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Pathomechanism of Liver Fibrosis and Mesenchymal Stem Cells in its Resolution Process

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Abstract

Liver fibrosis is a disease process that, without adequate treatment, can lead to liver failure and can be life-threatening. This disease is reversible and appropriate therapy can prevent further liver damage. Liver transplant therapy is the only treatment for an end-stage liver disease that works, but it has various obstacles and limitations in its implementation. Therefore, nowadays, mesenchymal stem cells (MSCs) have become a hope of therapy for liver fibrosis. Our literature review describes the pathomechanism of liver fibrosis and the steps of its resolution, accompanied by the possible role of MSCs in supporting the process. The activation of several complex pathways regulates liver fibrosis, and its resolution, involving Transforming Growth Factor (TGF)-β, signal transducer and activator of transcription-3, and Wnt/β-catenin signaling is involved in Hepatic Stellate Cells (HSCs) activation, which are precursors of myofibroblasts (MFs) and causes fibrosis. The presence of the High-mobility group box-1 pathway, which also induces the production of proinflammatory cytokines and the role of matrix metalloproteinases (MMPs)/tissue Inhibitors of MMPs s and Syndecan-1, is incorporated into the extracellular matrix (ECM). In repairing liver damage, four steps of liver fibrosis resolution are required, such as preventing further damage, restoring the intrahepatic balance of inflammation, removing and inactivating MFs, and ECM degradation associated with arresting the eight pathways of the fibrosis mechanism. MSCs can help resolve liver fibrosis and speed up wound healing, increase hepatocyte survival, and suppress HSCs activation by blocking fibrosis mechanism pathways such as TGF-β and pro-inflammatory factors such as tumor necrosis factor-alpha, interferon-gamma, IL-6, IL-17, and IL-23, in addition to an elevated level of an anti-inflammatory factor like IL-10.

Introduction

Scar formation is a response of liver tissue to repeated and continuous liver injury or chronic liver disease (CLD), which leads to liver failure [1]. CLD can be induced by Hepatitis B and C infection, fatty liver disease (FLD), whether caused by alcohol or not, and autoimmune diseases (such as autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis) [2], [3]. The scar tissue is induced by an increase of extracellular matrix (ECM) synthesis, such as fibrillar collagen, primarily collagen I and III. This deposition of ECM will cause interaction of macrophages, myofibroblasts (MFs), and epithelial cells that lead to hepatocellular dysfunction. This condition is a morphological feature of liver fibrosis [1], [4], [5].

Liver fibrosis is one of the top ten diseases that causes death in the world and still no satisfactory definitive treatment. Epidemiological data show that liver fibrosis causes more than one million deaths per year, or equal to 2% of total deaths worldwide [6], [7] Liver fibrosis can be reversible as evidenced by current clinical and histological findings. To avoid further liver damage, it is crucial to assess the extent of liver fibrosis and prescribe the proper treatment [2], [8]. At present, the most effective treatment option for liver fibrosis is liver transplantation [9]. However, liver transplantation has many limitations, such as the limited number of liver donors, expensive cost, and rejection by the immune system [7], [9], [10]. The discovery of isolation, propagation, and preservation methods of mesenchymal stem cells (MSCs), as well as research on their potential in regenerative therapy gives hope for their use as alternative therapy for patients with liver disease [7], [11].

Recent studies reported that MSCs provide a new alternative pattern for controlling inflammation, repair, and regeneration of liver fibrosis. By increasing hepatocyte survival and inhibiting the activation of Hepatic Stellate Cells (HSCs), MSCs help to accelerate wound healing [4], [5] Several preclinical researches using MSCs have been conducted and given an indication that MSCs can support liver fibrosis regression [12]. Therefore, it has been considered important to evaluate treatment response in clinical trials [8]. Aspects of the cellular heterogeneity of MSCs and the complex nature of MSCs make this cell very interesting to be studied [12]. To give us a better understanding of the pathomechanism of liver fibrosis

and its resolution, this article discusses the cellular mechanism of fibrosis and liver fibrosis resolution, as well as the role of MSCs therapy on the fibrosis resolution.

Pathomechanism of Liver Fibrosis

Liver fibrosis develops by activating several complex pathways intended to repair damaged liver tissue but ultimately results in uneven scarring [13]. Liver injury triggers the activation of several subsets of innate immune cells, including macrophages, neutrophils, eosinophils, natural killer (NK) cells, dendritic cells (DCs), and innate lymphoid cells, as well as adaptive immunity cells, including T lymphocytes (T cells), regulatory T (Treg) cells, B lymphocytes, regulatory B cells, and T helper (Th) cells [14]. Destruction of hepatocytes initiates fibrosis that results in the release of inflammatory cytokines and the activation of liver macrophages (Kupffer cells or KCs); activation and transformation of HSCs into fibrogenic and proliferative MFs; and leukocyte migration to the injury site. Activated HSCs release reactive oxygen species (ROS), cytokines, and chemokines in addition to fibers and a significant amount of ECM proteins, that is, Type I, III, and IV collagen, elastin, fibronectin, and laminin, as well as proteoglycans, which promote inflammation process [13], [15]. Liver fibrosis has numerous intricate mechanisms that involve both cellular and extracellular signaling [15], including transforming growth factor (TGF-β), signal transducer and activator of transcription (STAT3), Wnt/β-catenin, apoptotic, matrix metalloproteinases (MMPs) dan tissue Inhibitors of MMPs (TIMPs), Syndecan-1 (SDC1), and regulation of high-mobility group box 1 (HMGB1) pathways.

The TGF-β signaling pathway is critical for HSCs activation [16]. TGF-β is a profibrogenic cytokine that causes fibrosis by activating the SMAD signaling pathway. It has also been shown to mediate the transformation of mesothelial cells through the epithelial mesenchymal transition into MFs in CLD [16], [17]. The decapentaplegic homologous protein (SMAD) 2/3–4 pathway is one of the intracellular pathways that are activated by TGF-β. This pathway can interact with other transcription factors (coactivators/corepressors) in the nucleus to regulate the formation of MFs, leading to an increase in MFs and an increase in connective tissue growth factor, which is what causes fibrosis [18]. Recent studies report that prolonged inflammation can induce Type-2 macrophage (M2) cells to release several growth factors, especially TGF-β, as potent mediators for the activation and differentiation of HSCs into MFs, which produce ECM [19]. TGF-β also increases the expression of pro-fibrogenic markers, such as α-SMA, MMPs, and TIMPs [20] (Figure 1).

Many protein ligands, such as cytokines, growth factors, interferons (IFNs), and peptide hormones, activate the Janus kinase (JAK) transduction pathway/STAT pathway, which regulates a variety of cellular processes, including cell growth, proliferation, differentiation, and apoptosis [21]. Numerous cellular processes, including MFs cell proliferation, liver cell survival, and induction of angiogenesis, are significantly influenced by STAT3, which also functions as a pro-or anti-inflammatory signal in regulating the onset and progression of liver fibrosis [21], [22]. It is known that JAK2 phosphorylates and activates STAT3, which is thought to encourage the proliferation of hepatocytes. Liver NF-kB-inducing kinase (NIK) may be activated in CLD by hepatocellular stress and liver inflammation. Active NIK will limit hepatocyte proliferation by inhibiting the JAK2/STAT3 pathway [22], [23]. Other research has demonstrated that IL-17 increases the STAT3 signaling pathway, encouraging Kupffer cells to release TGF-β and activating HSCs to generate MFs through promoting collagen synthesis. STAT3/IL-6 signaling regulates hepatocyte proliferation and is linked to acute and chronic liver fibrosis.

Furthermore, IL-22 produced by Th17 cells and STAT3 induces HSCs senescence in liver fibrosis [16]. Various studies have shown that T17 cells and γδ T cells (15%~25% of liver T cells) produce IL-17A. T17 promotes the formation of hepatic granulomas by secreting IL-17A. Furthermore, the absence of IL-17A signaling has been linked to decreased liver fibrosis in murine schistosomiasis [24]. Patients' fibrotic tissue samples frequently reveal elevated levels of STAT3. It is known that STAT3 functions independently as well as in conjunction with TGF-β, among other signaling networks [21]. Datasets from the past 10 years of research suggest that STAT3 and its associated cytokines have complex biologic effects on various factors that cause fibrosis. These examinations likewise show that using STAT3 inhibitors in a liver injury model leads to promising activity against, so the STAT3 pathway is a viable objective for treating fibrotic illness in patients [22] (Figure 1).

A protein known as β-catenin is an adhesion molecule and transcription factor. The Wnt protein controls the transcription factor activity of this protein, which is often released into the ECM. β-catenin is usually found in the cytoplasm, which is necessary for the development of organisms and is evidenced by embryonic death due to defects in gastrulation in β-catenin-deficient mice. Postnatal liver development requires Wnt/β-catenin signaling. This was seen in mice with a considerable reduction in liver weight due to β-catenin deletion in hepatocytes. The signaling network of Wnt/β-catenin, which is also involved in HSCs activation, causes mesenchyme depleted of β-catenin to express more of the HSCs marker α-SMA and to deposit more collagen in the developing liver [25] (Figure 1).

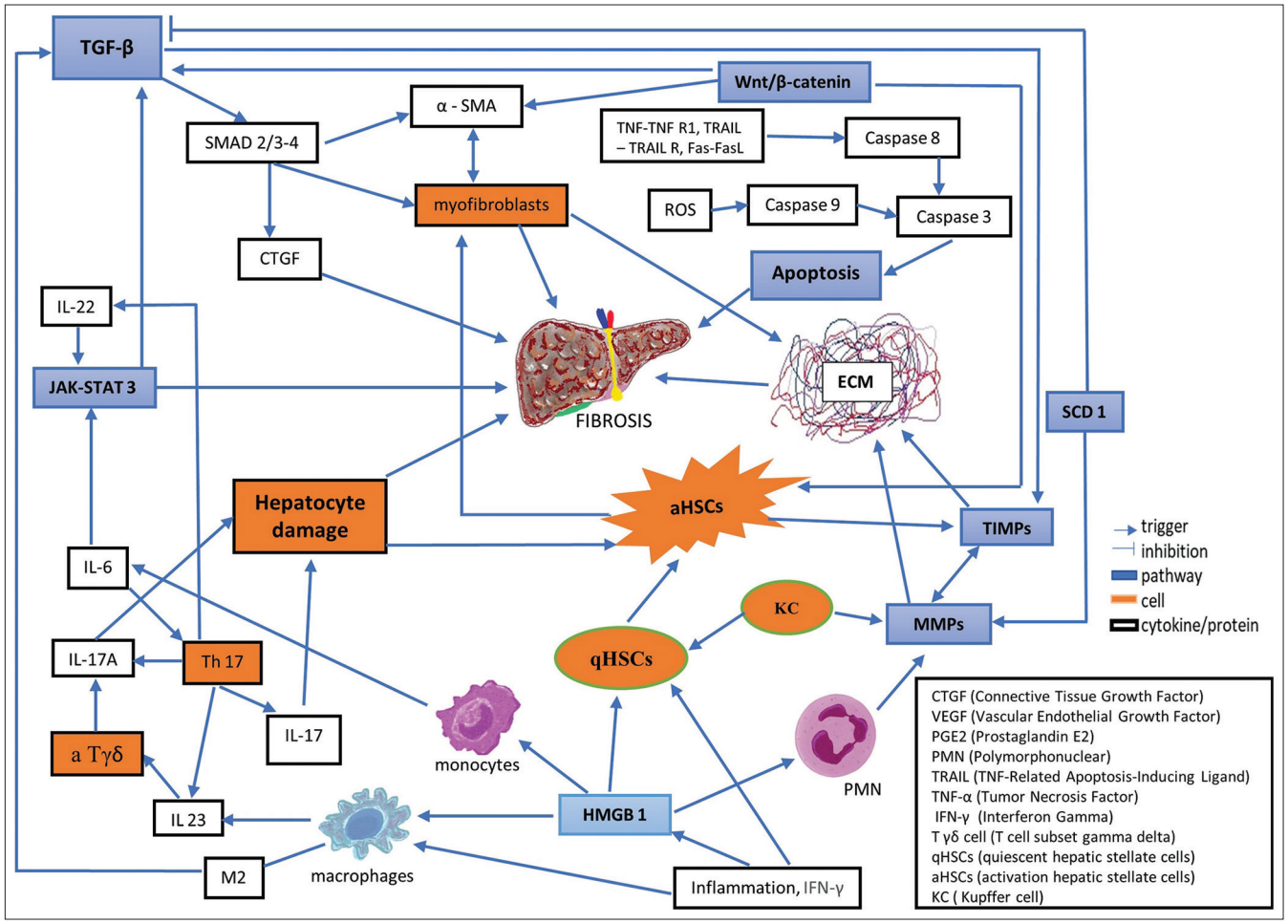

Figure 1: Eight proposed pathways that are involved in liver fibrosis

Apoptosis is a physiological response to remove damaged/old cells and maintains liver tissue homeostasis, which is essential in liver growth and regeneration by producing growth signals and increasing the development of progenitor cells. Liver fibrosis with different etiologies shows an increase in apoptosis. For example, in the case of hepatitis, in the acinar perivenous area of hepatocytes, there is an increase in apoptosis as a cytoprotective mechanism in clearing infections that occur in the liver [26]. Cell apoptosis is mediated by extrinsic and intrinsic signaling pathways. The extrinsic pathway involves specific ligands that activate their receptors (death receptors), including tumor necrosis factor 1 receptor, TNF TNF-related apoptosis-inducing ligand (TRAIL-R), and Fas as an apoptosis-inducing ligand receptor. Then, a death-inducing signaling complex is formed from an adapter molecule that binds to an apoptotic signaling molecule, which initiates apoptosis by activating caspase-8, which in turn activates caspase-3. Meanwhile, the intrinsic apoptotic pathway involves organelle dysfunction, for example, lysosomal permeabilization, mitochondrial dysfunction, and other organelle disorders. Among these organelles, mitochondria is the protagonists in the initiation and development of apoptosis. Mitochondrial dysfunction generates ROS, excess ROS is harmful and cause lipotoxicity, DNA damage, and protein damage. By causing the mitochondrial permeability transition pore (mtPTP) to open, mitochondrial dysfunction makes it possible for proapoptotic proteins like cytochrome c to be released into the cytoplasm. The apoptosome complex is formed in the presence of cytochrome c, activating factor protein-1, and caspase-9, which activate the effector caspase-3 and induce apoptosis [27] (Figure 1).

The most significant enzymes in the extracellular pathway of collagen degradation are MMPs [28]. Most MMPs are released as pro-enzymes, which are then activated in the extracellular environment. Inflammatory cells such as monocyte-derived macrophages, macrophages, and neutrophils, as well as HSCs (the body's main producers), KC, epithelial cells, fibroblasts, and endothelial cells, and these cells can all create MMPs. From liver damage, inflammation, fibrosis, cirrhosis, and hepatocarcinogenesis to disease resolution and liver regeneration, several MMPs are engaged in the many stages of liver illness. Where the vast majority of the underlying mechanisms are unidentified, MMPs can be employed as "direct" (describes ECM problems) and "indirect" (describes aberrant liver function) indicators for accurate diagnosis and staging of liver fibrosis because of the

varied expression of various MMPs at various disease stages [29]. TIMPs prevent the action of MMP. There are four TIMPs (TIMP1-TIMP4) that can interact with multiple subsets of MMPs, as opposed to 25 MMPs in mammals. Animals with Timp1 overexpression or knockout developed more severe liver fibrosis, and Timp3-KO mice developed more severe fibrosis despite higher MMP activity overall. TIMPs can influence myofibroblast activation and ECM turnover directly or indirectly by regulating cellular mechanisms that control cell proliferation, migration, and survival [28] (Figure 1).

Syndecans are a family of proteoglycans (syndecans 1–4) in mammals, which structurally have three domains: An extracellular domain (ectodomain), a transmembrane domain, and a cytoplasmic domain [30]. Numerous physiological and pathological processes are influenced by SDC1. SDC1 changes how various growth factors and their receptors work by binding to the ECM. In mice with SDC1 overexpression, decreased cell proliferation slowed the healing process. SDC1 also prevents the initial stages of liver fibrogenesis by upregulating MMP-14 and preventing TGF-β from being flagged. FLD non-alcoholic, cirrhosis, and HCC all cause a rise in serum protein expression and concentration, which makes them helpful as diagnostic indicators for liver fibrosis [31]. Increased expression of syndecans and cytokines results from glycosaminoglycan side chains in the extracellular domain of syndecans binding to inflammatory cytokines and chemokines, triggering feedback signaling and forming syndecan-chemokine complexes, resulting in a stable chemokine gradient. The interaction between leukocytes and endothelial cells is mediated by syndecans through selectins, which slows down leukocyte movement and ultimately stops leukocyte rolling. Adherent leukocytes initiate transmigration directed by a stable chemokine gradient to the site of inflammation [32]. SDC1 also causes TGF-β to decrease by inhibiting growth factor activation due to the bonds formed between the heparan sulfate chain on SDC1 that binds TGF-β [31] (Figure 1).

As a damage-associated molecular pattern, HMGB1 controls immunological responses, encourages chemotaxis, and causes antigen-specific responses [33]. Numerous acute and chronic liver disorders and after reperfusion of the liver graft result in markedly increased serum HMGB1 levels [33], [34]. In response to necrotic injury or tissue regeneration, HMGB1 can be released from cells either actively or passively [34]. Conditions that can cause the production of HMGB1 include chronic inflammation, which causes Kupffer cells (like M2) to secrete HMGB1. By attracting PMNs, monocytes, and macrophages or by shifting the Treg/Th17 balance in a favor of Th17 dominance through TLR4-IL-6 can induce the production of pro-inflammatory cytokine and harming hepatocytes, HBV infection can cause hepatocyte apoptosis that results in a passive release of HMGB1. This exacerbates inflammation and liver injury can lead to liver fibrosis [33]. Exogenous HMGB1 can proliferate fibroblasts, decrease MMP-1 levels, and increase TIMP-1 mRNA expression by acting as a profibrogenic molecule. It was demonstrated that HMGB1 treatment increased the expression levels of Type I and III collagen, elastin, and fibronectin. HMGB1 treatment also increased the expression levels of TGF-β1 and internal signaling molecules such as SMAD 2 and 3, the phosphorylated SMAD 2/3 complex, and NF-κB [34]. HMGB1 levels in plasma or serum are markedly increased in some acute and chronic liver disorders. Inhibiting the synthesis and release of HMGB1 or disrupting the HMGB1 signaling pathway with its receptor are a few examples of how HMGB1 might be employed as a therapeutic target to treat profibrogenic illness [33], [35]. Recent research has demonstrated the utility of HMGB1 as a biomarker for the detection of liver disease [33] (Figure 1).

Resolution Process of Liver Fibrosis

Liver fibrosis resolution can be thought of as a two-way and reversible process because fibrosis occurs when MFs overproduce ECM in response to wounding healing [28], [36]. The fibrotic process involves inflammatory cells and liver MFs, such as Kupffer cells and matrix-degrading MMPs [36]. On resolution of fibrosis, MFs are inactivated and cleared by NK cells, T cells, and macrophages [37]. An important mechanism required for the effective resolution of fibrosis can be broadly divided into four steps, that is, preventing the ongoing damage, restoring the intrahepatic equilibrium from inflammation, removing and deactivating MFs, and ECM degradation (Figure 2).

One important factor for balancing toward resolution of fibrosis is a cessation of chronic liver injury [28], [38], for example, antiviral treatment of HBV-induced liver fibrosis [28]. In rat fibrosis models, toxicity (e.g., carbon tetrachloride [CCl4], thioacetamide), cholestasis (e.g., bile duct ligation), or metabolic stress all cause fast fibrosis reversal within days after cessation (e.g., choline-methionine-deficient diet). Chronic injury is accompanied by the release of pro-inflammatory signals (such as HMGB1), hepatocytes' stimulation of inflammatory signaling cascades (such as TGF-β), and the release of various cytokines and chemokines. These processes end once liver damage has stopped. Experimental mouse models were used to study the processes of liver fibrosis progression and remission, enabling targeted therapies. In the mouse model, an injury induces a regenerative mechanism [38]. Treating the fibrotic ECM directly can help reduce the pathological effects of the lesion when the etiology is unclear, or there is no effective treatment for the cause of the injury [28].

Due to the recovery of hepatocyte cells and the influence of nearby non-parenchymal cells, changes in

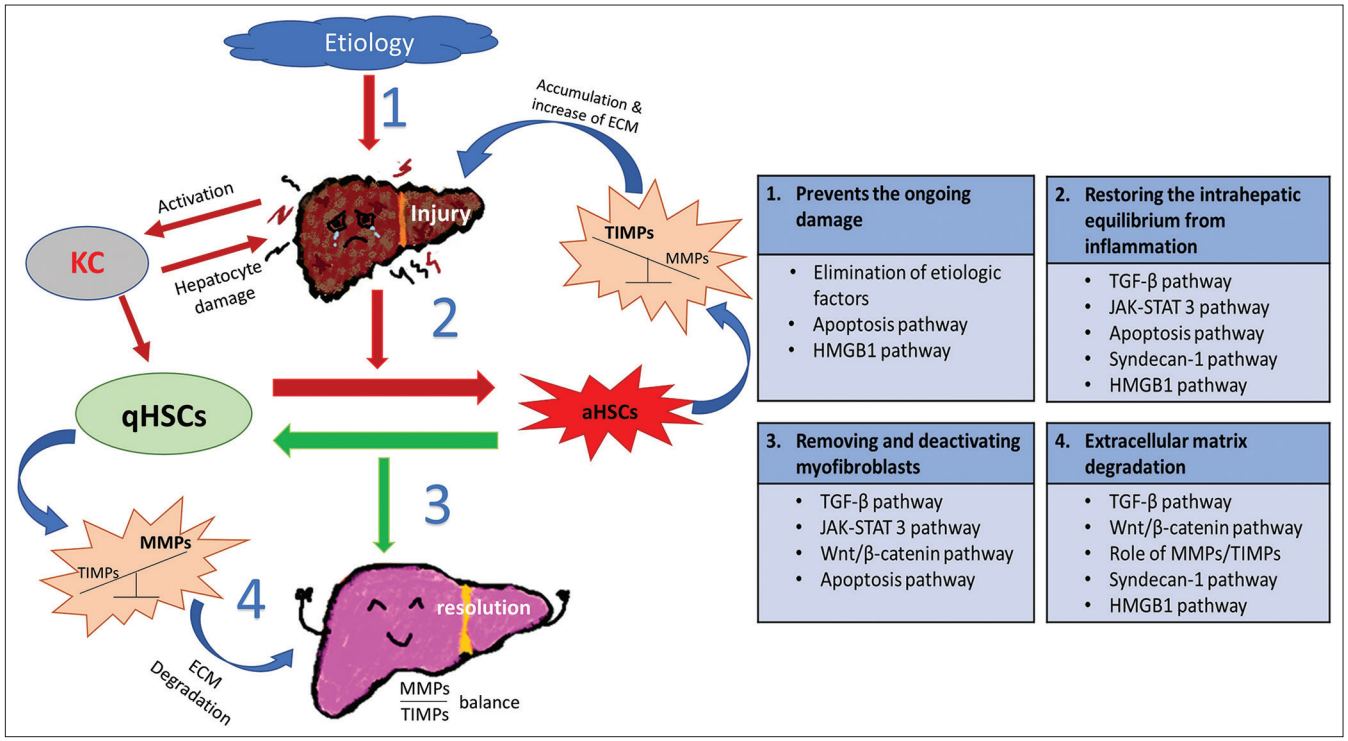

Figure 2: The four steps resolution process of liver fibrosis

the resolution's pro-inflammatory microenvironment may occur, allowing restorative and anti-inflammatory mediators to take over. The acquisition of a restorative phenotype by macrophages, characterized by high expression of matrix metalloproteinases (MMPs), growth factors (supporting hepatocyte recovery), and phagocytosis-associated receptors, was one of the most prominent phenotypes. In contrast, macrophage

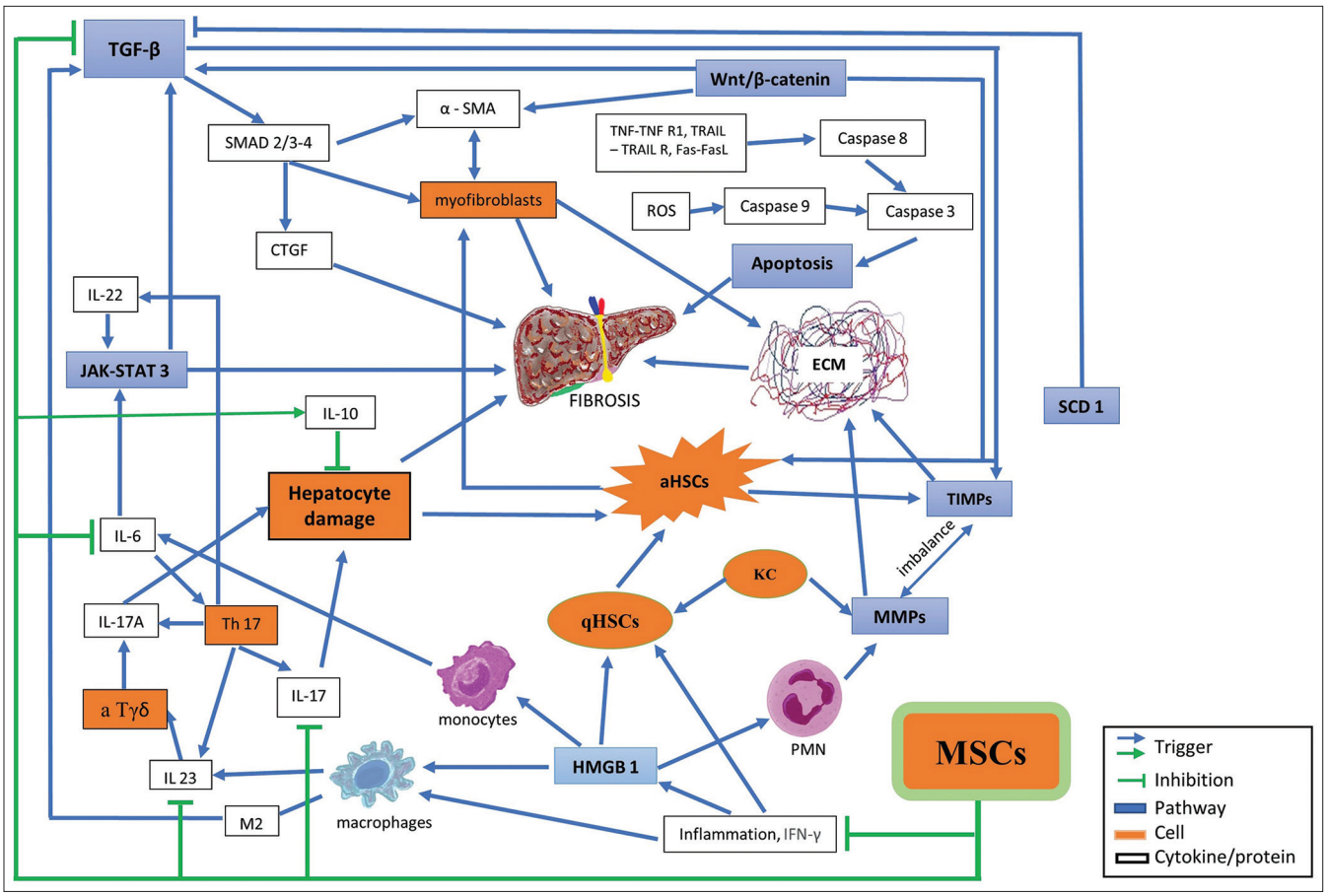

Figure 3: MSCs' role in pathways involved in liver fibrosis

differentiation toward restorative cells may be further aided by myofibroblast phagocytosis and/or hepatocyte apoptosis. There is also an increase in the number of DC and NK cells in the liver with the regression of liver fibrosis. At the same time, MMP-9 expression is supported by DC for matrix degradation. Through natural-killer Group 2 member D and TRAIL, NK cells activate apoptosis and age MFs. T cells that express the T cell receptor gamma delta also use the Fas/FasL interaction to cause myofibroblast apoptosis [38].

HSCs, which change into MFs, are the primary cells in the liver that produce collagen. The key to fibrosis regression is the inactivation of MFs, and three possible mechanisms have been proposed: apoptosis, aging, and inactivation. The MFs phenotype of aging is characterized by decreased expression of cell cycle and fibrogenic genes, making it susceptible to NK cell-mediated apoptosis. MFs undergo apoptosis during fibrosis regression, driven by NK, T, and possibly CD8+ cytotoxic T cells as well as the loss of anti-apoptotic signals. In addition, about half of MFs become inactive and revert to a "silent" HSCs phenotype; however, these inactivated HSCs remain "primed," which means that on fibrogenic stimulation, they can more readily reactivate into MFs [38], by inhibiting TGF-β, STAT3, Wnt/β-catenin, the apoptotic pathway can remove and inactivate MFs.

TIMP-1 and TIMP-2 expression rapidly decreased during the recovery process, but matrix-degrading MMPs continued to be expressed. This increased matrix degradation and collagenase activity in the liver was necessary for fibrosis reversibility [36]. MMP, a family of enzymes with different substrate affinities for matrix components, is the most significant degrading effector. Restorative macrophages supply these fibrinolytic mediators, especially MMP12 and MMP13, in addition to releasing anti-inflammatory mediators. However, distinct MMPs can also be expressed by HSCs and neutrophils. However, some advanced fibrosis factors, such as collagen cross-linking and elastin deposition, provide some resistance to matrix degradation [38]. The matrix remodeling process may persist as part of wound healing in the absence of additional injury and finally result in the resolution process of fibrosis [28].

Role of MSC in Liver Fibrosis Resolution

MSCs are immunomodulatory and multipotent cells that resemble fibroblasts; they can multiply rapidly *in vitro* when certain circumstances are met [39]. MSCs used in medicine come from the following sources: MSCs from adult tissues (peripheral blood, adipose tissue [AT], bone marrow, and dental pulp) and MSCs from neonate tissues (placenta, amnion, and umbilical cord) [40]. MSCs have Immunoprivileged such as HLA-DR (−) expression, trilineage differentiation (adipogenic, osteogenic, and chondrogenic), low levels of MHC Class I, and lacked molecules MHC class II [11], [41], [42]. Due to their plasticity, immunoregulation, characteristic surface antigen phenotypes of CD73, CD90, and CD105, as well as their lack of expression of costimulatory molecules necessary for immune recognition, such as CD80, CD86, and CD40, MSCs can mobilize inflammatory or anti-inflammatory capabilities, based on the local microenvironment [11], [41], [43]. By reducing the generation of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and IL-10, MSCs improve the responsiveness of Th2 cells. MSCs have demonstrated great immunomodulatory potential in addition to their regeneration abilities, and they have shown promising therapeutic results, although they call for extremely large cell numbers and diverse individual responses [40]. MSCs can suppress the immune system only after being triggered by inflammatory cytokines; they lack this ability by nature [43].

When cultured in liver conditions, MSCs can differentiate hepatogenically and can be isolated from a variety of tissues. By reestablishing liver differentiation and the activity of immunomodulators, anti-inflammatory, anti-fibrotic, antioxidant, and anti-apoptotic actions in liver cells, MSCs restore liver capability [39]. Exosomes produced by MSCs include a variety of payloads, such as lipids, proteins, and nucleic acids, which influence target cell behavior through diverse signaling pathways [11]. Even though MSCs suppress the immune system and promote angiogenesis in hepatocellular carcinoma, MSCs may promote the beginning and progression of tumors by inhibiting the Wnt signaling pathway [39]. IL-10, an anti-inflammatory cytokine, and TNF-α, IFN-γ, IL-6, IL 17, and IL 23 production were all markedly downregulated by MSCs (Figure 3) [11], [14], [39]. Paracrine effects in MSCs-derived secretions, such as the protein mediators hepatocyte growth factor (HGF), TGF- β, indoleamine 2,3-dioxygenase (IDO), and prostaglandin 2 (PGE2), are also essential for immunoregulation and anti-inflammatory signaling [11], [39]. MSCs homing capacity, survival rate, and paracrine effects *in vitro* and *in vivo*, as well as their capacity to enhance cell proliferation and liver function, can all be enhanced by using chemicals, hypoxia, inflammation in the microenvironment, and gene modification to protect them from injury caused by harsh microenvironments [39]. In injured liver tissue, many inflammatory reactions are detected and are the main cause of fibrosis and liver failure. Recent research has demonstrated that MSCs immunomodulatory abilities can decrease inflammation in the liver and chronic diseases through a variety of methods [44], [45]. Another research treatment with AT-derived MSCs showed an increase in liver function, a decrease in IL-1β and TNF-α, which describes an anti-inflammatory effect, and an increase in IL-10, which describes the downregulation of inflammatory cytokines [46].

MSCs play a therapeutic role in this situation by secreting beneficial substances. Exosomes of the MSCs, for example, are used to deliver microRNA into cells, promoting liver regeneration and assisting in the repair of liver structure [47]. Several studies have shown that MSCs have an effect on the fibrosis signaling pathway and stimulate the highest levels of HGF. TGF-β concentrations decreased significantly 3 days after treatment with various MSCs doses and higher MSCs doses (2×10^6 MSCs) resulted in the lower TGF-β levels compared to a lower MSCs dose (1×10^6 MSCs) [19]. Bavarsad *et al*. used activated HSCs to assess the therapeutic effect of WJ-MSCs exosomes pretreated with TGF-β1 *in vitro* on ECM protein reduction by inhibiting TGFβ1/SMAD signaling in activated HSCs. Low levels of TGFβ were found to increase the anti-fibrotic capacity of WJ-MSCs exosomes [43]. Another study by Yang *et al*. used a mouse liver model infected with the tapeworm Echinococcus multilocularis (E. multilocularis) to activate HSCs and increase collagen deposition around the lesion, both of which contribute to severe liver fibrosis. The administration of adipose-derived stem cells effectively reduce liver damage and fibrosis in mice by regulating the SMAD7 signaling pathway and decreasing levels of TGF-β receptor activation, aHSCs, and ECM deposition [48]. Therefore, MSCs inhibit HSCs activation and reduce fibrosis by reducing TGF-β release (Figure 3).

Conclusion

Liver fibrosis is a complicated process involving eight pathways of liver fibrosis mechanisms in response to intracellular and extracellular microenvironment changes, including TGF-β, STAT3, Wnt/β-catenin, apoptosis, MMPs, TIMPs, SDC1, and HMGB1. In the mechanism of liver fibrosis, these pathways are associated with hepatocyte damage, activation and differentiation of HSCs into proliferative MFs, and increased synthesis and accumulation of ECM, which lead to fibrosis, except SDC1, whose overexpression inhibits TGF-B. For effective fibrosis resolution, four crucial steps are required, such as preventing ongoing damage by eliminating etiologic factors, inhibiting apoptotic dan HMGB1 pathways, restoring the intrahepatic equilibrium from inflammation by inhibiting TGF-β, STAT3, apoptosis, HMGB1, and increasing syndecan 1 pathway, removing and deactivating MFs by inhibiting TGF-β, STAT3, Wnt/β-catenin, the apoptotic pathway, and ECM degradation. MSCs therapy supports the resolution of liver fibrosis without causing side effects by releasing beneficial substances. Exosomes of the MSCs, for instance, are utilized to deliver microRNAs into cells, inhibit HSCs activation, promote hepatocyte survival by differentiating into hepatocyte-like cells, and assist in liver structural repair. Pro-inflammatory factors such as TNF-α, IFN-γ, IL-6, IL-17, and IL-23 production is decreased, and the anti-inflammatory cytokine interleukin (IL)-10 secretion is significantly increased by MSCs. MSCs not only reduce damage to the liver but also reduce the severity of fibrosis, leading to the resolution of fibrosis in the liver.

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