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Mini Review

Liver Regeneration with Hematopoietic Stem Cells

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Abstract

The human body's liver has the best capacity for regeneration. But a variety of assaults, including as viral infections, drug or alcohol addiction, and metabolic stress, can result in chronic inflammation and fibrosis, which then results in irreversible liver damage. Liver illnesses continue to be a major cause of death globally despite improvements in surgery and pharmaceutical therapies. Cell therapy for liver illness has become a promising regenerative therapy to address the lack of donor liver organs for orthotopic liver transplantation. Primary hepatocytes or functional hepatocytes produced by reprogramming Induced Pluripotent Stem Cells (IPSC) are examples of sources. Hematopoietic Stem Cells (HSCs), Mesenchymal Stromal Cells (MSCs), Endothelial Progenitor Cells (EPCs), as well as adult and foetal hepatic progenitor cells, have all been used as stem cell transplants to promote regeneration. Due to their autologous character, simplicity of isolation, and ability to be preserved in cryo, HSCs, which are often identified by the expression of CD34 and CD133, and MSCs, which are identified by the expression of CD105, CD73, and CD90, are desirable sources. The study focuses on the application of HSCs from bone marrow for liver regeneration and provides proof of continuous interactions between the hematopoietic and hepatic systems. This connection is established during embryogenesis, when the foetal liver develops as the junction between the two systems, bringing together cells from separate cellular origins (mesoderm and endoderm) in one organ. A further indication that this link between the two systems is still present is the fact that the adult liver continues to be one of the few sites for extra medullary hematopoiesis, albeit in a diseased manner.

Keywords: Hematopoietic stem cells (HSCs) • Liver regeneration

Introduction

The liver performs crucial physiological functions such as lipid metabolism, drug detoxification, and glycogen storage to meet the body's energy needs. Orthotopic Liver Transplantation (OLT) is still the sole curative option for severe liver failure, which is a significant cause of death globally, despite improvements in medical technology and surgery [1]. OLT is the only procedure with a long-lasting clinical benefit, despite requiring lifelong immunosuppression and having a chance of post-surgery problems and graft rejection. However, there is an increasing need for alternate treatment alternatives due to the shortage of organ donors. The first clear option for a cell-based method to restore liver function has emerged as hepatocyte transplantation [2]. Despite significant advancements in procedure standardisation, there are still significant problems with cell engraftment and effectiveness. Since stem cells have the ability to self-renew and develop into other cell types, several cell transplantation procedures have been put forth.

Endothelial Progenitor Cells (EPCs), foetal liver cells, Hematopoietic Stem Cells (HSCs), Induced Pluripotent Stem Cells (IPSCs), and Mesenchymal Stromal Cells (MSCs) are among the cells employed in transplantation for liver therapy. Immune cell treatments are additionally offered for liver disorders. The goal of stem cell-based therapies is to regenerate the liver tissue in order to slow the progression of liver failure. The replenishing of injured tissue, the availability of soluble substances, or fusion with resident cells are three possible methods underpinning the regenerative capacity of stem cells. When autologous stem cells are used for transplantation rather than allogeneic ones, immunological tolerance is transmitted and there is no longer a need for life-long immunosuppression to prevent allograft rejection [3].

Adipocytes, chondrocytes, and osteoblasts are possible derivatives of Mesenchymal Stromal Cells (MSCs). Numerous sources, such as bone marrow, the umbilical cord, the placenta, and amniotic fluid, can yield them. Their ability to be greatly increased in culture under strictly monitored conditions to produce a high number of cells for transplantation is one of their key advantages. In patients with chronic liver disease, MSC-based transplantation improves liver function, especially in the months immediately after treatment with few adverse effects. MSCs' paracrine and immunomodulatory characteristics promote angiogenesis, lower oxidative stress, and apoptosis in a variety of organs, including the liver. Additionally, MSCs can regenerate the damaged liver both invivo and invitro, differentiating into hepatocytes and BECs, and their Extracellular Vesicles (EVs) may also be helpful in liver therapy. MSCs have been used in numerous clinical trials to treat patients with cirrhosis or liver failure, improving liver indices and function [4].

Somatic cells are reprogrammed via a mix of known factors, including Oct4, Sox2, Klf4, and c-Myc, to produce Induced Pluripotent Stem Cells (IPSC) can develop into hepatocyte-like cells and are a desirable source of transplantable cells due to their ease of production and lack of ethical constraints. In mice, hepatocyte-like cells engraft, and their treatment guards against liver damage. Kupffer cells and EVs with antifibrotic properties in mice models of liver injury can both be produced by IPSCs. However, notwithstanding the difficulties in producing IPSCs, clinical trials should still use them [5].

The first evidence of bone marrow-derived EPCs in peripheral blood dates to the 1990s. Following transplantation in rats, EPCs are attracted from the bone marrow to regions of neovascularization, where they exert cytoprotective effects and lessen fibrosis thanks to paracrine mechanisms. Patients with liver cirrhosis have higher EPC levels, and administration of drugs to animals with liver injury and cirrhosis improves survival and enhances hepatocyte proliferation. Autologous EPC transplantation was well tolerated and improved liver function in patients with hepatic cirrhosis, demonstrating the therapeutic potential of these cells. Prior to transplantation, bone marrow mononuclear cells are briefly cultured on fibronectin in the presence of certain cytokines [6]. Hepatocytes are the most logical cell type for transplantation and a promising, minimally invasive OLT substitute because they do not require extensive surgery or ongoing immunosuppression. The ability to treat numerous patients with a single donor is one of the key benefits of using adult hepatocytes, which are often isolated from whole donor livers that have been rejected for OLT. Hepatocyte transplantation appears to lower mortality in individuals with liver failure and also acts as a transition to OLT. According to experimental evidence, the degree of hepatocyte engraftment affects the transplant's success, and metabolic disorders give transplanted cells a selection advantage [7]. HSCs have been studied for more than 60 years, and there is a wealth of knowledge about their identification, potential isolation, and biological characteristics, particularly in relation to the rebuilding of the hematopoietic system. Bone marrow transplantation, a curative treatment for haematological malignancies, aplastic anaemia, and primary immunodeficiencies, is made possible by HSCs. The fact that autologous HSCs can now be mobilized in the systemic circulation without the requirement for invasive procedures is one of the key benefits of employing HSCs for transplantation.

Additionally, there is no need for in vitro culture and no need for ex vivo manipulation, unlike with MSCs or EPCs. At the same time, the quantity of cells that can be transplanted is constrained by the difficulty to grow HSCs in vitro [3].

Years of study have yielded significant knowledge on the biology, purpose, and supportive milieu of HSCs. At the pinnacle of the hematopoietic system, these cells represent a rare (0.01% of the total bone marrow) multipotent population that is endowed with the ability to self-renew, ensuring that a stem cell population is sustained over the course of life. The adult hematopoietic system produces all blood cell lineages through a carefully regulated balance between differentiation and self-renewal, and frequently refills short-lived blood lineages like neutrophils and platelets to maintain blood system homeostasis. Operationally, HSCs are identified by their capacity to restore the hematopoietic system after myeloablation. Studies on transplantation in lethally radio treated mice have provided proof of this ability. HSCs initially differentiate to create long-term HSCs and short-term HSCs, which differ in their potential for self-renewal and commitment to a particular lineage. Common Myeloid Progenitors (CMPs) and common lymphoid progenitor cells are produced as a result of short term HSC differentiation into hematopoietic progenitor cells. Megakaryocyte-Erythrocyte Progenitors (MEPs) and Granulocyte-Macrophage Progenitors (GMPs) are both produced by CMPs. Granulocytes, monocytes, and dendritic cells are produced by GMPs, whereas erythrocytes and megakaryocytes are produced by MEPs. CLPs are in charge of T and B lymphocyte production. Progenitor cells (CMPs, CLPs, GMPs, and MEPs) and terminally differentiated blood cells both lack the ability to self-renew. Most HSCs remain latent, in the G0 phase, and have the unusual capacity to divide symmetrically and asymmetrically, resulting in the production of an identical HSC and a progenitor cell. The intricate interaction of internal and extrinsic factors carefully controls the dynamics of the hematopoietic system's organizational structure. Transcriptional regulators [Runx1, GFI1, Scl, GATA2, EVI1], epigenetic regulators [TET2, DNMT3A, EZH1], and miRNAs are examples of intrinsic factors that support HSC self-renewal. MiR-125a, miR-125b, miR-155, miR-99a, miR-126, miR-196b, miR130a, miR-542, miR-181, miR-193, and miR-let7e appear to be shared by both human and mouse HSC, indicating an evolutionary conservation of these molecules [8].

Although the hypoxic profile of HSCs also depends on cell-intrinsic mechanisms, extrinsic variables that HSCs are exposed to include the low oxygen levels of the bone marrow microenvironment. Stem Cell Factor (SCF), thrombopoietin, and C-X-C motif chemokine ligand 12, also known as Stromal Cell-Derived Factor 1 (SDF-1), are important cytokines linked to the maintenance and self-renewal of adult HSCs in the bone marrow. While osteopontin and TPO maintain quiescence, notch ligands may promote proliferation. HSC self-renewal and differentiation capacity are also controlled by canonical signalling in a dose-dependent manner through beta catenin. The modest activation of signalling is necessary for HSC function and repopulation capacity, whereas higher levels encourage T-cell differentiation. Hematopoiesis occurs in the adult in the bone marrow, where HSCs are found in specialised regions called endosteal and vascular niches. Osteoblasts, endothelial cells, MSCs, megakaryocytes, and adipocytes are present in the endosteal niche, which is situated adjacent to the trabecular bone. Endothelial cells, CXCL12-Abundant Reticular (CAR) cells, and Nestin +GFP cells, which are enriched in MSCs, make up the vascular niche, which is situated next to the bone marrow's extravascular spaces. These locations and cells work together to maintain HSC functionality and control [9].

Discussion

Millions of people throughout the world suffer from acute and chronic liver illnesses, which can lead to cirrhosis, liver failure, and hepatocellular cancer. The only curative option is OLT, however because of its drawbacks and difficulties, researchers are now looking for other options. The use of HSCs and/or MSCs infusions in patients with end-stage liver disease has been the subject of numerous clinical trials.

Stem-cell-based approaches represent intriguing possibilities for liver therapy. Despite the fact that blood cells and liver cells both come from the embryonic mesoderm and endoderm, respectively, evidence of the transdifferentiation potential of HSCs in the early 2000s showed their regenerative potential for liver therapy. The search for liver therapeutics is ongoing, and new information suggests that techniques involving acellular mediators, such as EVs, may be investigated. EVs can be produced from progenitor cells like HSCs and used to send certain signals to the diseased liver. EVs help pack a wide range of substances, including as lipids, nucleic acids, and proteins, and they exhibit the traits of the mother cell. Additionally, they might contain signal activators, which could be helpful in therapy. For their assistance in liver regeneration, EVs and exosomes from a variety of cell types, including hepatocytes, cholangiocytes, hepatic stellate cells, and Kupffer cells as well as stem cells, have been fully characterized. Additionally, EVs can be modified to serve as medicine delivery systems by adding compounds to them [10].

Conclusion

For a number of liver disorders, cellular treatments represent promising alternatives to OLT. In this article, we talk about current developments in the therapeutic use of bone marrow HSCs for liver regeneration. The argument for employing HSCs as a treatment approach in patients with liver illnesses is supported by evidence of the interaction between the hepatic and hematopoietic systems since development. Clinical therapeutics based on HSCs are further supported by encouraging results from current clinical trials. To develop better and safer protocols for their administration, either alone or in conjunction with other cellular and acellular products, in the setting of liver illnesses, more knowledge about the processes determining the regeneration potential of HSCs is still required.

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