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Review: Potential of Stem Cells as Regenerative Medicines against Liver Diseases

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Abstract
Liver is a vital gland that performs various essential functions in the human body. Injury due to infection, genetic, chemical and physical defects is the major cause in the deterioration of the functions of liver. Only successful treatment for this problem was the transplantation but transplantation has some limitations including shortage of the donor. Regenerative medicines based on stem cells therapies have proved as a best alternative treatment procedure. Stem cells play a key role in the recovery of the normal function of liver. This is done by repairing or by regenerating the liver cells. Some types of stem cells also play a role to protect the liver cells from rejection in a transplantation process or regenerative process by suppressing the immune response or by anti inflammatory activity such as mesenchymal stem cells. This makes the stem cells based therapies successful. Many types of stem cells have been reported to regenerate or repair the liver. Liver itself also has three types of stem cells that are specific to regenerate the liver cells. Recently, work was performed on human dental pulp stem cells to cure liver diseases. Another use of the stem cells is to develop the bioartificial liver devices as well as they play a significant role in the screening of the effective drugs against liver diseases. They also play a role to understand the pathways of the diseases by developing the disease models in the laboratory. This review summarize that regenerative medicines based on the stem cells are the future to cure any type of liver injury with a high rate of success.
Keywords: Regenerative medicines, Stem Cells. Cell therapies, Liver treatment

1. Introduction

Liver is defined as a gland that performs the endocrine and the exocrine functions of the body [1]. A number of essential functions that are involved in the homeostasis of the body of the human, are performed by liver. The damaged liver cannot be able to carry out these functions effectively and only treatment for this problem was the transplantation. But in the transplantation, the problem is the shortage of donors. This problem was solved by developing bioartificial liver devices and by producing the hepatocytes by stem cells [2, 3].

Regenerative medicine is defined as a field of multi disciplines because it deals with the restoration of the functions of damaged organs by replacing them and by repairing the injured or damaged organs. Cell based therapies are used for that purpose [4]. Transplantation based and the cell based regenerative therapies have been practiced from many years [5]. Stem cells as well as cutured cells are used in regenerative medicines to regenerate the organs, to screen the effective drugs and to study the pathways of the diseases by developing the models of the diseases in the laboratory [6]. The purpose of the regenerative medicines is to recover the functions of the organs that are damaged due to infection or genetic disorder or due to physical or chemical defects [7]. Different methods have been discovered to generate and isolate the stem cells from different sources and to use them in the regenerative medicines [8].

Stem cell is a main key in regenerative medicines. In the past decade the understanding about liver physiology has been improved and shortage of organ donors diverted the attention toward the use of stem cells to cure liver diseases [9]. Stem cells are defined as cells that can divide indefinitely and differentiated into specialized cells. On the basis of differentiation ability the stem cells are categorized as: (1) Totipotent; they have unlimited differentiation ability, (2) Pluripotent; they have capacity to differentiate in every type of tissue and (3) Multipotent; they have ability to generate the tissues of that organ from where they were extracted [10, 11]. Extrahepatic and hepatic stem cells as well as hepatocytes derived from embryonic and adult stem cells were used to regenerate or repair the liver during last 10 to 15 years [12]. Both stem cells; the embryonic and the adult, have the potential to develop organs and recent studied were focused on the reprogramming of adult cells to convert them into specialized stem cells in order to use them in the regenerative therapies [13]. Stem cells are effective candidates that have therapeutic potential to cure liver diseases and were used to treat the liver diseases. Their main types with their treatment potential for liver diseases were reported [14].

"Cancer stem cell hypothesis" was stated that cancer of the liver is due to the malignant transformation of the stem cells of the liver. So, recent advances were highlighted and focused on to understand the signaling pathways of these stem cells, identification of cellular origin and biology of the liver by developing the models of these cells. Thus, elimination of these cancer stem cells of liver would provide the therapeutic potential in the future to cure the cancer of liver [15].

2. Mesenchymal stem cells as regenerative medicine against liver diseases

Mesenchymal stem cells were observed to treat the both types of injuries of the liver; the chronic and the acute. It was observed that they treat the injuries of liver by enhancing the tissue repair, by the suppression of inflammation as well as by differentiating themselves into the liver cells. The one drawback that was observed, was the initiation of the fibrotic process [16].

Mesenchymal stem cells have the ability to differentiate into liver cells as well as have immunomodulating, anti apoptotic and anti inflammatory activity. In animal model study, these cells were investigated as a promising candidate to repair the tissues of liver and to regenerate the liver. [17]. It was also observed that progenitor cells as well as the cells in the liver and in the bone marrow were involved in the repairing of liver. This repairing was done because these progenitor cells were produced some soluble factors to contact with myofibroblasts to regenerate the liver [18]. In another study, the reduction in the fibrotic area was reported in the mouse model of liver fibrosis when genetically engineered mesenchymal stem cells for hepatocyte growth factor (HGF) were injected intravenously into the mouse model. It was examined that these engineered cells were migrated in higher number as compared to non engineered cells due to their higher response to SDF-1alpha that was secreted in excess amount in liver fibrosis [19]. To cure liver fibrosis, inflammatory response was induced by the bone marrow derived stem cells which secrete the TGF-beta1 and activate the cells of myofibroblasts that resides in liver [20]. In the treatment of liver fibrosis, the higher expression of HNF1alpha, cytokeratin 18, 8 and TAT was reported when injured liver tissues were treated with mesenchymal stem cells. This high expression enhanced the differentiation ability of MSCs to differentiate into heptocytes. Efficacy of this differentiation was judged by transplanting these cells into a mouse model where a decrease in expression of Caspase- 3, HGF and Bax was reported [21].

Autologous bone marrow derived stem cells were also reported to cure the chronic liver disease by improving the liver function [22]. It was also reported that nanofibers were used to enhance the better differentiation of MSCs into heptocytes like cells as well as to maintain the function of these cells into a culture of long term [23]. It was investigated that MSCs suppressed the apoptotic activity of the liver cells as well as suppressed the inflammatory response and thus revert the liver fibrosis by producing different cytokines and growth factors. Anti-fibrotic and anti inflammatory activity of MSCs was confirmed by the morphological study of liver tissues [24, 25]. The role of bone marrow derived MSCs to enhance the survival of transplanted liver was observed because they suppressed the immune system via the production of some soluble factors [26]. It was investigated that human MSCs were yield high expression of beta1-integrin CD29 and CD44 and thus these stem cells have showed the priority to bind with the injured liver tissues to cure the liver diseases [27]. MSCs were also proved effective to protect the damaging of the liver due to radiation. It was studied in a mouse model that after radiation the expression of SDF1 alpha was increased which was resulted into the targeted migration of MSCs towards the liver in order to protect and to repair the liver by producing some trophic factors [28].

In a hepatectomy mouse model, the improvement in the efficiency of hypoxia-preconditioned MSCs was reported by Yu and colleagues. It was identified by them that vascular endothelial growth factor was a main factor of the efficiency of hypoxia-preconditioned MSCs [29]. Cellular plasticity was investigated as an important factor in the cell based therapies to cure the liver diseases. Bone marrow derived stem cells were shown the potential of plasticity [30]. It was confirmed by a recent study of mouse model that bone marrow derived mesenchymal stem cells increase the proliferation of the liver cells. [31]. The endocrine and the paracrine factors of the bone marrow derived mesenchymal stem cells that have therapeutic potential to treat liver fibrosis were studied in the in vitro cell culture system [32]. In a mouse model, it was also investigated that bone marrow derived mesenchymal stem cells (BMSCs) have therapeutic potential to cure the acute hapatic failure [33].

Recently, it was discovered that colonization rate of MSCs were significantly increased in the result of targeted migration when these cells modified with chemokine CXC receptor 4 (CXCR4) gene. The outcome was the efficient functional recovery in damaged liver [34]. It was also investigated in an experimental study of liver fibrosis that soluble factors derived from bone marrow derived mesenchymal stem cells have anti-fibrotic activity [35]. In a recent discovery, nano-engineered mesenchymal stem cells were proved as promising therapeutic carriers to treat the different diseases and in case of the liver a remarkable accumulations of nano-engineered MSCs were observed to cure the injury [36]. By a systematic search of all the published work on the clinical perspective of autologous bone marrow derived mesenchymal stem cells (ABMSCs) on a number of patients, it was concluded that the transplantation of ABMSCs was proved beneficial to cure liver failure. ABMSCs could be maintained for a time period of more than 24 weeks and therapeutic effects of ABMSCs could be lasted for six months [37]. Thus, MSCs have therapeutic potential to cure liver disorder but unwanted differentiation of mesenchymal lineage as well as the conflicts about their engraftment were demonstrated as some limitations of MSCs based therapy [38].

3. Stem cells derived from adipose tissue as regenerative medicine against liver diseases

In a mouse model of acute liver injury, the promotion in the liver function was reported by the adipose derived stem cells. Reduction in the markers of liver injury such as ammonia and aspartateaminotransferase etc. was also reported. The most beneficial route for this type of treatment was the tail vein [39]. It was investigated that adipose derived autologous stem cells were the promising candidates to treat the severe failure of the liver. For that purpose a mouse model of toxic liver damage was subjected to two-third hepatectomy and then adipose derived stem cells of human were transplanted into the remaining lobe of the liver. In the result, the improvement and the regeneration of the liver was observed [40].

By the recent study of injured mouse model that was injured due to ischemia reperfusion injury, it was determined that ADSCs were not only effective to cure the liver injury but also revitalized the regeneration of the liver in case of hepatectomy. It was also observed that trophic factors produced by ADSCs were involved in the protection of hepatocytes [41]. A novel method was reported to differentiate the ADSCs into mature heptocytes. In this method, ADSCs were cultured onto a chemical media for a short period of time to differentiate them into spherical-culture hepatocytes like cells (SCi-Heps). These SCi-Heps have shown the functional properties of mature liver cells in an in vitro experiment. These cells were used to regenerate the functional human liver in an in vivo experiment in a murine model. It was resulted in the possiblity to regenerate the human liver with autologous stem cells [42]. It was demonstrated that when the mesenchymal stem cells derived from adipose tissues were systematically administrated and transplanted into the damaged liver of mouse model, the result was in the tissue repair. Some paracrine factors were responsible for their therapeutic efficacy [43].

Recently, in vitro as well as in vivo study of adipose derived mesenchymal stem cells (ADMSCs) was revealed that these cells have capability to differentiate into transplantable and mature liver cells. It was also identified that trichostatin A (TSA) was essential to enhance the differentiation of ADMSCs to cure the liver disorders [44].

4. Human pluripotent stem cells (hPSCs) as regenerative medicine against liver diseases

Human pluripotent stem cells (hPSCs) were studied to regenerate the functional liver cells. These cells were used in the stem cells based regenerative medicines and also they played a role in effective drug discovery by developing the in vitro models of diseases [45]. It was observed that pluripotent stem cells were not differentiated into mature hepatocytes and did not have features of adult hepatocytes. Different tools were developed to differentiate the pluripotent stem cells (PSCs) into hepatocytes like cells and to trace out the mature hepatocytes from the progeny of pluripotent stem cells (PSCs) [46]. It was reported that differentiated pluripotent stem cells were used in the replacement therapies to treat the liver diseases [47].

5. Human induced pluripotent stem cells (hiPSCs) as regenerative medicine against liver diseases

For the treatment of end stage liver disease, hiPSCs are the potential sources for heptocytes. In vitro differentiation of hiPSCs into heptocytes was reported. From hiPSCs, the production of multistage liver cells in a mouse model and the production of the liver protein that is specific to human was also reported [48]. Patient specific iPSCs are valuable candidates for drug discovery to treat a number of diseases including liver diseases. Gene targeting and disease models that were based on iPSCs were proved as beneficial tools to screen the clinically effective drugs to treat the liver diseases [49]. hiPSCs were identified as promising candidates to differentiate into functional population of liver cells [32]. A major problem in the development of the therapies is the lack of mechanistic study of liver cells of live human. hiPSCs were examined to produce the metabolic models as well as the live cell based models of the disease to screen the effective therapeutic drugs and to develop the effective cell based therapies [50].

It was also identified that the functional liver was produced by the transplantation of the small buds of liver that was produced from the induced pluripotent stem cells. So, this study was used to grow organs in the lab in order to overcome the shortage problem of the donor [51]. It was reported that the longevity and the functional maturation of the hepatocytes that were derived from induced pluripotent stem cells was enhanced by micropatterned co-culture (iMPCC) instead of conventional culture. In future, the iMPCCs would provide help to study the molecular mechanism of the differentiation of the induced pluripotent stem cells into liver cells, to build the models of the liver diseases and to screen the drugs [52]. A method was developed to evaluate the lack of tumor formation as well as the differentiation activity of the hiPSCs derived hepatocytes in an immunodefficient mouse model. This study was also used to understand the moleculer and the cellular mechanisms that were involved in the inherited metabolic diseases of the liver [53].

6. Human embryonic stem cells as regenerative medicine against liver diseases

By using mouse models, it was reported that the injured liver tissues were recovered by the hepatocyte like cells that were derived from human embryonic stem cells. These embryonic derived hepatocyte like cells were used to

replace the injured cells as well as to support the regeneration of the liver within the organism [54].

It was investigated that the selective media, that was used to select the hepatocytes like cells that were produced from the mouse differentiated embryonic stem cells, was not only effective to select these cells but also involved in the differentiation as well as in the growth of these cells with partial functionality. Thus, these cells have shown the therapeutic potential in the repopulation of the liver [55]. It was demonstrated that inhibition of miR-199a-5p in the embryonic stem cells derived hepatocytes like cells was resulted in the promotion of the differentiation of hepatocytes. This inhibition was also contributed in the repopulation and in the engrafting of liver when transplantation of these hepatocytes like cells was performed. So, modulation of miR-199a-5p was lead to the production of more mature hepatocytes for the treatment of the liver diseases [56]. Now, the use of embryonic stem cells were gradually decreases due to the ethical concerns and induced pluripotent stem cells were used clinically to cure diseases including the liver diseases [57].

7. Liver stem cells as regenerative medicine against liver diseases

Liver transplantation was the only treatment for acute liver failure and it faced the problem of the shortage of organ donors. So, there was a need for alternative sources. Induced pluripotent and hepatic stem cell as well as hepatocytes derived from embryonic and adult stem cells were observed as alternative sources for transplantation [58]. It was also reported that liver stem cells are produced cholangiocytes and heptocytes. Heptoblasts are responsible for the production of these cells and different extrinsic signal are involved in the regulation of heptoblasts [59]. Liver stem cells were identified as boundless and clinically beneficial sources of cells and hepatocytes derived from them were used in bioartificial liver devices, cellular transplantation as well as in the testing of drugs to cure liver diseases [60]. Parenchymal liver cells are functional units that are used as regenerative medicine for liver. Transplantation of heptocytes has medium range efficiency so there was a need for safe and alternative cells source with greater regenerative functionality. From this point of view; progenitor cells derived from the liver are more advantageous as compared to the other sources of stem cells [61]. Liver stem cells are categorized into three groups; (i) Hematopoietic stem cells (HSCs), *(ii) Hepatic stem cells (HSCs) and* (iii) Hepatic stellate cells (HSCs)

7.1. Hematopoietic stem cells (HSCs) as regenerative medicine against liver diseases

In case of acute liver failure, the therapy based on hematopoietic stem cells was identified as a possible way to recover the liver [62]. *It was reported that, for the suppression of the fibrogenesis in the liver and to cure the liver cirrhosis, the transplantation of autologous hematopoietic stem cells in the celiac artery of the patient was an effective treatment [63].*

7.2. Hepatic stem cells (HSCs) as regenerative medicine against liver diseases

It was investigated that in the early stages of the development of the liver, the undifferentiated hepatic stem cells were firstly increase their quantity by self renewal activity and then differentiate into hepatocytes and cholangiocytes. In the result, the liver was developed in a process that was regulated by the transcription factors that were produced from these stem cells [64]. Recently, it was reported that some trophic factors were involved in the regeneration of the liver that were produced by hepatic mesenchymal stem cells. An experimental study on mouse model to regenerate the liver after surgery or repurfusion injury of liver, the paracrine effects of these liver derived mesenchymal stem cells were reported [65].

7.3. Hepatic stellate cells (HSCs) as regenerative medicine against liver diseases

Hepatic stellate cells (HSCs) were described as mesenchymal stem cells that present in the liver. The regeneration of liver was observed by the formation of mesenchymal tissues, hepatocytes, progenitor cells and the cholangiocytes when these cells were transplanted into a mouse model of injured liver [66]. A recent study was demonstrated the influence of inflammation on the immune-potential of the hepatic stellate cells as well as on the mesenchymal stromal cells that were derived from human liver. It was also observed that among all toll like receptors that were expressed by both of these cells, the inflammation increased the expression of toll like receptor 3 in both of these cells while increased the expression of toll like receptor 2 in mesenchymal stromal cells only. So, it was concluded that both of these cells have immunosupression activity and stopped the mitogen activated T cells proliferation [67].

8. Stem cells derived from the placenta or amniotic as regenerative medicine against liver diseases

Placenta or amniotic is an easily available source of stem cells with no ethical, age or environmental related concerns. It was observed that the stem cells derived from placenta were not involved in tumor formation. The immunomodulating and the anti-inflammatory activities were also performed by these cells. These cells also have potential to differentiate into all three types of germ layers so they were used in stem cells based therapies to treat the liver diseases [68]. The increase in the efficiency of bioartificial liver treatment was observed when

liver cells were three dimensionaly co-cultured with the human placenta derived mesenchymal stem cells in a fluidized bioreactor. By this, the improvement in metabolic functions and the protection of liver cells was also examined [69].

9. Multilineage differentiating stress enduring cells (Muse cells) as regenerative medicine against liver diseases

Muse cells were isolated from the population of mesenchymal stem cells. These cells were observed as pluripotent stem cells and have ability to differentiate into mesodermal, endodermal and ectodermal cells. In order to cure the chronic liver diseases, methods were established for their isolation and transplantation [70].

10. Mesenchymal stem cell derived from umbilical cord as regenerative medicine against liver diseases

Recently, in a clinical study of human and mouse it was examined that mesenchymal stem cells that were derived from umbilical cord improved the function of the liver. These stem cells were proved safe. These cells were also played a role to decrease the level of ascites in the patients of liver cirrhosis disease. So, these cells have shown the therapeutic potential to cure the liver cirrhosis and to improve the liver function [71].

11. Fetal liver stem/Progenitor cells (FLSPCs) as regenerative medicine against liver diseases

It was identified that FLSPCs were differentiated into mature hepatocytes by combining with some Notch receptors. Among Notch receptors, Notch3 was the first receptor that was identified. Further studies revealed that the Notch3 was an important marker in the differentiation process and was not the only factor that was responsible for the differentiation of FLSPCs into mature hepatocytes [72].

12. Human Dental pulp stem cells (hDPSCs) as regenerative medicine against liver diseases

Recently, it was investigated that when hDPSCs combined with melatonin then a significant suppressive effect was observed in the diseased condition of liver fibrosis. It was also observed that the level of ammonia, aspartate transaminase and alanine transaminase was restored. So, it was demonstrated that melatonin was involved in the modification of NF-kappaB, p38, BMP and ERK pathways and enhanced the differentiation of hDPSCs into hepatocytes. Therefore, melatonin was proved useful to treat the liver cirrhosis [73]. Recently, it was investigated in the laboratory experiments that the stem cells derived from human exfoliated deciduous teeth (SHED) have the ability to differentiate into hepatocytes and these hepatocytes were succesfully transplanted into mouse model to treat the secondary biliary cirrhosis and the acute liver injury. SHEDs are easily available adult stem cells and have the capability to proliferate in excess quantity before differentiation. Thus, these cells are novel and a safe source of stem cells to use in the regenerative medicines to treat the liver diseases [74].

13. Conclusion

It is concluded that the regenerative medicines that are based on the stem cells, hold the promise to cure any type of liver injury as well as to restore the functions of liver to support life. Mostly work was performed on mesenchymal stem cells because they have anti inflammatory and immunomodulating activities but other types of stem cells were also played a significant role to regenerate the liver. Liver itself also has niches of some types of stem cells that are specific to produce the hepatocytes. Trophic factors were also played a significant role in the differentiation of stem cells into liver cells. It was also observed that differentiation ability of stem cells into hepatocytes was enhanced by some chemicals enhanced. So, stem cells based regenerative medicines are the future to treat the injury of vital glands of the human body.

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