Cytokine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Review article

Interdependent and independent multidimensional role of tumor microenvironment on hepatocellular carcinoma

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ARTICLE INFO

Keywords:
Hepatocellular carcinoma
Cancer associated fibroblasts
Growth factors
Inflammatory cytokines

ABSTRACT

The novelty of an effective therapeutic targeting for hepatocellular carcinoma (HCC) is based on improved understanding of each component of tumor microenvironment (TME) and its correspondent interactions at biological and molecular levels. In this context, new expansions for the treatment against TME and its communication with HCC are under exploration. Despite of the fact that blockage of growth factor receptors has become a treatment of choice in late phases of HCC in clinical practice, still a precise targeted treatment should address all the components of TME. Targeting one specific element out of cellular (cancer associated fibroblasts, endothelial cells, hepatic stellate cells, Kupffer cells and lymphocytes) or non-cellular (extracellular matrix, growth factors, inflammatory cytokines, proteolytic enzymes) parts of TME may not be a successful remedy for the disease because of well-designed hindrances of each component and their functional alternativeness. Meanwhile there are some elements of TME like epithelial-mesenchymal transition and CAF, which are considerably important and need thorough investigations. Ascertaining the potential role of these elements, and a single or combinational drug therapy targeting these elements of TME simultaneously, may provide the appreciable considerations to eventually improve in clinical practices and may also minimize the chances of re-occurrence of HCC.

1. Introduction

Liver is one of the most vital organs in the body and any deformity in liver causes serious adverse events in the whole body. Among carcinomas, hepatocellular carcinoma (HCC) is deadliest malignancy [1]. Regardless of the recent advancements in the treatment and early identification, HCC remains a highly lethal disease [2]. Out of the most prevalent carcinomas worldwide, it is fifth most common in men and 7th most frequent in women [3]. Overall, it is the third leading cause of cancer-related deaths worldwide [4]. Foremost cause of bereavements in HCC patients is the progression of tumor along with metastasis [5]. Unfortunately, the fundamental mechanisms of tumor initiation, progression and metastasibility (ability to metastasize) are still needed to be revealed.

Most of HCC patients predominantly have chronic liver disease that leads to the liver cirrhosis which is a major risk factor for the development of HCC [6]. Chronic liver injury is linked with inappropriate regulation for growth of hepatocytes which results in the development of dysplastic nodules, regenerative nodules, and consequently HCC [7]. Researchers demonstrated that cirrhotic liver-derived hepatocytes (CLDH) possess a specific cellular signaling phenotype that points to a modification of MAPK-independent cell survival pathway to a MAPK-dependent cell survival pathway [8,9]. It is studied that CLDHs increase the vimentin protein and type 1 collagen countenance that functions as biomarker for morphological features of mesenchymal cells based on epithelial to mesenchymal transition (EMT). This transition is very indispensable during early embryonic developments, cancer progression and tissue repair in the adult organisms. It is believed to be one of the major connecting points between inflammation, cancer and progression of degenerative fibrotic diseases [10,11].

2. Microenvironment of cancer in liver

The fundamental role of TME, including cross-talk between tumor

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http://dx.doi.org/10.1016/j.cyto.2017.09.026
Received 1 May 2017; Received in revised form 3 September 2017; Accepted 22 September 2017

Table 1
Cellular constituents of TME in hepatocellular carcinoma.

TME constituents	Focus of study/key findings	Reference
Hepatic stellate cells [20–23]	Molecular basis and translational potential activation of HSCs	Kong et al. [20]
	Molecular mechanisms of HSCs	Aravalli et al. [21]
	Role of adiponectin in HSCs	Man et al. [22]
	Epithelial-mesenchymal transitions of HSCs and development in disease	Thiery et al. [23]
Cancer associated fibroblasts [9,24,25]	HCC microenvironment and therapeutic targets	Yang et al. [9]
	Cancer-associated fibroblasts activation mechanism and the role of inflammation based on NF-κB	Erez et al. [24]
	Association of TGF β with connective tissues growth factor and CAF in tumor–stroma cross-talk and tumor progression in HCC	Mazzocca et al. [25]
Lymphocytes and Kupffer cells [26–30]	Involvement of Kupffer and Dendritic cells in the cancer microenvironment	Ma et al. [26]
	Regulatory cytotoxic T cells association with HCC	Gao et al. [27]
	Role of the PD-1: PD-L1 pathway in immune resistance of HPV and its connection with lymphocytes	Sofia et al. [28]
	Association of Tim-3 Receptor with CD8 + T cells in HCV infection and its effect on HCC	Sakhdari [29]
	Role of Kupffer cells in the pathogenesis of liver disease	Kolios et al. [30]
Endothelial cells [31–33]	Transforming growth factor-β signaling pathway association of endothelial cells in cutaneous melanoma	Perrot et al. [31]
	TGF-β1 and CD105 combined effect to promote the migration of HCC derived endothelium	Benetti et al. [32]
	Endothelial cell abnormalities and its connection with carcinomas	Baluk et al. [33]

HSCs, hepatic stellate cells; NF-κB, nuclear factor-κB; TGF β, transforming growth factor β; CAF, cancer associated fibroblast; PD-1: programed cell death; PD-L1, programed cell death ligand 1; HPV, hepatitis virus; Tim-3, T-cell immunoglobulin and mucin domain subtype 3; CD8, cluster of differentiation protein subtype 8.

cells and their surrounding microenvironments; and the contribution of TME in the pathogenesis of HCC is not mysterious any longer [12]. It is revealed that TME displays a crucial role in restraining the process of metastasis, tumor invasion, EMT, hepato-carcinogenesis and liver fibrosis [9,13].

Thorough investigations on TME disclose its components which are basically modified forms of normal elements of the body cells. Studies on HCC and its microenvironment highlight five basic constituents which are cellular constituents, growth factors, proteolytic enzymes, extracellular matrix (ECM) and inflammatory cytokines. In order to increase the understanding we divide them in two major groups of cellular and non-cellular elements. The cellular [14,15] and non-cellular elements [16–19] of the TME along with previous studies targeting those elements are highlighted in Tables 1and 2 respectively.

In previous studies, different aspects of HCC have extensively been discussed on individual basis; however most constituents of TME in HCC focusing the mechanism pathways and their combined effect with other cellular and non-cellular parts of TME have not been discussed and reviewed in depth. This review provides the specific role of each component of TME in the pathogenesis of HCC with currently available details of the mechanisms as well as the cross talk of TME components concentrating on its unambiguous role in HCC progression, metastasis and pathogenicity (Fig. 1).

The importance of TME in the development of cancer is not a myth anymore; however there are still many features yet to be examined and reviewed on scientific basis, which needs a comprehensive understanding of all the components of TME not only on individual basis but also on the basis of cross relationship with other factors of TME; this review highlights both of these features.

Table 2
Non-cellular constituents of TME in hepatocellular Carcinoma.

TME constituents	Focus of study/key findings	Reference
Growth factors [34–39]	TGF-β Mediated Crosstalk Between Malignant Hepatocyte and Tumor Microenvironment in HCC	Gupta et al. [34]
	Role of nuclear factor-κB in progression of carcinomas	Zubair et al. [35]
	Transactivation of the TIEG1 associated growth inhibition in relationship with TGF-β- in HCC	Jiang et al. [36]
	Association of PDGF and TGF-β with TME in HCC	Leonardi et al. [37]
	Molecular pathogenesis of HCC and effects of PDGF and TGF-β	Yamazaki et al. [38]
	Association of Cancer associated fibroblasts, PDGF and other growth factors in cancer pathogenesis	Franco et al. [39]
Proteolytic enzymes [17,37,40,41] [17,51,66,70,72]	Activation of PPARγ in hepatic fibrosis and association with proteolytic enzymesis	Wang et al. [17]
	The regulation of fibrosis and role of proteolytic enzymes	Royce et al. [40]
	Proteolytic Enzymes contribution in TME with regard to HCC.	Leonardi et al. [37]
	Potential capabilities of metalloproteinases in human HCC	Kohga et al. [41]
Extracellular matrix (ECM) [42–48]	The role of epigenetic alterations in HCC	Frau et al. [42]
	Role of ECM in HCC metastasis and its link with α3β1 integrin-Rho GTPase signaling	Fu et al. [43]
	Heparan sulfate signaling and its connection with ECM in tumorigenesis	Knelson et al. [44]
	Integrin-dependent response to laminin-511 and its effects on tumor cell invasion and metastasis	Kusuma et al. [45]
	Deregulation of signaling pathways in prognostic subtypes of carcinoma HCC a comparison of different species ECM of TME.	Calvisi et al. [46]
	Genetic considerations and its association with Sulfatase 1 and sulfatase 2 in HCC	Yang et al. [47]
	ECM role in cancer and therapeutic opportunities	Desgrosellier et al. [48]
Inflammatory cytokines [49–52]	Association of cytokines in liver regeneration and Hepatocarcinogenesis	Dahan et al. [49]
	Immune-suppressive cells that facilitate tumor progression and promote and deter cancer-associated inflammation	Sinha et al. [50], Burke et al. [51]
	Therapeutic effects of hepatocyte growth factor and the role of Inflammatory cytokines on liver fibrosis	Seo et al. [52]

TGF β, transforming growth factor β; TIEG1, TGF β-inducible early response gene-1; PDGF, platelet derived growth factor; PPARγ, peroxisome proliferator-activated receptor gamma; ECM, extracellular matrix.