Editorial

Adult-derived human liver stem/progenitor cells as sensors of inflammation: a potential therapy for liver disorders

Soura Mardpour[1,2], Amir Ali Hamidieh[3]

[1]Tissue Engineering and Applied Cell Sciences Department, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran; [2]Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran; [3]Pediatric Stem Cell Transplant Department, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Correspondence to: Amir Ali Hamidieh, MD. Pediatric Stem Cell Transplant Department, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran. Email: aahamidieh@tums.ac.ir.

Comment on: Najar M, Crompot E, Raicevic G, *et al.* Cytokinome of adult-derived human liver stem/progenitor cells: immunological and inflammatory features. Hepatobiliary Surg Nutr 2018;7:331-44.

Submitted Jan 01, 2019. Accepted for publication Jan 14, 2019.
doi: 10.21037/hbsn.2019.01.11
View this article at: http://dx.doi.org/10.21037/hbsn.2019.01.11

Advanced liver diseases remain one of the major health issues worldwide. Progressive fibrosis, inflammatory damage, deprivation of metabolic capacity and parenchymal cell death are the main characteristics of end-stage liver diseases. Orthotopic liver transplantation has been considered as the therapy of choice in patients suffering from liver failure such as fulminant liver failure, cirrhosis and hepatocellular carcinoma (HCC). Severe liver donor scarcity has led to the continuous increase of patients with end-stage liver diseases that were listed for liver transplantation. Amongst other treatment strategies, stem cell-based therapies have achieved clinical breakthrough and bridge to liver transplantation (1). In this regard, hepatocyte transplantation provides functional substitution of damaged liver tissue. Adult human primary hepatocytes are mostly isolated from the marginal donor organs that were not applicable for transplantation. Different challenges including scarce supply of the hepatocytes, limited in-vitro expansion potential, low cell viability, the need for scaling up, poor integration into liver parenchyma and *in vivo* proliferation potential after transplantation lead to notable trends of studies utilizing other sources. Using functional differentiated hepatocytes generated from embryonic/induced pluripotent stem cells or adult stem cells such as mesenchymal stromal cells (MSCs) in experimental models showed structural and metabolic improvement in damaged liver tissue (2,3). Undoubtedly, understanding molecular mechanism which are happened during liver injury comprising activation of hepatic stellate cells and tissue macrophages, secretion of pro-inflammatory cytokines, infiltration of immune cells inside damaged tissue, excessive matrix deposition has led to developing new effective treatments. MSC's pleiotropic properties including multipotency, immunosuppressive potential, trophic factor secretion during tissue repair, anti-fibrosis, anti-apoptosis and the lack of immunogenicity when administered in allogenic context make them an ideal cell type in clinical setting.

It is believed that MSC exert therapeutic effect not only by differentiation towards functional hepatocytes (cell replacement strategy), but cell empowerment mechanism also activated in which inflammatory niche was modulated and regression of fibrosis concurrent liver regeneration is initiated through the secretion of trophic factors. Thus, despite restoration of lost tissue and attenuation of liver necrosis, transplanted MSCs could ease liver immune-active niche which subsequently leads to matrix regression or resolution (4).

Hepato-mesenchymal feature of adult-derived human liver stem/progenitor cells (ADHLSCs) makes them suitable and alternative candidate with outcomes better than or at least comparable to those seen with hepatocytes in liver diseases. ADHLSCs displayed engraftment and integration to recipient tissue and promote anti-inflammation and liver

regeneration after infusion in hepatectomized and cirrhosis experimental models and clinical trials (5-7).

Focus has now turned to investigate immunological features and mechanisms underlying this therapeutic value of ADHLSCs which may potentially contribute to liver treatment. In this issue of *HepatoBiliary Surgery and Nutrition*, Najar *et al.* report data of cytokinome of ADHLSCs in undifferentiated (mesenchymal-like cell) and differentiated HD (hepatocyte-like cells) state with pro-inflammatory cytokine treatment (8).

Hemostasis inflammation and liver fibrosis are initially essential for regeneration of damaged tissue. Liver regeneration is driven by secretion of some inflammatory factor such as IL-1α, IL-6 and TNF-α. In this regard, several studies emphasized on critical pro-regenerative role of IL-6 and TNF-α when impaired liver regeneration were observed in animal after targeted disruption of IL-6 and TNFα. In this paper, Najar *et al.* showed that pro-inflammatory cytokines such as IL-6, TNF-α, IL-8, CCL5 were highly upregulated in hepatocytes and in both undifferentiated ADHLSCs and HD ADHLSCs when primed with inflammatory cytokines. Of note, reduction of IL-12 superfamily IL-12A, p19, p28 (IL-27) and EBI-3 (IL-35) was observed under differentiation condition. However, ADHLSCs and HD ADHLSCs displayed highly expression of IL-12 superfamily specially p28 and EBI-3 after pre-incubation with inflammatory cytokines.

Although, it was initially believed that IL-27 exhibit pro-inflammatory function, the majority of studies investigated immunomodulatory properties of this cytokine (9-11). Moreover, the importance of IL-35 as the critical immunomodulatory mediators and inducers of T and B regulatory cells is supported by depleting EBI-3 from IL-35-secreting MSCs and adding exogenous IL-35 in *in vitro* culture system and *in vivo* experimental autoimmune models (12).

Dysregulated liver inflammation as a result of persistent inflammation has been considered a hallmark of autoimmunity and chronic diseases (13). In this regard, using liver cell-based therapies with immunomodulatory properties may aid liver tissue to regenerate itself through balancing inflammatory mediators inside the microenvironment.

Based on author results, upregulation of anti-inflammatory proteins such as IL-1RA, TDO and specially IDO was also detected in cytokine-treated ADHLSCs, HD ADHLSCs and hepatocytes which is similar to those from MSCs.

It should also be noted that MSCs have been shown to be as sensors of inflammation and capable to adapt pro-inflammatory (in high levels of inflammation) and anti-inflammatory (in low levels of inflammation) phenotypes (13,14). For the sake of clarity, we also performed proteomics analysis of MSC generated extracellular vesicles (EVs) and found two distinct categories of cytokines, chemokines and chemokine receptors with pro- and anti-inflammatory functions (15). Thus, irrespective of immunosuppression as dominant phenotype of MSCs and their secreted cytokines and EVs in inflammatory, chronic and autoimmune diseases, they may switch towards immune-stimulatory function under the specific condition in response to infectious diseases. In this study, Najar *et al.* provide valuable information and presents an intriguing view that ADHLSC may also sense inflammatory cues and generates appropriate response to inflammatory condition by adjusting their cytokine profile similar to those occurs in MSCs. Further High-throughput studies focused on proteomics analysis are likely to establish that ADHLSCs could be effectively applicable in liver disorders.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Than NN, Tomlinson CL, Haldar D, et al. Clinical effectiveness of cell therapies in patients with chronic liver disease and acute-on-chronic liver failure: a systematic review protocol. Syst Rev 2016;5:100.
2. Heidariyan Z, Ghanian MH, Ashjari M, et al. Efficient and cost-effective generation of hepatocyte-like cells through microparticle-mediated delivery of growth factors in a 3D culture of human pluripotent stem cells. Biomaterials 2018;159:174-88.
3. Itaba N, Matsumi Y, Okinaka K, et al. Human mesenchymal stem cell-engineered hepatic cell sheets accelerate liver regeneration in mice. Scientific Reports 2015;5:16169.
4. Christ B, Bruckner S, Winkler S. The Therapeutic Promise of Mesenchymal Stem Cells for Liver Restoration.

Trends Mol Med 2015;21:673-86.
5. Khuu DN, Nyabi O, Maerckx C, et al. Adult human liver mesenchymal stem/progenitor cells participate in mouse liver regeneration after hepatectomy. Cell Transplant 2013;22:1369-80.
6. Sokal EM, Lombard CA, Roelants V, et al. Biodistribution of Liver-Derived Mesenchymal Stem Cells After Peripheral Injection in a Hemophilia A Patient. Transplantation 2017;101:1845-51.
7. Hsu MJ, Prigent J, Dollet PE, et al. Long-Term In Vivo Monitoring of Adult-Derived Human Liver Stem/Progenitor Cells by Bioluminescence Imaging, Positron Emission Tomography, and Contrast-Enhanced Computed Tomography. Stem Cells Dev 2017;26:986-1002.
8. Najar M, Crompot E, Raicevic G, et al. Cytokinome of adult-derived human liver stem/progenitor cells: immunological and inflammatory features. Hepatobiliary Surg Nutr 2018;7:331-44.
9. Cox JH, Kljavin NM, Ramamoorthi N, et al. IL-27 promotes T cell-dependent colitis through multiple mechanisms. J Exp Med 2011;208:115-23.
10. Stumhofer JS, Hunter CA. Advances in understanding the anti-inflammatory properties of IL-27. Immunol Lett 2008;117:123-30.
11. Wojno ED, Hunter CA. New directions in the basic and translational biology of interleukin-27. Trends Immunol 2012;33:91-7.
12. Cho KA, Lee JK, Kim YH, et al. Mesenchymal stem cells ameliorate B-cell-mediated immune responses and increase IL-10-expressing regulatory B cells in an EBI3-dependent manner. Cell Mol Immunol 2017. [Epub ahead of print].
13. Robinson MW, Harmon C, O'Farrelly C. Liver immunology and its role in inflammation and homeostasis. Cell Mol Immunol 2016;13:267-76.
14. Bernardo ME, Fibbe WE. Mesenchymal stromal cells: sensors and switchers of inflammation. Cell Stem Cell 2013;13:392-402.
15. Mardpour S, Hamidieh AA, Taleahmad S, et al. Interaction between mesenchymal stromal cell-derived extracellular vesicles and immune cells by distinct protein content. J Cell Physiol 2019;234:8249-58.

Cite this article as: Mardpour S, Hamidieh AA. Adult-derived human liver stem/progenitor cells as sensors of inflammation: a potential therapy for liver disorders. HepatoBiliary Surg Nutr 2019;8(3):286-288. doi: 10.21037/hbsn.2019.01.11

