


REVIEW

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Mesenchymal stromal cells induce inhibitory effects on hepatocellular carcinoma through various signaling pathways

Jafar Ai^{1†}, Neda Ketabchi^{2†}, Javad Verdi¹, Nematollah Gheibi³, Hossein Khadem Haghighian⁴ and Maria Kavianpour^{1,5*} 

Abstract

Hepatocellular carcinoma (HCC) is the most prevalent type of malignant liver disease worldwide. Molecular changes in HCC collectively contribute to Wnt/ β -catenin, as a tumor proliferative signaling pathway, toll-like receptors (TLRs), nuclear factor-kappa B (NF- κ B), as well as the c-Jun NH2-terminal kinase (JNK), predominant signaling pathways linked to the release of tumor-promoting cytokines. It should also be noted that the Hippo signaling pathway plays an important role in organ size control, particularly in promoting tumorigenesis and HCC development. Nowadays, mesenchymal stromal cells (MSCs)-based therapies have been the subject of in vitro, in vivo, and clinical studies for liver such as cirrhosis, liver failure, and HCC. At present, despite the importance of basic molecular pathways of malignancies, limited information has been obtained on this background. Therefore, it can be difficult to determine the true concept of interactions between MSCs and tumor cells. What is known, these cells could migrate toward tumor sites so apply effects via paracrine interaction on HCC cells. For example, one of the inhibitory effects of MSCs is the overexpression of dickkopf-related protein 1 (DKK-1) as an important antagonist of the Wnt signaling pathway. A growing body of research challenging the therapeutic roles of MSCs through the secretion of various trophic factors in HCC. This review illustrates the complex behavior of MSCs and precisely how their inhibitory signals interface with HCC tumor cells.

Keywords: Mesenchymal stromal cells, Hepatocellular carcinoma, Wnt signaling, Toll like receptor, Nuclear factor-kappa B, JNK pathway

Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver malignancy, occurs predominantly in patients with underlying chronic liver disease and cirrhosis [1]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, combined with the advanced stage of liver fibrosis are thought to be the major risk factors for HCC [2].

There are alternative treatments available for this particular type of cancer, including chemotherapy with anti-cancer agents like sorafenib, radiotherapy, and immunotherapy, as well as the surgical resection of tumoral lesions. Ultimately, liver transplantation is an accepted modality of treatment in this background [3]. Although a liver transplant may offer the best chance of survival in patients with end-stage liver disease, the potential complications of this procedure lead to an urgent need to develop new treatment strategies for HCC. Cell therapy research propose some new mechanisms for tissue regeneration that would be used as a suitable replacement alone or in combination with other medications [4, 5].

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In recent years, considerable research has been devoted to developing effective HCC treatment options. In particular, mesenchymal stromal cells (MSCs) based therapies have been the subject of *in vitro*, *in vivo*, and clinical studies for liver dysfunction management purposes [6]. In addition to the differentiation capacity of MSCs as intrinsic drug stores, they are also able to secrete various trophic factors, affecting a large number of cells through the body [4]. MSCs, also known as fibroblast-like cells possess self-renewal capacity and multiple differentiation abilities to distinct lineages, such as osteocytes, adipocytes, and chondrocytes [7]. Mainly in the bone marrow, they have either been identified in various tissues and organs such as adipose, umbilical cord, kidney, brain, liver, and lung. These organs contain a subpopulation of stem cells as sources of putative MSCs for therapeutic purposes, largely due to findings related to their effectiveness in the treatment of several diseases [8].

The presence of these cells is confirmed mainly by evaluating the cell surface markers, such as CD29, CD51, CD73, CD90, and CD105, as well as the lack of CD45 and CD31 [9]. Still, the evidence of the homogenous population of such cells have not been identified in any research studies. The International Society for Cell and Gene Therapy (ISCT) proposed two criteria for the definition of MSCs based on heterogeneous and nonclonal cell populations, which are a mixture of stem cells with different multipotential properties, committed progenitors, and differentiated cells [10]. Despite the tumor homing nature and induction of cancer cell growth arrest by MSCs [9, 10], still little is known about the signaling molecules and how they work in such cells [11].

Molecular carcinogenesis of HCC could be variable due to either inactivation or loss of tumor suppressor genes such as cyclin-dependent kinase inhibitor 1A (P21, Cip1), tumor protein p53 (TP53), retinoblastoma (RB) and phosphatase and tensin homolog (PTEN) and/or activation of oncogenes including protein kinase B (PKB) and neuroblastoma Ras (N-Ras) [12, 13]. In addition, HCC is strongly correlated with abnormalities of signal transduction network that regulate self-renewal ability, proliferation and differentiation capacity of stem cell, for example, MAPK, mTOR, Notch, and Wnt/ β -catenin pathways or another cytokine such as HGF, IGF, VEGF, and PDGF signaling [14, 15]. The homing potential of human MSCs to lesions of Kaposi's sarcoma and their inhibitory activity on tumor growth by down-regulating the PKB is an example of the therapeutic potency of MSCs co-cultured with animal tumor cells [16]. Hajighasemlou et al. have indicated the huge therapeutic potential of intertumoral injection of MSCs as a cell-based therapy in HCC [17]. Increased MSC migration toward tumor sites is associated with improved biochemical test results due to their

growth suppression effect on HCC cells. Nevertheless, we need more experimental data in which signaling pathways are highly involved in this background? In this review, we will discuss the inhibitory effects of MSCs on HCC cell proliferation with the key focus on related signaling transduction network.

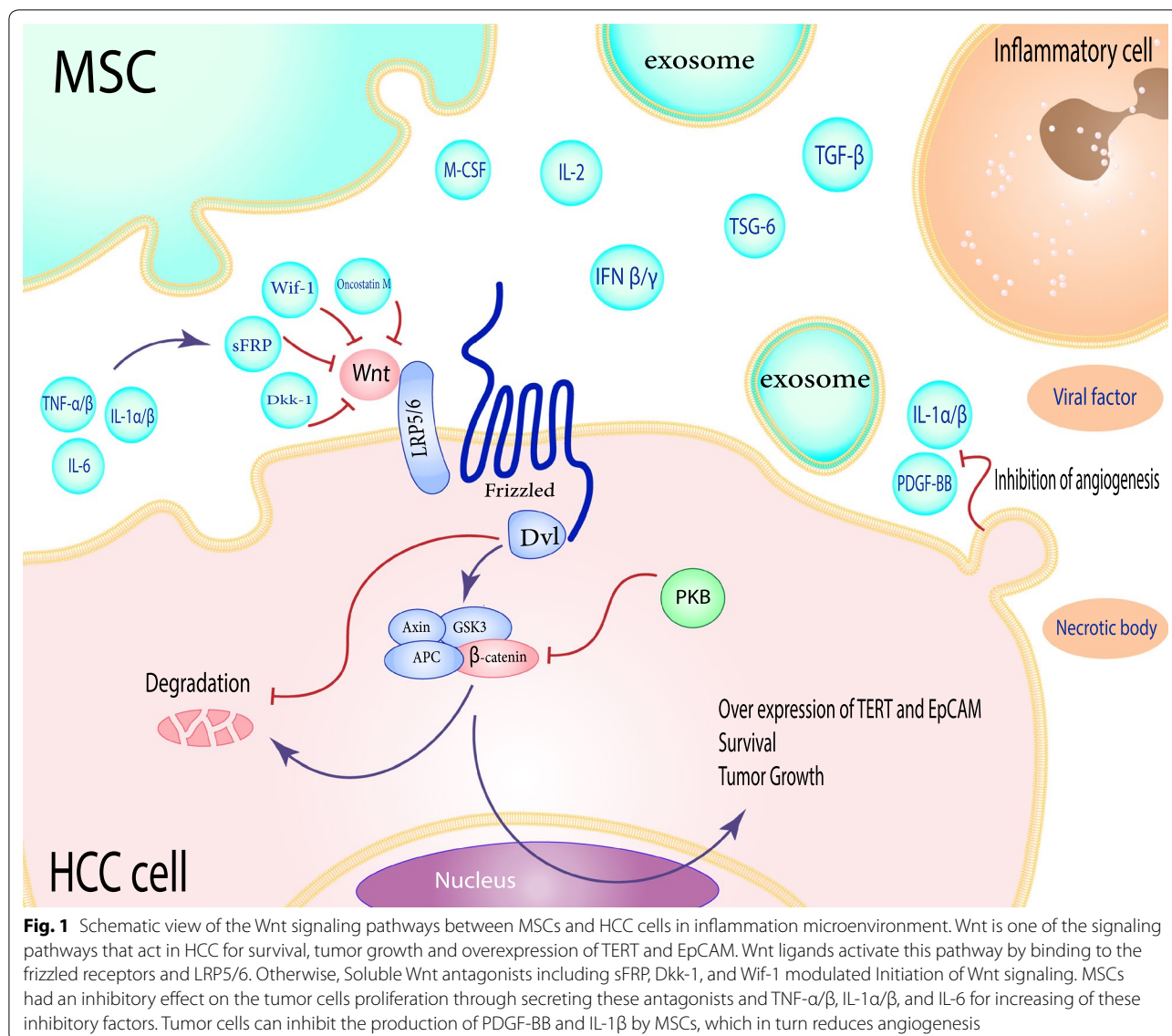
Downregulation of Wnt signaling in HCC

Among the multiple signaling pathways, a significant amount of research has been done studying the Wnt signaling alteration as a common pathogenic basis of HCC [14]. The HCC tumor microenvironment is associated with a hyperactive Wnt signaling pathway, as well as the acquisition of stemness features by tumor cells [18]. It seems likely that the increased expression of downstream target genes is a key step within the pathological consequences of Wnt signaling in HCC cells [19].

The canonical Wnt signaling pathway launches its promotion effects by stabilization of cytosolic β -catenin and its nuclear translocation as a transcriptional regulator, whereby it works as a co-activator of T-cell factor (TCF) proteins [20]. An initiating event is probably caused by the Wnt ligands, through binding to the Frizzled (Fzd) receptors and co-receptors, lipoprotein receptor-related protein (LRP) 5 and 6 [21]. Members of the Wnt proto-oncogene family can lead to tumor formation by accelerating proliferation and cell cycle progression [21]. Thus, for example, increased expression of the anti-apoptotic protein B-cell lymphoma 2 (BCL-2) and proliferating cell nuclear antigen (PCNA) has been linked to Wnt3a in cancer cells [22]. Soluble Wnt antagonists, including soluble frizzled-related protein (sFRP), dickkopf-related protein 1 (DKK-1) and Wnt inhibitory factor-1 (WIF-1) differentially modulate the initiation of Wnt signaling in both normal and malignant cell populations [23, 24] (Fig. 1).

Yet, in spite of many advances in signal transduction pathways, the impact of MSCs on Wnt signaling and their inhibitory effect on HCC cell growth remain largely unknown. To date, there is a lot of evidence that MSCs release some factors such as DKK-1 that compete with Wnt for binding to LRP5/6, thus inhibits the Wnt signaling pathway [11, 25].

Qiao et al. have elucidated the inhibitory properties of MSCs on the dynamic growth of human breast cancer cell lines. These results indicate that MSC-conditioned medium induces down-regulation of β -catenin, while overexpression of DKK-1 enhances the inhibitory effect of MSCs on the Wnt signaling pathway [25] (Fig. 1). Similarly, Zhu et al. reported the DKK-1 secretion by MSCs cause decreased proliferation of chronic myelogenous leukemia cancer cells [26]. Furthermore, mechanisms underlying the inhibition of proliferation and promotion



of apoptosis have been investigated in human HepG2 cell lines. MSC-derived DKK-1 protein could inhibit the expression of Wnt-related factors, including c-Myc, BCL-2, survivin, and β -catenin, thus leads to the dysregulation of this signaling pathway [11].

Telomerase reverse transcriptase (TERT) gene is involved in regulating the stemness properties by influencing the telomere length maintenance of normal stem cells [27]. TERT expression is controlled through binding of β -catenin to its promoter region; thereby creating a regulatory link between telomerase function and Wnt signaling [28]. In addition, epithelial cell adhesion molecule (EpCAM) overexpression has been observed during liver development, regeneration and following

the recovery from cirrhosis [29]. While absent in adult hepatocytes, this cell-surface tumor marker is identified as a direct transcriptional target of the Wnt signaling in HCC [30] (Fig. 1).

Abnormal cytoplasmic and nuclear accumulation of β -catenin, as well as the elevated level of Wnt receptor, frizzled-7 (FZD-7) in up to 90% of HCCs, revealed the importance of MSCs inhibitory properties on the Wnt signaling pathway [31, 32]. Hence, a great amount of effort has been put in this issue for approaching a stem cell-based therapy and also improving the effectiveness of inhibitory drugs in HCC patients [33].

MSCs reduce inflammation in HCC

There is strong scientific evidence that infections with specific types of bacteria or viruses like hepatitis may increase the risk of HCC via induction of inflammation [34]. Similarly, contamination with aflatoxin B1 or environmental pollutants, including aromatic amines, vinyl chloride, polycyclic aromatic hydrocarbons, and nitrosamines are thought to be the general risk factors for HCC development [35].

The role of molecular changes in the acquisition of drug resistance phenotype may help to identify the prognostic markers and novel therapeutic approaches for HCC treatment [36]. The pro-tumorigenic effects of inflammation sustain via a feed-forward cytokine and chemokine network that attract more inflammatory cells toward the tumor microenvironment [37]. Multiple signal transduction pathways such as nuclear factor-kappa B (NF- κ B) and c-Jun NH2-terminal kinase (JNK) are highly involved in the pathogenesis of viral diseases. For instance, the HCV core and HBV X (HBx) proteins are the most powerful inducers described to date, participating in the activation of NF- κ B and activator protein 1 (AP-1) transcription factors [38]. Yen et al. have examined different signaling pathways related to the HBx-induced HCC development, as the overexpression of this protein lead to the upregulation of I κ B kinase β (IKK β), tuberous sclerosis complex 1 (TSC1) and mammalian target of rapamycin (mTOR) in HCC cells. Moreover, the elevated levels of pIKK β , pTSC1, and pS6K1 are strongly correlated with a poor prognosis in HBV-associated hepatoma [39]. Here, we have tried to provide a comprehensive look into the role of toll-like receptors (TLRs), NF- κ B and the JNK signaling pathways in HCC development.

TLR signaling in HCC

TLRs are able to recognize the various patterns of pathogen- and host tissue-derived molecules and thus give rise to inflammation [40]. Their function has been mediated by the Toll/interleukin-1 receptor (TIR) domain [41]. TLR4 belonging to the pattern recognition receptor (PRR) superfamily, commonly play a central role in innate immunity. The 95 kDa integral membrane protein consists of an extracellular domain named leucine-rich repeat (LRR), as well as a cytoplasmic TIR domain, directing ligand recognition and signal transduction, respectively [42]. It has a limitless capacity for detecting pathogen-associated molecular patterns (PAMPs) or different classes of damage-associated molecular patterns (DAMPs), all lead to the production of required cytokines and pro-inflammatory proteins [43]. The adapter protein myeloid differentiation factor 88 (MyD88) acts as an intracellular signal transducer in cooperation with interleukin-1 receptor-associated kinase 1 and 4 (IRAK1/4),

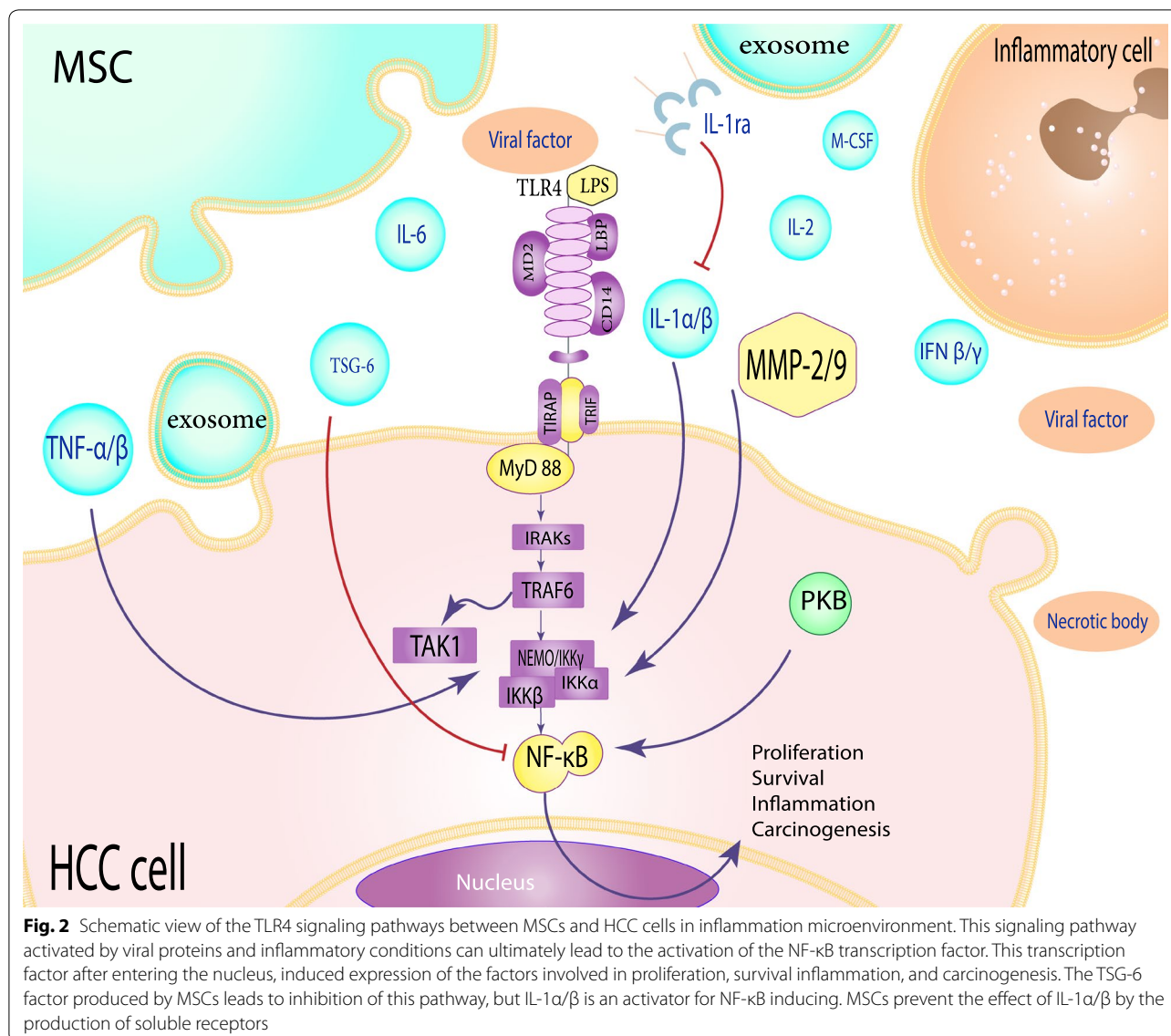
following the TLR4 activation [44]. Following the phosphorylation of these factors by TRAF6, TAK1 kinase is recruited into the cluster of signaling pathways [45]. Once activated, TAK1 activates the I κ B kinase (IKK) complex that finally gives rise to NF- κ B and JNK activation [46] (Fig. 2).

There are numerous factors that can activate the TLRs signaling in the liver, such as HBV, HCV, alcohol, and nonalcoholic steatohepatitis (NASH). Among TLRs, TLR4 and 9 suppress viral replication in HBV-transgenic mice [47, 48]. HBV replication cycle occurring via the upregulation of TLR2 thus results in a marked increase in tumor necrosis factor-alpha (TNF- α) production [49]. HCV core and NS3 proteins cause inflammation and activate TLR2 on immune cells to release cytokines [50, 51]. Moreover, excessive alcohol intake is highly associated with increased intestinal permeability and elevated levels of endotoxin [52]. In vivo studies have indicated that lipopolysaccharides (LPS) levels are significantly increased in cirrhosis, and can directly activate the hepatic stellate cells [53, 54]. LPS activates the TLR4-mediated pathway and thus, enhances the expression of proinflammatory cytokine [55, 56]. TLR4 and MyD88 deficient Mice have a considerable reduction in the number of chemically induced HCC, highlighting a direct influence of TLR signaling on hepatocarcinogenesis [57]. MyD88, as a TLR adapter protein, is necessary for NF- κ B activation, and its downregulation is strongly associated with liver tumorigenesis suppression [58]. Therefore, the indispensable role of TLR4-MyD88 signaling in HCC development creates new approaches to disease prevention and treatment [36] (Fig. 2).

NF- κ B signaling activation in HCC

NF- κ B is present broadly in the majority of cells and is a key transcription factor in cellular proliferation, differentiation, carcinogenesis, and apoptosis [59]. Across several studies, researchers have shown that NF- κ B contributes to tumorigenesis by affecting the tumor cells and tumor-associated inflammatory cells mechanisms [60–62]. Overall, the inhibition of NF- κ B activity provides convincing evidence of a novel therapeutic implication for HCC [63]. Numerous proinflammatory stimuli upregulate NF- κ B, by phosphorylation of IKK and degradation of the κ B inhibitor (I κ B) proteins [64]. Members of the TNF family, like the B-cell activating factor (BAFF), CD40 ligand, and lymphotoxin β (LT β) demonstrating a key role in activating the NF- κ B pathway [65].

Active NF- κ B controls the expression of several anti-apoptotic proteins, including cIAPs, c-FLIP, and BCL-X that are essential for maintaining cancer cells [66]. Tumor cells with continuous NF- κ B activity are highly resistant to antitumor agents and thus, specific inhibition of

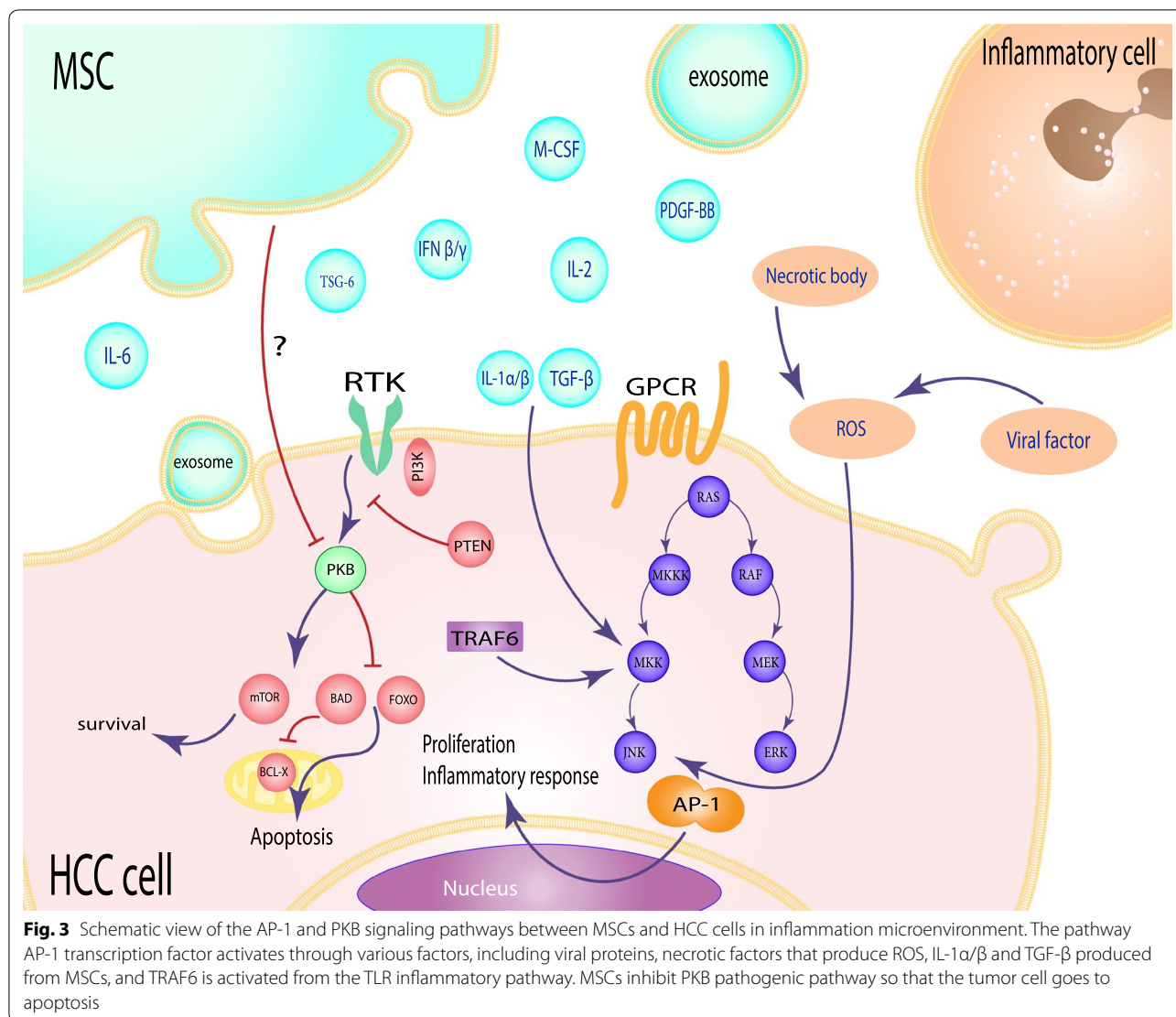


NF-κB may promote cell sensitivity to applied treatment [67]. Overexpression of IKKα and IKKβ kinases, essential for NF-κB activation, is definitely needed for the acquisition of malignant HCC properties [68]. Surprisingly, downregulation of NF-κB and p-IκBα has been demonstrated in treated HCC cell lines, but how MSCs can regulate the NF-κB signaling pathway mostly remain unclear [69]. However, the role of various factors present in the MSCs-conditioned media should not be ignored for the downregulation of the NF-κB pathway in tumor cells (Fig. 2).

JNK Signaling activation in HCC

The JNK is a major member of the mitogen-activated kinases (MAPKs) family, together with extracellular

regulated kinase (ERK) and p38 [70]. JNKs activation in response to stress signals and pro-inflammatory stimuli would eventually enhance the phosphorylation of MAPK kinases MKK4 and MKK7 [71]. They also phosphorylate the transcription factors c-Jun, JunD, as well as the activating transcription factor (ATF), which contribute to AP-1 complex formation [72]. A number of studies have emphasized the importance of active JNK signaling for hepatocyte proliferation and apoptosis [73]. It is clearly recognized that cellular immortality occurs due to a DNA mutation in association with JNK activation [74]. Phosphorylation of c-Jun proto-oncogene via the JNK pathway may promote the development and progression of HCC disease [75] (Fig. 3). Approximately 70% of HCC tissues show



positive immunostaining for phosphorylated JNK, which revealed the vital role of this protein kinase in human HCC pathogenesis [36].

Tong et al. described the spontaneous occurrence of intestinal tumors in JNK1 knockout mice, suggesting a suppressor role for JNK1 in intestinal tumor development [76]. Possibly, signal transmission by a number of growth factors provokes JNKs by activating the receptor tyrosine kinases, as well as the phosphorylation of various receptors [77]. In vitro modeling of HCC studies revealed the pathogenic impact of several HBV and HCV proteins on JNK activation [78]. Viral proteins such as the HBV X and HCV core proteins generally induce the accumulation of reactive oxygen species (ROS) in hepatocytes [79, 80]. Sustained production of ROS then activates the JNK via either stimulating upstream MEK kinases (MEKKs)

or inhibiting MAP kinase phosphatases (MKPs) [81, 82]. Thus, ROS-JNK signaling is found to be a major determinant of HCC progression [83, 84] (Fig. 3).

Molecules involved in MSCs homing to tumor micro-environments are mainly consisting of several inflammatory cytokines (TNF- α , IL-1 β , IFN- γ , and IL-6), chemokines (CXCR4, CXCL7, CXCL6, and CXCL5) and growth factors (PDGE, HGF), [85, 86]. Interestingly, MSCs are able to suppress tumor cell growth by releasing inhibitory factors-containing exosomes against the proliferation of signaling pathways [87]. Moreover, the secretion of IL-1ra by MSCs prevents the IL- α/β activity by producing TSG-6, followed by the downregulation of NF- κ B signaling and decreased the production of inflammatory cytokines. Secretion of prostaglandin E2 (PGE2) is another effective way of reducing inflammation by

MSCs that accomplished by the production of IL-10, as a potent anti-inflammatory cytokine [88, 89]. Khakoo et al. indicated that MSCs inhibit the target cell PKB signaling activity through a contact-dependent way [16]. In total, the downregulation of NF- κ B is suggested to be a beneficial behavior of MSCs to inhibit tumor cell proliferation and invasion (Fig. 2).

Hippo signaling pathway in HCC

The control of organ size following multiple cell proliferation is fundamental through the developmental process, as an increased organ size due to injury should be returned to normal values by regeneration [90]. The Hippo signaling pathway is mainly involved in the regulation of organ growth and overall organ size. This signal transduction cascade mediates cell proliferation, differentiation, and survival, as well as the homeostasis and development in cooperation with other signaling interactions. Any disruption in key components of this pathway has a great potential in tumor formation and in particular HCC [91]. Recent studies have shown the essential role of Hippo signaling in stem cell regulation, especially in liver cancer progenitor cells that ultimately lead to hepatocarcinogenesis [92, 93].

This signaling pathway consists of a number of highly conserved components: the protein kinase Hippo (Hpo), the scaffold protein Salvador (Sav), the protein kinase Warts (Wts), and Mob as a tumor suppressor (Mats) that are homologous to mammalian Mst1/2, WW45, LATS1/2, and Mob1, respectively. Their essential role in organ size control is considered as the main reason for possessing an evolutionary conservation pattern, as any mutation in genes encoding Hippo signaling proteins can lead to significant changes in organ morphology or growth parameters [94].

Similar to other pathways, Hippo signaling is negatively controlled by phosphorylation via the growth modulator Yorkie (Yki) or its mammalian homolog Yes-associated protein (YAP). So that the overexpression of this factor or mutations in core Hippo pathway components resulted in the activation of two major cell proliferation markers, Cyclin E and Drosophila inhibitor of apoptosis protein 1 (DIAP1) to prevent cell death [95, 96]. In recent studies, YAP has been reported as an oncogene in many human tumors, especially for those with HCC. Zhao et al. reported a significant increase in YAP expression in nearly 54% of patients with HCC compared to normal liver tissue. This study concluded that the uncontrolled YAP expression could play an increasingly important role through HCC development [97]. The same results were also observed in the study by Xu et al., in which 62% of examined samples showed a higher level of protein

expression, associated with tumor aggressiveness and unfavorable prognosis of HCC [98].

Since the Hippo signaling pathway has recently been discovered, more extensive studies should be performed related to the effect of MSCs on HCC development. A novel study suggested that the transcriptional co-activator with PDZ-binding motif (TAZ), one of the nuclear effectors of this signaling cascade, can effectively modulate cell proliferation and the formation of epithelial-mesenchymal transition (EMT) in HCC [99]. The expression of TAZ is significantly increased in HCC, as the knockdown of this downstream regulatory target can prevent tumorigenesis and reduces HCC cell migration. The EMT process occurs as a result of decreased expression of epithelial genes such as E-cadherin and the increased expression of mesenchymal genes such as N-cadherin, vimentin, Snail, and Slug [100]. Eventually, the two most important factors of the Hippo signaling pathway, TAZ, and YAP, have a significant impact on the key step of transdifferentiation process development [101]. Surprisingly, the hypoxic state of tumor microenvironment cause increased secretion of prostaglandin E2 (PGE2) from the surrounded MSCs and ultimately increase the YAP protein level in HCC cells [102, 103]. Due to a lack of research that comprehensively analyze the effect of MSCs on Hippo signaling, genetic modification of mesenchymal cells or considering these multipotent stromal cells as drug delivery vehicles may possibly decrease the negative feedback effects of this signaling cascade and prevent HCC tumor progression.

Discussion

HCC is considered as a common malignant condition, caused by impaired hepatic stem cell function [104]. There are multiple signal transduction pathways, regulate the self-renewal, differentiation and cell fate specifications of precursor cells. Therefore, understanding the exact mechanism of these signaling cascades may provide an alternative way to explore the link between stemness and tumorigenesis [105]. Increasing evidence has indicated that adult stem cells may be considered as an effective therapeutic tool for cancer therapy [106]. Certain studies have described the intrinsic ability of MSCs to decrease the growth rate of numerous cancer cell types [107]. Ma et al. directly injected human umbilical cord MSCs (hUC-MSCs) xenograft transplanted into immunodeficient mice, bearing MDA-MB-231 breast cancer stem cells. Surprisingly, the hUC-MSCs lead to reduced tumor volume and tumor weight in mice models [108]. Zhang et al. investigation on hUC-MSCs, transfected with IL-21 gene determined the ability of such modified cells to suppress the proliferation of ovarian cancer cells in vitro and in vivo [109]. Subramanian et al. research

confirmed that hUC-MSCs did not transform into tumor-associated fibroblasts, making them invulnerable than bone marrow MSCs [110].

MSCs are thought to suppress tumor growth in different ways: induction of inflammatory cell infiltration, angiogenesis inhibition, suppression of Wnt, NF- κ B, and PKB signaling molecules. Paracrine effects of these multipotent cells also lead to cell cycle arrest and apoptosis via Dkk1 and oncostatin M activity [11, 25, 69, 111–114]. Ryu et al. reported that adipose tissue-derived MSCs are able to grow at high cell density, followed by the prevention of MCF-7 cell growth through IFN- β production [115]. Moreover, MSCs primed with IFN- γ or cultured with tri-dimensional systems can express TNF-related apoptosis-inducing ligand (TRAIL), which triggers tumor

cell-specific apoptosis [116, 117]. The result of Loebinger et al. study confirmed that MSCs could reduce colony formation of squamous and adenocarcinoma lung cancer cells by expressing TRAIL. This protein binds to its receptors and leading to the activation apoptosis pathway in tumor cells. [118].

In addition, Zhao et al. study indicated that 3D cultured MSCs have an inhibitory effect on HepG2 cell proliferation, by releasing the IL-24 and the activation of the JAK1-STAT3 signaling pathway. This study suggested a more feasible way for MSCs to inhibit tumor cell growth and invasion [119].

In contrast to numerous research that expresses the inhibitory role of MSCs on tumor cells, some reports showed enhanced tumor growth due to the homing

Table 1 Dual effect of MSCs on HCC

References	Effects	Cell lines	Results
Hou et al. [11]	Inhibit	HEK 293 and HepG2 cell lines	Wnt signaling pathway may have a function in MSC-mediated tumor cell inhibition
Yan-rong Lu et al. [113]	Inhibit	murine hepatoma H22, lymphoma (YAC-1 and EL-4) and rat insulinoma INS-1 cell lines	MSCs had potential inhibitory effects on tumor cell growth in vitro and in vivo without host immunosuppression, by inducing apoptotic cell death and G0/G1 phase arrest of cancer cells
Li et al. [132]	Inhibit	MHCC97-H cell line	MSC could be useful in controlling metastatic recurrence of HCC
Zhao et al. [133]	Inhibit	HepG2, Huh7, SMMC7721, and Bel7402 cell lines	inhibited HCC cell proliferation and division induced HCC cell death through the downregulation of Akt signaling
El Asmar et al. [105]	Inhibit	DENA and CCl4 induction in rat model	tumor suppressive effects as evidenced by down regulation of Wnt signaling target genes concerned with anti-apoptosis, mitogenesis, cell proliferation and cell cycle regulation
Li et al. [134]	Inhibit	MHCC97-H cell line	The metastatic potential of tumor cells was downregulated after hMSC engraftment and hMSCs induce further tumor cells apoptosis
Qiao et al. [135]	Inhibit	H7402 and HepG2 cell lines	The Wnt signaling pathway may have a role in hMSC-mediated targeting and tumor cell inhibition
Qiao et al. [69]	Inhibit	H7402 cell line	NF- κ B downregulation is one of reasons for the depression of tumor cell proliferation mediated by hMSCs
Bruno et al. [136]	Inhibit	HepG2 cell line	MVs from human MSCs inhibited in vitro cell growth
Ma et al. [137]	Inhibit	H22 cell line	BMSCs pulsed with TEX could enhance its antitumor activities
Abd-Allah et al. [138]	Inhibit	HEPA 1-6 cell line	MSCs could inhibit cell division of HCC and potentiate their death
Seyhoun et al. [139]	Inhibit	HepG2 cell line	Combination therapy MSCs and sorafenib to the treatment of HCC that significantly improves the results
Hajjghasemlou et al. [140]	Inhibit	HepG2 cell line	Local injection of MSCs can be used as cell therapy to fight neoplasms
Hernanda et al. [141]	Promote	Huh7 cell line	MSCs are enriched in human HCC tumor compartment and could exert trophic effects on tumor cells
Yan et al. [142]	Promote	MHCC97L cell line	HCC progression, and may be a potential therapeutic target
Gong et al. [143]	Promote	HepG-2 cell line	promote the growth of microvascular in hepatoma cells
Jing et al. [144]	Promote	SMMC-7721 cell line	MSCs in tumor inflammatory microenvironment could promote tumor metastasis through TGF β -induced EMT
Bhattacharya et al. [145]	Promote	SK-Hep1 cell line	stimulation of cancer-associated fibroblasts and EMT markers
Liu et al. [146]	Promote	HCCLM3 cell line	significantly enhance the tumor cell metastasis, which was due to the EMT of HCC cells induced by TGF- β

CCl4 carbon tetrachloride, DENA diethylenetriamine, EMT epithelial to mesenchymal transition, HCC Hepatocellular carcinoma, hMSCs human mesenchymal stem cells, MVs Microvesicles, TGF- β transforming growth factor beta

capability of MSCs to tumor sites [120]. The Supportive of confounding behavior effect of MSCs toward tumor cells are highly associated with the dose of injected multipotent stromal cells to targeted organs [113]. Depending on the exact experimental conditions, MSCs can exert tumor-promoting or tumor-limiting outcomes (Table 1). Various hypotheses have been recommended to explain the dualistic behavior of MSCs in cancer. TLR4-primed MSCs are polarized into pro-inflammatory MSC1 phenotype, whereas TLR3-primed MSCs are specialized as classical immunosuppressive MSC2 [121]. In cancer models, MSC1-based treatment of established tumors in a case of strong immune system attenuates tumor growth and metastasis, while MSC2-treated animals would display an increase in tumor growth rate and metastatic potential [122]. As both hypotheses are not mutually exclusive likely both are concomitantly true, making our prediction about the role of MSCs on the cancerous process extremely difficult. However, the reasons behind this apparent discrepancy need to be further investigated.

On the other hand, in some instances, tumor cells can inhibit the PDGF-BB and IL-1 β production by MSCs, which in turn reduces the angiogenesis and tumor growth [123] (Fig. 1). In a recent study by Pan et al., trophic factors released from MSCs suppress the translation initiation factor eIF4E via the MAPK signaling pathway. Therefore, the secretion of vascular endothelial growth factor (VEGF) could be a revolutionary new way of treating cancer by altering the tumor cell fate specifications [124]. MSCs also produce the exosomes-loaded with miR-122 that significantly increases the sensitivity of HCC cells to sorafenib, leading to *in vivo* tumor growth arrest [125].

Targeted localization of MSCs in tumor sites will have a significant impact on the achievement of specific anti-tumor therapy [126]. MSCs exhibit an intrinsic homing property, enabling a collective cell migration to inflammatory sites. The exploitation of this process will be a valuable asset to directed therapy [127]. The capability to express exogenous gene products, genetic stability and allogeneic properties turn MSCs into efficient carriers for antitumor therapy [128]; previously demonstrated not only in tumor models but also in a wide range of other diseases such as graft-versus-host disease, multiple sclerosis, and arthritis [129–131].

Therefore, MSCs have multiple immunosuppressant properties that required for tumor growth inhibition and also likely to be effective in cancer treatment via producing several factors such as microRNAs. Nevertheless, more detailed information about the interactions between MSCs and tumor cells will help us to develop novel therapeutic approaches in the future. Yet, an

important issue remains unanswered regarding the time and the approximate number of such regulatory cells that are delivered to target organs. However, their role as an adjunct in patients with liver tumors looks hopeful and promising.

Conclusions

Recent studies have suggested the use of cell-based therapeutic approaches for cancer treatment. Here we discussed the inhibitory role of normal human MSCs on HepG2 cell proliferation, proposing the valuable impact of these multipotent stromal cells on liver cancer therapy. While the exact molecular mechanisms between the MSCs and tumors cells are still unknown, but the overall results of several studies revealed the suppression effect of MSCs on HCC through both inflammation mediators and vital signaling pathways. Therefore, further research needed to develop a novel clinical application of MSCs for HCC patients.

Abbreviations

AP-1: activator protein-1; APC: adenomatous polyposis coli; CD14: cluster of differentiation 14; BAD: Bcl-2-associated death promoter; DKK-1: dickkopf 1; Dvl: dishevelled; EpCAM: epithelial cell adhesion molecule; ERK: extracellular signal-regulated kinases; FOXO: forkhead box; GPCR: G protein-coupled receptors; GSK3: glycogen synthase kinase 3; IKK: I-kappa-B kinase; IRAKs: IL-1 receptor-associated kinases; IL: interleukin; IFN: interferon; JNK: c-Jun N-terminal kinases; LBP: lipopolysaccharide binding protein; LRP5/6: low density lipoprotein receptor-related protein 5/6; MD2: myeloid differentiation factor 2; MyD88: myeloid differentiation primary response gene 88; mTOR: mammalian target of rapamycin; M-CSF: macrophage-colony stimulating factor; MMP: matrix metalloproteinases; MEK: MAPK/ERK kinase; MKKK: mitogen-activated protein kinase kinase kinase; MKK: mitogen-activated protein kinase kinase; NF- κ B: nuclear factor; NEMO: NF-kappa-B essential modulator; PI3K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homolog; PKB: protein kinase B; PDGF: platelet-derived growth factor; RTK: receptor tyrosine kinases; sFRP: soluble frizzled related proteins (sFRP); TERT: telomerase reverse transcriptase; TRIF: TIR-domain-containing adapter-inducing interferon- β ; TNFa: tumor necrosis factor α ; TLR4: toll-like receptor 4; TIRAP: TIR domain-containing adaptor protein; TRAF6: TNF receptor associated factor 6; TGF β : transforming growth factor beta; TAK1: TGF β -activated kinase; TSG-6: TNF-stimulated gene 6; Wif-1: Wnt inhibitory factor-1.

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JV and MK contributed in conception, design and drafting of the manuscript. NK, NGH, HKH and MK contributed in data collection and manuscript drafting. JA oversaw the study. All authors read and approved the final manuscript.

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Availability of data and materials

The primary data for this study is available from the authors on direct request.

Ethics approval and consent to participate

This study was considered exempt by the KAUMS Institutional Review Board.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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