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Review Article

Peripheral stem cell therapies in decompensated liver disease

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Abstract: Decompensated liver disease is a severe and progressive disease which means patients have to accept orthotopic liver transplantation (OLT). Due to the lack of transplanted organs, the infusion of stem cells seems to be a feasible alternative treatment. Among various stem cells, hematopoietic stem cells (HSCs) have many advantages, such as the easier accessibility, the slighter trauma, and the feasible and safe efficacy. In this article, the authors introduce HSCs as well as other cells that commonly used, analyze the viable routes for infusion of HSCs, and attempt to clarify the mechanism of effectiveness of HSC infusion. Although the mechanism of HSC infusion is not very clear, many clinical trials have shown that the treatment is indeed valid and safe. The most effective route seems to be via the hepatic artery or portal vein. The possible mechanisms include apoptosis of hepatic stellate cells, suppression of the expression of type I collagen, upregulation of the expression of Bcl-2, downregulation of expression of IL-6, secretion of various growth factors, elevated serum level of MMP-9 and stromal cell-derived factor-1 (SDF-1), etc. Overall, therapy of HSCs is a reliable method for decompensated liver disease and shows a promising future.

Keywords: Stem cell, transplantation, bone marrow, cell therapy, liver disease

Introduction

Liver disease is a common disease worldwide and many patients with liver dysfunction enter a refractory and irreversible stage as it advances. Conventional and adjuvant treatment cannot improve the severely injured hepatic condition. Therefore, the decompensated liver has to accept hepatic transplantation which is the only viable treatment for end stage liver disease. However, the shortage of donor organs is hardly able to meet the demand of the patients and the high costs of transplantation limit application [1]. In this condition, stem cell therapy is regarded as a viable alternative to patients who cannot get timely OLT. In all types of stem cells, bone marrow-derived stem cells (BMSCs) are widely used in clinical trials. HSCs, as a part of BMSCs, although the safety and efficacy is repeated evidenced in many clinical studies, the detailed mechanisms of their therapeutic function are still not very clear [2]. HSCs not only have the capacity to differentiate into hematopoietic lineages, but the capacity to convert into hepatocytes which have normal physiological function [3]. But a systematic review showed that this conversion may exert little influence on the regeneration of the liver [4]. However, the relatively easier accessibility of HSCs which can be isolated from peripheral blood and the reliable efficacy show an attractive perspective of HSC therapy in the future [5, 6].

Various types of cell therapies

Recently, various cells have been investigated to treat liver disease, including HSCs, mesenchymal stem cells (MSCs), fetal liver stem cells, embryonic stem cells (ESCs), endothelial progenitor cells (EPCs), induced pluripotent stem cells (iPSCs), etc. In addition, MSCs, HSCs, and EPCs chiefly constitute BMSCs. The commonly used cells are HSCs and MSCs, and these stem cells appear to be a feasible alternative. Various types of cells have shown remarkable progress

and fantastic outlook in the cell therapy of decompensated liver disease.

Hematopoietic stem cells

HSCs or hemocytoblasts can be isolated from the peripheral blood after injection of G-CSF which elevates the concentration of HSCs in the blood. Umbilical blood and bone marrow are also reliable sources to harvest and enrich HSCs. The specific expression markers of HSCs, $CD34^+$ and $CD133^+$, form the basis for identification and isolation. The therapeutic function of HSCs has been verified in many trials recently. In patients with end stage liver disease, a clinical study showed that the serum level of alanine transaminase (ALT), albumin, total bilirubin, and prothrombin time (PT) significantly decreased in 12 months compared to pre-transplantation [7]. In patients with alcoholic liver cirrhosis, hepatic function also improved significantly after the injection of HSCs [2]. A randomized controlled trials (RCTs) that included 140 patients reported that $CD34^+$ and $CD133^+$ stem cell infusion generated a desirable outcome up to 6^{th} month, with liver enzymes and synthetic function almost restored to the normal level [8]. The infusion frequency also seems to have an influence on the outcome of treatment. Zekri et al. [9] reported that repeated infusion of HSCs had more sustained efficacy compared with a single infusion during a 1-year follow-up. In addition, the short-term efficacy of transplantation of HSCs was relatively reliable, but the long-term efficacy was controversial. A clinical trial suggested that although there was significant increase of albumin in 1 month, this discrepancy was not sustained at 3 months after the infusion of the $CD34^+$ stem cells, and this article reported some adverse effects after the transplantation, such as the discomfort in the chest and painful feeling in the catheter site, but those were all slight symptoms [5]. In 2018, an open-label, randomized, controlled phase 2 trial by Newsome et al. [10] showed that $CD133^+$ stem cell therapy could not improve liver function in patients with liver cirrhosis. Maybe this was a frustrating outcome to many researchers, but the included patients were all with compensated liver cirrhosis which was different from other studies that involving decompensated liver disease. The future of HSCs seems promising but the mechanism of its function is not clear and well-designed robust trials are needed to determine the effectiveness and other latent problems.

Due to the easier accessibility and reduced trauma compared with other stem cells, HSC therapy has its own advantages over other stem cells. There are mainly 4 routes to infuse the peripheral stem cells for the treatment of decompensated liver disease in human: hepatic artery, peripheral vein, portal vein, and splenic artery. Therefore, choosing a viable administration route is very important for clinical application. A meta-analysis involved 20 single-arm trials showed that infusion via the hepatic artery was better than the peripheral vein, and there was no significant difference between the portal vein and the hepatic artery except that the AST level of hepatic artery route was lower [11]. However, the stem cells in this article contained not only HSCs but the overall condition of many kinds of stem cells. Huang et al. [7] showed that there was no significant difference between the portal vein and hepatic artery in patients with end-stage liver disease by the transplantation of HSCs. Sun et al. [12] reported that transplantation via the portal vein and hepatic artery with $CD34^+$ cells gave a similar result. Nevertheless, Mohamadnejad et al. [13] showed that the administration of $CD34^+$ stem cells via the hepatic artery is not safe in patients with decompensated liver cirrhosis. It is hard to determine which route is the best to improve liver function. But transplantation via the hepatic artery or portal vein seems to be a relatively better way to get a more desirable outcome.

After infusion of HSCs, fusion between HSCs and hepatocytes can generate a hybrid cell which can express hepatocyte phenotype by reprogramming the cell or the reduction division that generate diploid daughter cells [4, 14]. Subsequently, the newly-formed cells can replenish the injured liver function in a certain extent. However, some experiments have shown that generation of bone marrow-derived hepatocytes may exert little influence on the recovery because the lower proliferative frequency on the repair of the liver is hard to replenish the injured liver function, and the endogenous progenitor cells seem more important in the regeneration of the liver [4, 15]. Moreover, it has been suggested that the high-

er concentration of albumin and matrix metalloproteinase (MMP) generated by the newly-formed hepatocytes can induce apoptosis of hepatic stellate cells and suppress expression of type I collagen so that liver fibrosis is ameliorated and the injured liver function could be improved [16, 17]. In addition, it seems that hepatic growth factor (HGF), MMP-9, and SDF-1 are involved in the $CD34^+$ stem cell recruitment to the injured liver. Kollet et al. [18] indicated that the increased level of MMP-9 and HGF induced by hepatic injury and elevated activity of SDF-1 induced by irradiation or inflammation was important for the migration of HSCs into liver. It has been repeatedly reported that the growth factors and cytokines released into the blood can activate hepatic endogenous progenitor cells, thus improving the repair of the injured tissue [6, 19]. It has also been suggested that upregulation of expression of Bcl-2 and downregulation of IL-6 suppress immune response and liver apoptosis [6]. Although the mechanism is not very clear and still has many controversies, the outcome of treatment is indeed valid in clinical trials. The detailed mechanism needs to be disclosed with further fundamental researches in the future.

Mesenchymal stem cells

In addition to HSCs, MSCs are also a part of bone marrow-derived stem cells. A meta-analysis showed that there is no statistical difference between MSCs and HSCs in the treatment of liver disease [11]. To isolate enough MSCs, the main origin is via bone marrow aspiration which is a traumatic operation which may have some inconvenience in its application. Nevertheless, adipose tissue-derived MSCs (AT-MSCs) which can be collected form cosmetic liposuctions and umbilical cord blood derived MSCs (UCB-MSCs) seem to be less invasive. A study compared these 3 types of MSCs and suggested that UCB-MSCs had the strongest proliferation capacity and AT-MSCs had the highest colony frequency [20]. Therefore, AT-MSCs and UCB-MSCs may be an attractive alternative to bone marrow-derived MSCs (BM-MSCs) in the treatment of decompensated liver disease. MSCs can be isolated from different tissues (such as umbilical cord blood, the placenta, adipose tissue, amniotic fluid, dental tissue, skin, hair follicles and tonsils, trabecular bone, synovial membrane, peripheral blood, fetal lung) and exhibit the capacity to differentiate into hepatocyte like cells (HLCs) [6, 19]. Many clinical trials have shown that transplantation of MSCs has the capacity to improve liver function significantly. A meta-analysis involved 14 clinical trials showed that patients with decompensated liver disease had an improvement in liver function and ascites after administration of MSCs, and the level of serum albumin, total bilirubin, and MELD scores were ameliorated [21]. Salama et al. [22] reported that there was significant difference between the MSCs-infused group and the control group in many serum parameters up to 6^{th} month, and this RCT showed that 54% of patients had near normalization of hepatic synthesis function and enzyme levels. MSCs also have some advantages over other cells commonly used in the cell therapy of liver disease, such as easier acquisition and stronger proliferation [19]. However, in a clinical trials, patients with liver failure caused by hepatitis B indicated that the short-term efficacy was desirable but the long-term efficacy was not significantly improved [23]. This clinical outcome is similar to the efficacy features of HSCs mentioned above where the long-term effect seems controversial. Moreover, although many clinical studies have shown that administration of MSCs is safe and feasible, the fibrogenic potential and the capacity of promoting the pre-existing tumor growth should attract the attention of researchers [19]. The detail therapeutic rationale of MSCs is relatively clearer than HSCs in terms of liver repopulation. Rather than true transdifferentiation into HLC, the reason of therapeutic efficacy is mediated by paracrine effect secreting trophic and immunomodulatory factors, such as interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), HGF, and insulin-like growth-factor binding proteins [6]. Moreover, transplanted MSCs can exert their effects via the increased expression of AKT and ERK as well as decrease of caspase-3 activation to inhibit hepatic apoptosis and promote cell repopulation [24]. In addition, soluble factors, such as nitric oxide, prostaglandin E2 (PGE2), IL-6, IL-10, indoleamine 2,3-dioxygenase (IDO), and human leukocyte antigen G (HLA-G) can induce regulatory T cells which may have the capacity of anti-fibrosis and proliferation [19, 25].

Unsorted bone marrow cells

Unsorted bone marrow cells (BMCs), which include multipotent progenitor cells, have the

capacity to differentiate into hepatocytes and have been shown safe and feasible in clinical trials [26]. Bone marrow-derived mononuclear cells (BM-MNCs) should be classified into this category. In patients with advanced chronic liver disease, a clinical study reported that infusion of BMCs is feasible and safe, and most patients had a decrease in mean serum bilirubin and international normalized ratio (INR) levels, and an elevation in serum albumin [27]. In a rodent model with CCl4-induced liver fibrosis, another study indicated that liver fibrosis was ameliorated after administration of BMCs, and migrating BMCs exist along with fibers expressed MMP-9 on the cell surface [28]. Therefore, infusion of BMCs indeed has the potential to regenerate the injured tissue in the recipient liver. The rationale of the therapeutic function of liver disease may be attributed to the effect of HSCs and MSCs among BMCs, and these two types of cells do have the capacity to replenish the injured liver function, whose mechanism are mentioned above. Furthermore, macrophages among BMCs seems to have some positive effect on mice with chronic liver injury [29]. After injection of bone marrow-derived macrophages, expression of colony stimulating factor-1, insulin-like growth factor-1, and VEGF was elevated, so that these paracrine signals improves the liver function [29]. In addition, fibroblast growth factor (FGF), a higher degree of which indicates the severe liver damage, seems to promote the efficacy of BMCs in carbon tetrachloride-induced liver fibrosis in mice [30, 31]. Interestingly, the interaction between BMCs and hepatic epithelial stem cells enhances differentiation of the latter into mature hepatocytes, thus leading to liver repopulation [31].

Other types of cells

Fetal liver stem cells are located in ductal plates and have the capacity to differentiate into mature hepatocytes and cholangiocytes which have the normal function [32]. The administration of fetal liver stem cells is very reliable in patients with decompensated liver disease. A meta-analysis suggested that there was no significant difference between the effectiveness of fetal stem cells and MSCs, but the efficacy of fetal liver stem cells was better than HSCs and had a significant discrepancy [11]. Khan et al. [33] reported that the improvement of liver function is remarkable after transplantation of fetal liver stem cells in patients with decompensated liver cirrhosis and the serum level of ALT, albumin, bilirubin, alkaline phosphatase and MELD score showed a significant improvement compared to the baseline after 6 months. After transplantation of the fetal liver stem cells, they can migrate to the injured liver and have the capacity to differentiate into hepatocytes [34]. You et al. [35] suggested that the Notch signaling pathway is an important molecular mechanism to induce the fetal liver stem cells differentiation and regulate the self-renewal process. Fetal liver stem cells seem promising but the ethical concerns and the possibility of teratoma make the application chiefly in animal experiments and preclinical trials.

ESCs isolated from the embryo are the pluripotent cells which can differentiate into all types of adult cells, and the ESCs-derived hepatocytes are identical to the normal hepatocytes in terms of morphology and physiology [36]. He et al. reported that the infusion of embryonic stem cells improve the liver function and correct the metabolic defects of mice with fumaryl acetoacetate hydrolase knockout ($Fah^{-/-}$) after serial liver repopulation [37]. Another study showed that transplantation of ESCs improved liver function of mice with liver injury induced by acetaminophen [38]. ESCs provide a valuable insight to dig out the molecular mechanism of differentiation of hepatocyte and will pave the way to understanding the cell therapy more deeply.

EPCs or angioblasts are the precursor cells of vessel endothelium and play important roles in the regeneration of the endothelial lining of vessels. In a rodent model with carbon tetrachloride-induced hepatic injury, EPCs improved the liver function of mice and the main reason for increased survival was the secretion of growth factors as well as the direct neovascularization [39]. Antifibrosis and repopulation effects of the injected EPCs *in vivo* were suggested to be mediated by many growth factors including HGF, epidermal growth factor (EGF), transforming growth factor-α (TGF-α), VEGF, etc. [6].

Human iPSCs are similar to ESCs in terms of morphology surface antigen, gene expression, telomerase activity and have the capacity to

differentiate into all three germ layers [40]. Consequently, iPSCs have the capacity to differentiate into hepatocytes and it has been demonstrated by many experiments [41]. Importantly, iPSCs can be induced *in vitro* via reprogramming of the somatic cells through ectopic expression of transcription factors such as OCT4, SOX2, KLF4, c-MYC (i.e. OSKM cocktail) or OCT4, SOX2, NANOG and LIN28 by using retroviral vectors [6, 40]. Moreover, the different origin of iPSCs seems to affect the differentiation capacity of iPSCs, and the extensively used type is somatic fibroblast which is highly efficient [42]. Espejel et al. [41] reported that infusion of iPSCs can regenerate the mice liver with FAH deficiency. Furthermore, iPSC-derived liver buds (IPSC-LBs) are very promising and it is possible to provide the whole organ for patients who need liver transplantation in the future [43]. IPSCs not only have a strong ability to differentiate into other cells, but solve the ethical problem of ESCs and avoid the immune rejection of allogeneic stem cells after the administration. However, the genomic instability causes some safety concerns that halts the application of iPSCs. The genetic mutation is likely to arise during the differentiation of iPSCs into needed cells so that the malignant tendency is identified in many trials [44]. Furthermore, some reprogramming factors can also generate the risk of cancer formation with their oncogenic potential [45]. Overall, iPSCs show a revolutionary outlook and the better understanding of the mechanism of their therapeutic function will help to avoid the latent risk of cancer.

Future perspective

For patients with decompensated liver disease, peripheral stem cells seem to be valid and safe in many patients, and provide an alternative treatment or temporary bridge for patients who cannot get timely liver transplantation. Although peripheral stem cells have a very hopeful future, there are also many problems confronted. For example, the treatment lacks uniform procedures, the dose of injected stem cells, and the detailed information of adjuvant treatment are not given in many clinical trials. Therefore, the rationale of HSCs in liver repair is still not very clear and correlated studies is mainly about animal experiments, the best infusion routes have many controversies, the long-term effectiveness of stem cell therapy is uncertain, the fate of injected stem cells are not well traced *in vivo* with the imaging technology which can identify the survival condition and long-term efficacy. If these problems are successfully addressed, peripheral stem cells may have a chance to be widely used in the clinic.

It is important to look for a method to monitor the migration of the infused stem cells in vivo. The commonly-used methods include optical imaging, nuclear imaging, magnetic resonance imaging (MRI), magnetic particle imaging (MPI), etc. in animal models [46]. In clinical patients, 111In-oxine can be used to label MSCs in patients with cirrhosis, and the percentage of moving cells can be recorded clearly to imply the distribution of the stem cells after the administration. In a clinical study tracking MSCs with 111In-oxine, the outcome indicated that the radioactivity emerged in lungs at the beginning of the therapy, and then gradually moved to the liver and spleen [47]. The quantitative method of monitoring stem cells *in vivo* is very meaningful and this method will indeed hasten the application of stem cells and help figure out the rationale of the stem cell therapy.

Conclusion

Cell therapy for decompensated liver disease has been gradually applied to clinical trials recently. Among these various stem cells, MSCs, HSCs and BMCs are most widely used in the clinical trials. All of these stem cells show attractive clinical outcomes. Additionally, peripheral stem cells, as a reliable source of HSCs, are not only produce easier accessibility and slighter trauma, but are demonstrated to be safe and effective in the treatment of decompensated liver disease in many studies. Additionally, these characteristics will generate some advantages over other stem cells in the cell therapy. The most effective administration route seems to be via hepatic artery or portal vein in many studies. The detailed mechanisms of the effectiveness of HSCs are not very clear. For instance, the activation of endogenous hepatocytes, the generation of the MMP and growth factors, upregulation of the expression of Bcl-2 , downregulation of IL-6 and elevated activity of SDF-1 may contribute to the regen-

eration of the injure liver. Subsequently, uniform procedures of the clinical trials are needed to enhance the validity and reliability of the outcomes of the experiments. Moreover, many ungiven treatment details constrain the data analysis and increase much indeterminacy. Since there are considerable problems confronted, robust randomized controlled clinical trials, and deeper studies are needed to address them and expedite the wide clinical application.

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