulatory T cells; MDSC, myloid-dervied suppressor cells; Tlr3, toll-like receptor 3; iNKT, invariant natural killer T cells; IFNγ, interferon-gamma; CTL, cytotoxic T cells; GITR, glucocorticoid-induced tumor necrosis factor receptor; Hsp70, heat shock protein 70; KCNN2, small conductance calcium-activated potassium channel protein 2; AFP, alpha fetoprotein; OPN, osteopontin; PSG9, pregnancy-specific beta-1-glycoprotein 9; PLK1, polo like kinase 1; SNVs, single nucleotide variants; CNAs, copy number aberration; SVs, structural variations; OSGIN1, oxidative stress-induced growth inhibitor; MDM2, mouse double minute protein 2; PTPRF, protein tyrosine phosphatase receptor type F; AT2R, angiotensin II type 2 receptor; CSCs, cancer stem cells; SP, side population; EpCAM, epithelial cell adhesion molecule; PROM1, prominin 1.

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Abstract

Hepatocellular carcinoma (HCC) is a highly heterogeneous disease displaying differences in angiogenesis, extracellular matrix proteins, the immune microenvironment and tumor cell populations. Additionally, genetic variations and epigenetic changes of HCC cells could lead to aberrant signaling pathways, induce cancer stem cells and enhance tumor progression. Thus, the heterogeneity in HCC contributes to disease progression and a better understanding of its heterogeneity will greatly aid in the development of strategies for the HCC treatment.

Keywords: Hepatocellular carcinoma; Heterogeneity; Angiogenesis; Invasion; Tumor microenvironment; Genetic variation; Signaling pathway; Cancer stem cells

1. Introduction

Hepatocellular carcinoma (HCC) is a leading malignancy worldwide [1]. Resection and liver transplantation remain the mainstay treatment. The rapidly growing tumor displays heterogeneity of histopathologic characteristics [2]. This review discusses the contribution of characteristics such as angiogenesis, extracellular matrix, immune microenvironment, tumor cells, genomic expression and signaling pathways in HCC progression (Fig. 1).

2. Angiogeneic heterogeneity correlated with tumor size (T stage)

HCC has wide variations in vascularity that are dependent upon tumor size (T stage) and histological grade. HCCs about 1.0 cm in size have artery-like vessels that are not well developed with incomplete capillarization of the blood spaces and a predominant portal supply within cancerous nodules. As tumor size increases, portal tracts decrease in number, and artery-like vessels gradually increase. HCCs measuring 1.0–1.5 cm are transitional from portal to arterial supply, with a reduction in portal flow prior to an increase in arterial flow. With increasing tumor size, vascular endothelial growth factor (VEGF) expression gradually decreased and about 36% of larger nodules (>3 cm) were VEGF negative; HCCs over 5 cm were less vascular than smaller lesions [3–5]. The intercapillary distance is proportional to the tumor size, with significantly different turnover rates of endothelial and neoplastic cells (Fig. 1A).

At different stages of tumor progression, angiogenic switch comes from the balance between pro- and anti-angiogenic factors [6]. Pro-angiogenic factors include VEGF, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), angiopoietin-1 and angiopoietin-2. On the other sides, anti-angiogneic factors are thrombospondin-1 (TSP1), endostatin, interferon-α, interferon-β and angiostatin. VEGF expression is up-regulated by hypoxia-induced factor-1a (HIF-1α) to switch angiogenic phenotype [7]. VEGF plays an important role in well-differentiated HCCs related to the hypoxia whereas other factors such as basic fibroblast growth factor (bFGF), transforming growth factor β (TGF-β), tumor necrosis factor alpha (TNF-α) and interleukin-8 (IL-8) contribute to angiogenesis at later stages of HCC [4]. Therefore, HCC is a hypervascularized tumor due to increased angiogenic phenotype [8]. Angiogenesis is not only required for tumor growth supplied with oxygen and essential nutrients but also facilitate metastasis.

Pigment epithelial derived factor (PEDF) is an angiogenesis inhibitor to induce cell death and prevent vascularization [9,10]. PEDF antagonizes VEGF and inhibits vascular permeability for angiogenesis. The ratio of VEGF to PEDF could be an indicator of pro-angiogenic activities [11]. A higher level of VEGF mRNA in tumor tissue correlates with increased post-resection recurrences, suggesting that an altered balance between angiogenic stimulators and inhibitors contributes to cancer progression. From an anatomical perspective, a significant change in the VEGF/PEDF ratio can be found at the inner edge of the HCC [12].

Therefore, angiogeneic heterogeneity is associated with angiogenic molecules such as VEGF, PEDF and HIF-1α (Fig. 1A). Anti-angiogenic therapy is important to prevent recurrence in HCC patients [13]. There are several anti-angiogenesis targets such as VEGF, VEGFR, bFGF, PDGFR and angiopoietin Ang-1, Ang-2. Sorafenib, a FDA approval kinase inhibitor, could reduce expression of VEGFR-2, VEGFR-3 and platelet-derived growth factor receptor (PDGFR) [14]. Other anti-angiogenesis inhibitors such as angiostatin, endostatin and tumstatin have been tested in clinical trials [15]. The angiogenic heterogeneity of HCC needs to be taken into the consideration because angiogenic factors could be different among various tumor sizes and time intervals during hepatocarcinogenesis.

3. Heterogeneity of extracellular matrix in HCC

Extracellular matrix (ECM) components include collagen, laminin, fibronectin, glycosaminoglycan and proteoglycan. Continuous repatterning of the ECM allows HCC tumor cells to invade via direct or indirect interactions among ECM, HCC and stroma cells [16]. The major tumor ECM