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Stem cell, biomaterials and growth factors therapy for hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma is an antecedent of liver illnesses, including viral hepatitis, alcohol abuse, or metabolic disease. Transforming growth factor-Beta (TGF-b) plays an important role in creating a favorable microenvironment for tumor cell growth via two major mechanisms: an intrinsic activity as an autocrine growth factor and an extrinsic activity by inducing microenvironment changes. Recently stem cell therapy as also been a promising and potential treatment for liver cancer and in addition signaling pathways like GF/GFR systems, SDF-1α/CXC4 ligand receptor interaction and PI3K/Akt signaling, and cytokines has been identified to regulate cell fate decisions, and can be utilized to positively influence cell therapy outcomes. Thus stem cell-based therapy, together with signaling pathways can become a practical option in regenerative processes for replacing dead hepatocytes cells. Targeted drug delivery systems (TDDS) via biomaterials are presently been explored for cancer therapeutics especially liver cancer as it allows the enhancement of drug concentration in the liver and decrease the dosage and side effects. This review is intended to give a comprehensive summary of available liver cancer therapy using stem cells, growth factor and biomaterials.

Contents

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1. Introduction

Liver cancer is the fifth most common cancer in the world and the third most common cause of cancer mortality [1]. Liver stem cell research promises to improve the outcomes of patients with liver diseases [2]. Advances in liver stem cell research may lead to new cell therapies and may facilitate the development of new drugs by providing faithful liver disease models [3]. In many tissues, stem cells have yet to be specifically identified and isolated. As a consequence, the current understanding of the mechanisms that facilitate proliferation and differentiation of tissue-specific stem cells is limited, which has also hampered the generation of therapeutically effective surrogate cells from alternative cell sources, such as pluripotent stem cells [4,5]. Tumor-initiating stem-like cells (TISCs) that emerge during chronic liver injury share the expression of signaling pathways, including those organized around transforming growth factor beta and b-catenin, and surface markers with normal LPCs [6]. Recent investigations of the role of TISCs in hepatocellular carcinoma have provided insight into the transcriptional and post-transcriptional regulation of hepato-carcinogenesis [7]. Targeted chemotherapies for TISC are in development as a means to overcome cellular resistance and mechanisms driving disease progression in liver cancer.

2. Tumor–stroma interaction: a new therapeutic target for liver disease

Drugs that target the tumor–stromal interaction by inhibiting receptors and their downstream signaling pathways have been proven to be effective in curing and managing liver diseases [8,9]. Sorafenib, an oral multi-kinase inhibitor is a drug designed to inhibits vascular endothelial growth factor receptor (VEGFR-2/-3), platelet derived growth factor receptor (PDGFR) and Raf kinase thereby interrupting the tumor–stromal interactions and subsequent leading to reduced cell proliferation and angiogenesis. The efficacy and health-safety of sorafenib have been shown in a recent clinical trials and currently its regarded as the standard of care for patients with advanced stage HCC [10]. Table 1 summarizes drugs currently undergoing clinical trials for the treatment of liver diseases.

Table 1
Clinical trials targeting the tumor–stromal interaction for the treatment of HCC.

Treatment	Phase	Target	Trial ID
Brivanib	3	VEGFR2, FGFR1	NCT00858871
Linifanib	3	VEGFR, PDGFR	NCT01009593
Sorafenib	3	VEGFR, PDGFR, Raf	NCT00492752
Sunitinib	3	VEGFR, PDGFR, c-KIT	NCT00699374
Ramucirumab	3	VEGFR2	NCT01140347
Erlotinib	3	EGFR	NCT00901901
PI-88	3	Heparanase, SULFs	NCT00568308
Bevacizumab	2	VEGF	NCT00162669
Cediranib	2	VEGFR, PDGFR, c-KIT	NCT00238394
BIBF-1120	2	VEGFR, PDGFR, FGFR	NCT01004003
E-7080	2	VEGFR, FGFR, PDGFR, c-KIT	NCT00946153
TSU-68	2	VEGFR2, FGFR, PDGFR	NCT00784290
XL-184	2	VEGFR2, MET, RET	NCT00940225
Vandetanib	2	VEGFR, EGFR	NCT00508001
Cetuximab	2	EGFR	NCT00142428
BIIB-022	2	IGF-1R	NCT00956436
Cixutumumab	2	IGF-1R	NCT00639509
CT-011	2	PD-1/2	NCT00966251
MEDI-575	1	PDGFR	NCT01102400
BAY73-4506	1	PDGFR, VEGFR, PDGFR, FGFR-1, Raf,	NCT01117623
GC33	1	GPC3	NCT00976170
AVE1642	1	IGF-1R	NCT00791544
Liver NK cell	1	Liver NK cell inoculation	NCT01147380

2.1. Transforming Growth Factor-b (TGF-beta) as a Therapeutic Target in liver disease

Changes in the TGF- b signaling pathway has also been identified to be a contributing factor to tumor growth [11]. The TGF-b signaling occurs through a canonical and a non-canonical pathway [12]. Three ligands are responsible for activating the canonical TGF-b signaling pathway when they bind to the TGF-b receptor II (TGF-bRII), heterodimerizes with the TGF-b-receptor I (TGF-bRI or ALK5), and transphosphorylates the kinase domain of both receptors namely (TGF-b1, TGF-b2, TGF-b3) [13]. This phosphorylation phase results into the activation and phosphorylation of SMAD2 and SMAD3 followed by activation of a SMAD signaling cascade that ultimately results in nuclear translocation and gene transcription for a wide range of tumor-promoting mediators [14]. However the non-canonical activation pathway is relatively unknown as its related with numerous intracellular phosphorylation of proteins, such as jun N-terminal kinase (JNK), p38 MAPK, ERK, or MEKK [15]. Conclusively this suggests that TGF-b signaling has numerous mechanisms to activate either the tumor cell.

2.2. TGF-b activation and liver disease

TGF-b is responsible in coordinating the homeostasis of microenvironment components and tumor cells by striking a balance in the activities of inflammatory cells [16]. In viral hepatitis there is a concomitant increased secretion of TGF-b and IL-10 with increased T regulatory cells which leads to local immunosuppressive effect and subsequently contribute to a persistent viral infection [17]. In corroborating the above fact, Thiery and colleagues reported that continued inflammation of the liver, reversible and irreversible remodeling are often observed, including fibrosis and early cirrhosis [18,19].

This remodeling is characterized by accumulation of extracellular matrix (ECM) proteins [20]. The rich ECM deposition is caused by activation of TGF-b, this leads to cirrhosis and ultimately to liver failure if the ECM deposition is not stopped. Cirrhotic state of a liver results into mutation in the dysplastic nodules, which can aggravate into early stages of hepatocellular carcinoma [21]. Gressner et al. reported that in the liver tissue, cancer cells grow rooted in a micro-environment supplemented with ECM and activated by TGF-b and connective tissue growth factor [22,23]. This tight interface between the cancer tumor and the neighboring

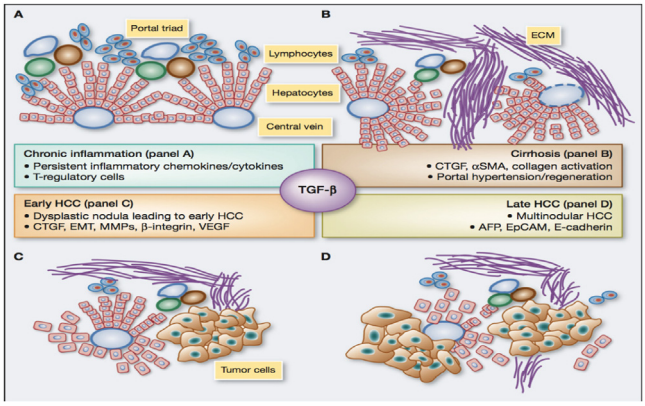

Fig. 1. Development from chronic inflammation to hepatocellular carcinoma (HCC; red circle, artery; green circle, bile duct; blue circle, vein). Hepatocellular carcinoma develops from preexisting chronic inflammation (A) that progresses to cirrhosis (B), followed by early (C) and late tumor lesions (D). CTGF, connective tissue growth factor; a-SMA, a-smooth muscle actin; MMP, matrix metalloproteinase.