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Review

Multipotent mesenchymal stromal cells in liver cancer: Implications for tumor biology and therapy☆

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ABSTRACT

Remodeling of tumor microenvironment is a hallmark in the pathogenesis of liver cancer. Being a pivotal part of tumor stroma, multipotent mesenchymal stromal cells (MSCs), also known as mesenchymal stem cells (MSCs), are recruited and enriched in liver tumors. Owing to their tumor tropism, MSCs are now emerging as vehicles for anticancer drug/gene delivery against liver cancer. However, the exact impact of MSCs on liver cancer remains elusive, as a variety of effects of these cells that have been reported included a plethora of tumor-promoting effects and anti-oncogenic properties. This review aims to dissect the mechanistic insight regarding this observed discrepancy in different experimental settings of liver cancer. Furthermore, we call for caution using MSCs to treat liver cancer or even premalignant liver diseases, before conclusive evidence for safety and efficacy having been obtained.

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Contents

1. Introduction

Liver malignancies including hepatocellular carcinoma (HCC), cholangiocarcinoma and hepatoblastoma are jointly the fifth most prevalent form of cancer and globally the third leading cause of cancer-related death, immediately after mortality due to lung cancer and colon cancer [1]. In addition, the liver is a favorite site for metastasis of other cancers, in particular colorectal cancer (CRC), esophageal cancer and pancreatic cancer. The liver microenvironment is favorable for

Abbreviations: MSCs, multipotent mesenchymal stromal cells; HCC, hepatocellular carcinoma; BM, bone marrow; TLR, Toll-like receptor; EMT, epithelial–mesenchymal transition; Tregs, regulatory T cells; NK, natural killer; DCs, dendritic cells

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growth and invasion of cancer cells, with increased extracellular matrix remodeling being considered a hallmark of malignant liver disease [2]. Although many of the details are still sketchy, it is now generally assumed that within this microenvironment, reciprocal tumor-stroma crosstalk influences the phenotype of tumor cells, progression and metastasis [3]. Being a pivotal part of the tumor stroma, multipotent mesenchymal stromal cells (MSCs), also known as mesenchymal stem cells (MSCs), were found to be present and play important roles in various types of cancers [4] and recently more insight into their role in liver malignancies has been revealed.

MSCs were initially identified to reside within the stromal compartment of bone marrow (BM) and characteristically have multi-lineage differentiation potential [5]. In addition to BM, MSCs now have been identified in various postnatal organs, where they often occupy a perivascular niche [6,7]. A recent study demonstrated that the adult human liver harbors resident MSCs that are phenotypically and functionally similar to BM MSCs [8]. Intriguingly, the evidence suggesting that MSCs involved roles in both primary [9] and secondary liver cancers is gaining momentum [10]. Nevertheless, despite the extensive investigations being done, the exact impact of MSCs on liver cancer remains elusive. Frustratingly, whereas various studies report tumor promoting effects of MSCs, others provide evidence for anti-oncogenic role of these cells. The specific accumulation of these cells in the tumor environment is not in doubt and thus owing to this tumor tropism, MSCs are now emerging as vehicles for anticancer drug/gene delivery [11] and clinical trials are being proposed. This review aims to dissect the mechanistic insight regarding this observed discrepancy in different experimental settings of liver cancer as to provide possible guidance to the appropriateness of clinical trials. Given the complexity of MSC action, we call for caution on such trials in humans with respect to therapeutic applications of these cells in liver malignancy until better evidence for safety and efficacy has been obtained.

2. What is the source of the MSC compartment in liver cancer?

2.1. Identification of MSCs in various organs/tissues

Mesenchymal stem cells (MSCs) were initially identified by placing whole bone marrow cells in plastic culture dishes and the subsequent expansion of a rare population of plastic-adherent cells [12]. However, the recognized biologic properties of the unfractionated population of cells do not seem to exactly meet the general criteria for stem cell properties. Therefore, these cells are also termed as multipotent mesenchymal stromal cells (MSCs) [13]. The characterization and definition of MSCs still relies solely on *in vitro* culture-expanded cell populations and consequently, both the spatial distribution and properties of native MSCs within their organ/tissue *in vivo* are much less known [14]. The identification of MSCs in various other organs/tissues (e.g. adipose, kidney, umbilical cord, brain, liver, lung, and bone marrow) [6,15,16], which have the common MSC features but also carry unique properties depending on their sources, has raised a lively debate regarding the origin of MSCs. Similarly, a resident population of MSCs has also been identified within the human adult liver that is phenotypically and functionally similar to BM MSCs but express a unique gene signature [8]. The question whether these MSCs are BM-derived hepatotropic cells with MSC-like properties that have subsequently acquired location-specific gene expression, or whether they resided locally throughout their developmental stages remains unanswered.

2.2. Migratory capacity of MSCs

In general, MSCs are proficient with respect to migratory capacity and nomadic in nature. They tend to be recruited by injured tissue where they are thought to contribute to tissue repair and wound healing [17]. As tumors are often considered to have many characteristics of “injured tissue”, it is probably not surprising to find MSCs in the tumor. Recent evidence has come forward in various pre-clinical models that MSCs can migrate into certain types of tumors and this is one of the rationales put forward for using MSCs as vehicles for anti-cancer drug/gene delivery [18,19]. This tumor-tropic migratory property of MSCs is attributed to two main determinants: their intrinsic properties and stimuli produced by the tumor [20]. Human MSCs express chemokine receptors CCR1, CCR2, CCR4, CCR6, CCR7, CCR8, CCR9, CCR10, XCR, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6 and CX3CR [17]. Production of their respective ligands is shared characteristic of inflamed tissue and malignant transformed tissue and thus these receptors are likely involved in the specific accumulation of MSCs in both processes. Accordingly, the cognate ligands of these receptors are efficient chemotactic stimuli for MSCs. Additional receptors implicated in MSCs' migration are Toll-like receptors (TLR). TLR1–6 have been identified on primary human MSCs and have been reported that TLR stimulation enhanced the migratory function of MSCs [21]. MSCs are relatively resistant to ischemia due to the absence of oxygen. MSCs can survive by anaerobic adenosine triphosphate production [22], which should give these cells a competitive advantage in tumor microenvironment. Intravenous infusion of MSCs has indeed been shown to result in specific accumulation of these cells in liver cancer-derived structures, indicating that liver tumors are able to recruit them at high efficiency [23]. Consistently, HCC has been shown to produce relatively high amount of *bona-fide* MSC chemo-attractants, including hepatocyte growth factor (HGF), SDF-1, basic fibroblast growth factor (bFGF), vascular endothelial growth factor A (VEGF-A) and vascular cell adhesion molecule 1 (VCAM-1) [23–25]. Thus, these data suggest that *ex vivo* expanded MSCs will likely display at least some specificity with regard to MSC accumulation in liver neoplasms.

2.3. Dualistic origin of MSCs in liver cancer?

The enrichment of MSCs in the tumor environment was reported for both human primary liver cancer [9] and liver metastases from colorectal cancer [10]. An intriguing question is to what extent the MSC compartment observed in liver tumor is derived from local sources (liver MSCs) or from the circulation in turn supplied by the BM (BM MSCs). In response to injury or infection, MSCs can be released from BM into the blood circulation and migrate towards the injured sites to promote tissue regeneration [26]. High frequencies of MSCs were found in liver tumor with extensive inflammation suggesting the recruitment of MSCs in response to infection/inflammation [9]. Moreover, high circulating levels of BM originated cells, such as endothelial progenitor cells, have been observed in HCC patients, which might subsequently home into the tumor and promote tumor growth [27]. We thus propose a dualistic origin of the MSC compartment in liver cancer, with MSCs constantly being recruited locally and from the circulation (Fig. 1). Future studies using somatic genomic signatures may provide a definite answer.

3. Dual roles of MSCs in liver cancer

The intrahepatic microenvironment is substantially different from other organs, and this may affect cancer development [28]. MSCs constitute an important component within the microenvironment of both the normal liver as well liver tumors and they appear to have pleiotropic functionality. This is reflected in the results obtained in experimental liver tumor models. Depending on the exact experimental conditions, MSCs can exert tumor-promoting or tumor-limiting effects (Table 1) [9,29–42]. Various hypotheses have been postulated to explain the dualistic behavior of MSCs in cancer. One school of thought attributes to an important role for TLRs and subsequent immuno-polarization of MSCs [43]. MSCs express several TLRs and their capabilities to migrate, invade, and secrete immune modulating factors are tightly regulated by specific TLR-agonist engagement. TLR4-primed MSCs are polarized into pro-inflammatory MSC1 phenotype; whereas TLR3-primed MSCs

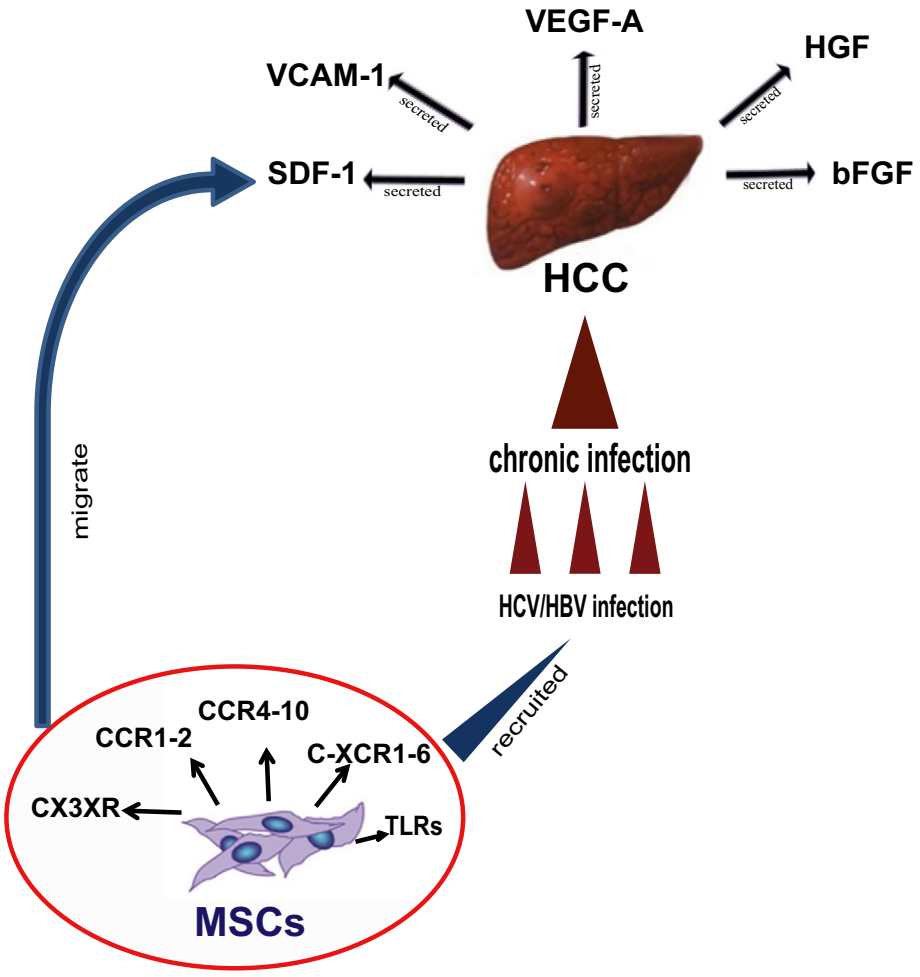

Fig. 1. A proposed model for MSCs recruitment into liver tumor. MSCs were shown to express chemokine receptors CX3XR, CCR1-2, CCR4-10, C-XCR1-6 and TLRs. HCC tumors can release various cytokines, chemokines and growth factors, including HGF, bFGF, SDF-1, VCAM-1 and VEGF-A, which have been described as chemoattractants for MSCs. We propose that both liver and circulating MSCs (released from BM or other organ/tissue) are possibly recruited into liver tumor and MSCs may be constantly recruited in the stages from chronic viral hepatitis to liver cancer development.

are polarized into the classical immunosuppressive MSC2 phenotype [43]. In cancer models, MSC1-based treatment of established tumors in an immune competent model attenuates tumor growth and metastasis but MSC2-treated animals would display increased tumor growth and metastasis [44]. The second hypothesis postulates a developmental phase-dependent MSC functionality [4,45]. MSCs appear to promote tumor growth when co-injected with tumor cells, but inhibit tumor progression when administered into established tumors [4]. Thus, the presence of MSCs during the early phase of tumorigenesis may contribute to angiogenesis that is required for tumor initiation. Indeed, an increase in vessel density was observed when MSCs were co-injected with HCC or other tumor cell lines [30,46]. Of note, tumor cells and the tumor microenvironment will in turn affect the ultimate function of these recruited MSCs. As both hypotheses are not mutually exclusive likely both are concomitantly true, making prediction as to the effects of MSCs on the cancerous process extremely difficult.

Table 1
Studies reporting effect of MSCs on liver cancer.

References	Source of MSCs	Effects
Hernanda et al. [9]	Human liver tumor/ adjacent	Promote tumor growth
Yan et al. [29]	Human liver tumor/ adjacent	Promote tumor growth
Gong et al. [30]	Human bone marrow	Promote tumor microvascular
Jing et al. [31]	Human bone marrow	Promote tumor metastasis
Bhattacharya et al. [32]	Human bone marrow	Promote tumor metastasis
Li et al. [33]	Human bone marrow	Promote tumor growth Inhibit tumor metastasis
Zhao et al. [34]	Human adipose tissue	Inhibit tumor growth
Abdel aziz et al. [35]	Human bone marrow	Inhibit tumor growth
Li et al. [36]	Human bone marrow	Inhibit tumor growth
Qiao et al. [37,38]	Human dermal tissue	Inhibit tumor growth
Bruno et al. [39]	Human bone marrow	Inhibit tumor growth
Hou et al. [40]	Not indicated	Inhibit tumor growth
Ma et al. [41]	Murine bone marrow	Inhibit tumor growth
Abd-Allah et al. [42]	Murine bone marrow	Inhibit tumor growth

4. Mechanisms of MSC-dependent tumor suppression in liver cancer

A variety of processes possibly implicated in MSC-dependent tumor suppression have been identified. Wnt signaling is aberrantly activated in a subset of HCC tumors. In chemically induced murine HCC tumors the administration of MSCs has been demonstrated to have tumor suppressive effects associated with Wnt signaling target genes being down-regulated, especially those related to anti-apoptosis, mitogenesis, cell proliferation and cell cycle regulation [35]. A mechanistic explanation is found by the active secretion of Wnt inhibitors, such as dickkopf-1, by MSCs [37,40] and is supported by the MSC-dependent inhibition of NF-kB signaling in cancer cells [38]. In addition, TLR signals can

stimulate down-stream effectors that may interfere LPS-TLR4 pathway and inhibit NF-kB activation during liver fibrosis [47].

Additionally, microvesicles released by MSCs have been shown to inhibit cell cycling and induce apoptosis or necrosis of different HCC cell lines *in vitro* and to inhibit growth of established tumors *in vivo* [39,48], providing a further anti-oncogenic MSC effector pathway. Conversely, MSCs pulsed with tumor-derived microvesicles exert an enhanced antitumor activity against HCC [41]. Although it is still unclear which factors are the direct effectors, the secretome of MSCs appears to play an important role in their tumor suppressing function.

5. Tumor promoting effects of MSCs in liver cancer

The reported context-dependent tumor promoting roles of MSCs have been attributed to their abilities of supporting angiogenesis, promoting tumor growth and metastasis, and modulating immune response (detailed disused in the following section) via paracrine or direct mechanisms [4]. Support of tumor angiogenesis by MSCs could be via their direct differentiation into pericytes or perhaps endothelial cells [49], or indirectly by secreting pro-angiogenic factors and inhibition of apoptosis in vascular smooth muscle cells and endothelial cells [50]. The process of angiogenesis involves a large number of proteases. For instance, a protease named SERPINE1, which is abundantly secreted by MSCs, has been shown to regulate proliferation, migration, and apoptosis of vascular smooth muscle cells and endothelial cells [48,51]. In mouse model, transplantation of BM MSCs promoted growth of microvascular in HCC tumor [30].

In addition, direct effects of MSCs on the tumor cells may contribute to HCC pathogenesis. MSCs have been shown to accelerate HCC metastasis, due to the induction of such epithelial–mesenchymal transition (EMT) [31], an effect which is even further enhanced by an inflammatory milieu (which characterizes many liver cancers). During EMT epithelial (cancer) cells lose cell polarity and cell–cell adhesion, and gain migratory and invasive properties. Supporting the existence of such effect is the observation of increased expression of cancer associated fibroblast (CAF) and EMT markers in a co-culture model of hepatoma cells and MSCs [32]. In HCC patients, MSC-dependent EMT induction is associated with a shorter tumor free survival and a worse overall survival [31], demonstrating the clinical relevance of this effect.

Secreted factors from patient HCC tumor-derived MSCs have been shown to promote tumor growth in xenograft mouse model associated with up-regulation of cell growth and proliferation-related processes and down-regulation of cell death-related pathways in HCC cells [9]. MMPs' proteases as well as various other factors secreted by MSCs, are capable of remodeling extracellular matrix and facilitate tumor progression [9,29]. Glycoproteins, such as osteonectin that is important in remodeling extracellular matrix, are highly expressed in the stromal myofibroblast of HCC patients and have been reported to promote HCC progression [52].

6. Potential immunomodulation by MSCs in liver cancer

6.1. Immune microenvironment in liver tumors

Immune surveillance plays key roles in protecting against cancer. The liver constitutes a relatively immunoprivileged microenvironment, and thus cancer cells may take advantage of the immunoregulatory mechanisms that are established in the liver [53]. Furthermore, HCC can use multiple mechanisms to evade host antitumor immunity, leading to disease progress even in the presence of tumor-specific immune responses [54]. In liver tumor, the composition as well as the function of immune cells have been dramatically altered [53,55]. In general, the frequency and functionality of anti-tumor immune cells are decreased [53,55]. In contrast, a variety of immunosuppressive cells with high activity are accumulated in the tumor, which can impede immunosurveillance and facilitate tumor growth [56]. Although MSCs have never officially

Table 2
Registered trials of mesenchymal stem cells (MSCs) in various liver diseases.

Disease	Phase	Source of MSCs	Status	Registered ID
Liver cirrhosis	1/2	Human umbilical cord MSCs	Not yet recruiting	NCT01573923
	1/2	Human bone marrow & umbilical cord MSCs	Not yet recruiting	NCT01877759
	2	Allogeneic MSCs	Recruiting	NCT01591200
	3	Autologous bone marrow MSCs	Enrolling by invitation	NCT01854125
	–	Autologous bone marrow MSCs	Unknown	NCT01499459
	1	Human umbilical cord MSCs	Unknown	NCT01224327
	1/2	Autograft MSCs	Completed	NCT00420134
	1	Human umbilical cord MSCs	Recruiting	NCT01728727
	1/2	Human umbilical cord MSCs	Completed	NCT01342250
	1	Human menstrual blood MSCs	Enrolling by invitation	NCT01483248
	2	Human umbilical cord MSCs	Recruiting	NCT01233102
	2	Autologous bone marrow MSCs	Unknown	NCT00993941
	2	Autologous bone marrow MSCs	Unknown	NCT00976287
	2	Autologous bone marrow MSCs	Unknown	NCT00476060
	1	Human umbilical cord MSCs	Recruiting	NCT01220492
	1	Autologous bone marrow MSCs	Unknown	NCT01454336
	1	Autologous adipose tissues MSCs	Terminated	NCT00913289
	–	Autologous adipose tissues MSCs	Enrolling by invitation	NCT01062750
	2	Allogeneic bone marrow MSCs	Unknown	NCT01223664
	2	Autologous bone marrow MSCs	Recruiting	NCT01741090
	2	Autologous bone marrow MSCs	Recruiting	NCT01875081
Liver failure	1	Human umbilical cord MSCs	Recruiting	NCT01218464
	1	Human umbilical cord MSCs	Recruiting	NCT01724398
	2	Allogeneic bone marrow MSCs	Unknown	NCT01322906
	1	Third party bone marrow MSCs	Recruiting	NCT01429038
	1/2	Allogeneic bone marrow & umbilical cord MSCs	Recruiting	NCT01844063
	2	Autologous bone marrow MSCs	Completed	NCT00956891
	2	Allogeneic bone marrow MSCs	Unknown	NCT01221454
Liver transplantation	1	Human umbilical cord MSCs	Recruiting	NCT01690247
Primary biliary cirrhosis	1	Human umbilical cord MSCs	Recruiting	NCT01662973
	1	Allogeneic bone marrow MSCs	Unknown	NCT01440309
Autoimmune hepatitis	1	Human umbilical cord MSCs	Recruiting	NCT01661842

Note: The trials are registered at ClinicalTrials.gov. Searched on 24th, April, 2014.

joined the immune cell club, they are well-recognized for their potent immunomodulatory capacity.

6.2. Immunomodulation by MSCs

MSCs can modulate the function of several cell types of the immune system including those from innate immunity including natural killer (NK) cells [57] and macrophages [58]. MSCs are also capable of modulating the differentiation, activation and function of dendritic cells (DCs) [59], the most efficient antigen presenting cells. The key function of dendritic cells (DCs) is translating innate to adaptive immunity and these cells are thought to have important link with HCC progression [60]. T cells are the main components of adaptive immune system and are crucial in controlling malignant disease, mediating both cytotoxicity of cancer cell themselves and release of anti-oncogenic cytokines [61,62]. MSCs can effectively inhibit T cell function through multiple pathways [63,64].

Regulatory T cells (Tregs) are a specialized subset of T cells that suppress activation of the immune system to maintain homeostasis and tolerance to self-antigens. In patient HCC tumor, increased frequencies of highly activated Tregs are infiltrating the tumor milieu and they are mainly localized in the stroma compartment of the tumors [55]. Furthermore, the frequency of Tregs in HCC has been associated with poor prognosis [65–67]. In contrast to suppress cytotoxic T cells, MSCs can induce the generation and expansion of Tregs [68]. Additionally, MSCs have been reported to induce the production of IL-10 by plamacytoid dendritic cells (pDCs), which in turn triggered the generation of Tregs [63]. However, potential interactions between these immune cells with MSCs or tumor stroma in general, have been poorly studied in the context of liver cancer, which certainly deserve more attention for further research.

7. Therapeutic application of MSCs in liver cancer: call for caution

7.1. Potential therapeutic application

Evidence from various preclinical models showing that MSCs can migrate into certain types of tumors has inspired the use of MSCs as vehicle for anticancer drug/gene delivery [11]. This notion was further supported by the fact that several studies have demonstrated potential anti-cancer effects of MSCs [31,35,45,69]. In experimental HCC models, genetically modified MSCs have been used to deliver anti-cancer gene and inhibition of HCC cell proliferation was demonstrated *in vitro* and *in vivo* [70,71]. Another approach is to deliver oncolytic viruses (e.g. measles virus) by MSCs into the tumor, in order to avoid pre-existing immunity against the virus [72]. These observations encourage clinical investigators to design trials for treating HCC, which remains an unusually deadly disease, using MSCs as a vector.

MSCs have been extensively investigated in clinical trials to treat various diseases [73,74]. For treating cancer, trials have also been initiated to treat ovarian cancer (NCT02068794), head and neck cancer (NCT02079324) and prostate cancer (NCT01983709). Although MSCs have not been used for treating liver cancer yet (to our knowledge), over 30 trials have been registered at ClinicalTrials.gov for treating various liver diseases (Table 2).

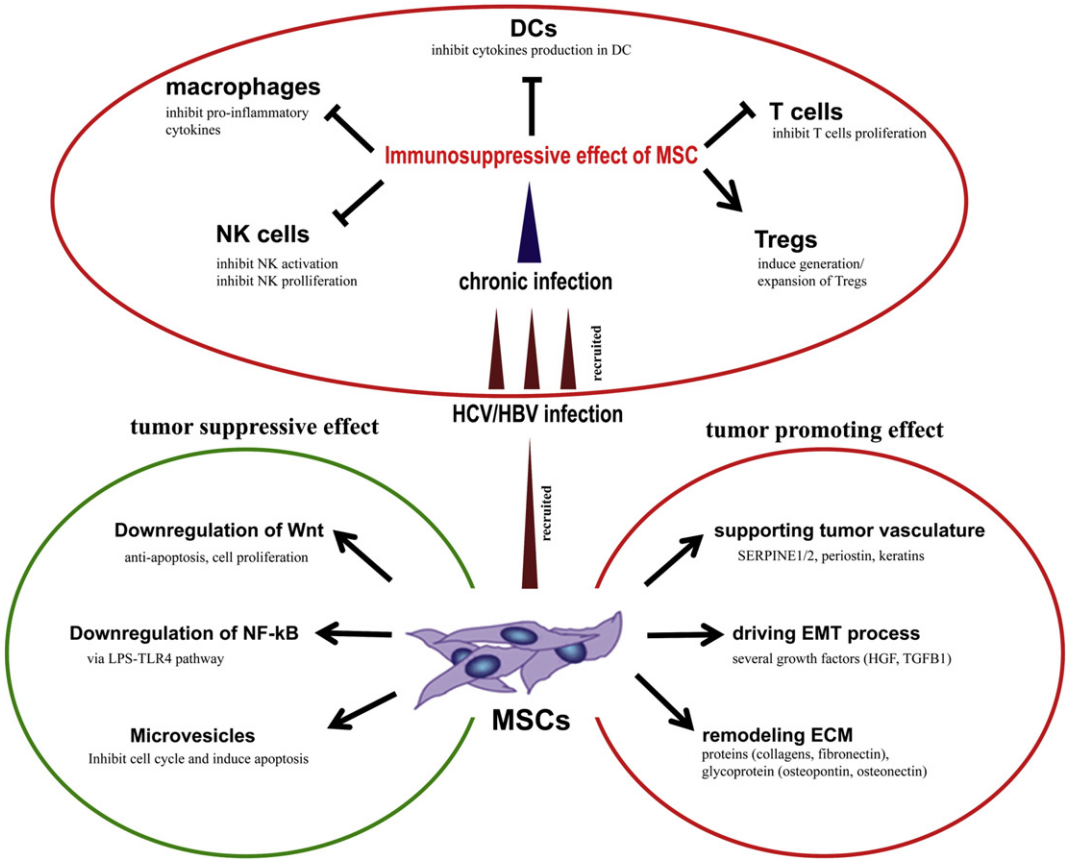

Fig. 2. Proposed mechanisms for the tumor-suppressive and tumor-promoting effects of MSCs. The properties of MSCs and the particular tumor microenvironment may result in dual roles of MSCs that can suppress or promote tumor progression. The tumor-suppressive mechanisms are mainly due to secreted factors and downregulation of Wnt and NF-kB pathway. The tumor-promoting mechanisms are mainly attributed to both secreted factors and direct effects via 1) supporting tumor vasculature, 2) EMT transition and 3) ECM remodeling. The immunosuppressive effects of MSCs (inhibit NK cells, macrophages, dendritic cells, T cells and support regeneration of Tregs) conceivably lead to tumor-promoting effect.

7.2. Reasons for caution

Harnessing the hepatic differentiation potential and anti-inflammatory function of MSCs, most of the current clinical studies aim to treat liver cirrhosis, a premalignant state [75,76]. Given the immunomodulatory properties of these cells, MSCs are also used for immunomodulation therapy of patients after liver transplantation [77] . Such studies almost unavoidably involve patients who are positive for hepatitis B or C virus infection. These infections are, however, important drivers of cirrhosis and HCC [78]. In addition, HCC is an important indication for liver transplantation and liver transplant patients also have increased incidence of developing de novo cancer [79].

Another concern is that the cellular fate and distribution of transplanted MSCs *in vivo* remain unclear. MSCs subcutaneously engrafted into immunodeficient mice were detectable up to 25 days [8]. In patients with liver cirrhosis, intravenously infused MSCs accumulated in the liver and spleen, which were detectable up to 10 days [80]. Magnetic resonance imaging (MRI) and radioactive labeling are commonly used for tracking infused stem cells [81. These technics however suffer from low sensitivity [82], and therefore are not able to precisely trace cell distribution and survival. Further, the functionalities of infused MSCs, including differentiation status and cytokine production, are not able to be defined *in vivo*.

Because of unclear clinical benefits in liver disease patients [75,76, 80], uncertainty of infused MSCs *in vivo* and the potential tumor-prompting effects of MSCs as demonstrated in various experimental liver cancer models as well as potential malignant transformation may occur during *ex vivo* expansion of MSCs [83], we thus call for caution of using MSCs to treat liver cancer or even premalignant liver diseases.

8. Summary

The tumor tropism property of MSCs has been demonstrated both in experimental liver cancer models and in patients. However, as discussed above MSCs may not only be tumor tropic but also tumor trophic. Both tumor-promoting and tumor-suppressive roles of MSCs have been described depending on the particular liver cancer models and methodologies used (Fig. 2). Because of their tumor tropism, the use of MSCs as vehicles for anticancer drug/gene delivery has reached clinical investigation. However, we call for caution in using MSCs to treat liver cancer or even premalignant liver diseases. Given their potent immunosuppressive and tumor promoting properties MSCs may in fact represent a target for anti-cancer therapy.

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