Hepatic immune tolerance induced by hepatic stellate cells

Ching-Chuan Hsieh, Chien-Hui Hung, Lina Lu, Shiguang Qian

Ching-Chuan Hsieh, Department of Surgery, Chang Gung Memorial Hospital at Chiayi, Chiayi 613, Taiwan
Ching-Chuan Hsieh, Chien-Hui Hung, Graduate Institute of Clinical Medical Sciences, Chang Gung University, Taoyuan 333, Taiwan
Lina Lu, Shiguang Qian, Department of Immunology, Lerner Research Institute, Transplantation Center, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH 44195, United States
Lina Lu, Shiguang Qian, Department of General Surgery, Transplantation Center, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH 44195, United States

Author contributions: Hsieh CC, Lu L and Qian S contributed to the conception, design, acquisition and interpretation of the data; Hung CH contributed to the revision of manuscript; all authors revised the article and approved the final version.

Supported by National Science Council, No. NSC 101-2314-B-182A-040-MY2 and No. CMRPG6A0523.

Conflict-of-interest statement: The authors declare no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Ching-Chuan Hsieh, MD, Department of Surgery, Chang Gung Memorial Hospital at Chiayi, 6 Sec. West Chia-Pu Road, Pu-Zi City, Chiayi 613, Taiwan. jeffrey570404@gmail.com
Telephone: +886-5-3621000
Fax: +886-5-3623002

Received: January 28, 2015
Peer-review started: January 29, 2015
First decision: April 13, 2015
Revised: April 27, 2015

Abstract

The liver, which is a metabolic organ, plays a pivotal role in tolerance induction. Hepatic stellate cells (HpSCs), which are unique non-parenchymal cells, exert potent immunoregulatory activity during cotransplantation with allogeneic islets effectively protecting the islet allografts from rejection. Multiple mechanisms participate in the immune tolerance induced by HpSCs, including the marked expansion of myeloid-derived suppressor cells (MDSCs), attenuation of effector T cell functions and augmentation of regulatory T cells. HpSC conditioned MDSC-based immunotherapy has been conducted in mice with autoimmune disease and the results show that this technique may be promising. This article demonstrates how HpSCs orchestrate both innate immunity and adaptive immunity to build a negative network that leads to immune tolerance.

Key words: Hepatic stellate cells; Myeloid-derived suppressor cells; Hepatic tolerance; Immunotherapy

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The liver is an immune privileged organ that contains cells exhibiting powerful immune regulatory activity. Hepatic stellate cells (HpSCs) possess weak antigen-presenting ability and function as immunological bystander cells in the regulation of the immune response by the way of induction of effector T cell apoptosis and the generation of myeloid-derived suppressor cells and regulatory T cells. The combination of these mechanisms indicates that HpSCs are a potent immunoregulatory entity capable of modulating immune responses in the liver. HpSCs can orchestrate both innate immunity and adaptive immunity to build a negative immune network that
leads to immune tolerance. Further understanding of hepatic immune tolerance will provide the basis for developing new immunotherapies that target transplant rejection, chronic viral infection and cancer.

Hsieh CC, Hung CH, Lu L, Qian S. Hepatic immune tolerance induced by hepatic stellate cells. World J Gastroenterol 2015; 21(42): 11887-11892 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i42/11887.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i42.11887

INTRODUCTION

Tolerogenic properties of the liver can be initially established by spontaneous acceptance of liver transplants in many species without the requirement of immunosuppression[1-3]. However, hepatocyte transplants are acutely rejected, apparently resulting from immune attacks, because syngeneic hepatocyte transplants survive indefinitely[4]. This finding suggests that liver nonparenchymal cells (NPCs) play an important role in protecting parenchymal cells from rejection. Yu et al[5] studied mouse liver NPCs and found that hepatic stellate cells (HpSCs) have potent immune regulatory activity.

HpSCs are located in the subendothelial space adjacent to the basolateral surface of hepatocytes and make up approximately 15% of the total cell population within the liver. They express very low amounts of major histocompatibility complex (MHC) and co-stimulatory molecules[6]; moreover, HpSCs exhibit low antigen uptake and insufficient processing ability[7,8]. HpSCs are the major site of vitamin A storage within the body[9,10] and have been extensively studied regarding their role in fibrogenesis and induction of cirrhosis. Once activated by an insult, HpSCs become myofibroblasts and deposit extracellular matrix, leading to liver fibrosis[11]. HpSCs are difficult to identify based on surface markers, even though intracellular desmin and α-smooth muscle actin (αSMA) have been used for the identification of quiescent and activated HpSCs, respectively. Nevertheless, a recent publication showed that HpSCs can be differentiated from other liver cells using their size, granularity, and high UV-fluorescence (due to their vitamin A content) in combination with the absence of scavenger activity[12]. This overview will discuss the relationship between HpSCs and immune cells and their participation in hepatic tolerance.

HPSCS AND MYELOID-DERIVED SUPPRESSOR CELLS

Myeloid-derived suppressor cells (MDSCs) represent an intrinsic part of the myeloid-cell lineage and are a heterogeneous population that is comprised of myeloid-cell progenitors and precursors of myeloid cells. In healthy individuals, immature myeloid cells (IMCs) generated in bone marrow quickly differentiate into mature granulocytes, macrophages or dendritic cells (DCs). In pathological conditions, such as cancer, various infectious diseases, sepsis, trauma, transplantation or some autoimmune disorders, a partial block in the differentiation of IMCs into mature myeloid cells results in an expansion of MDSCs[13]. In mice, MDSCs express both the myeloid lineage differentiation antigen Gr-1 (Ly6G and Ly6C) and the M integrin CD11b. The equivalent of the MDSC in humans is defined as the CD14 CD11b+ CD33’CD15’ phenotype or cells that express the CD33 marker but lack the expression of markers of mature myeloid and lymphoid cells and the MHC class II molecule HLA-DR[14-16]. However, MDSCs share many unifying features, including high expression levels of the immunosuppressive molecules arginase 1 and inducible nitric oxide synthase (iNOS) and, more importantly, their immunosuppressive function[17].

Cotransplantation of HpSCs with allogeneic islets effectively protects the islet allografts from rejection without the requirement of immunosuppression via inhibition of the CD8+ T-cell response, enhancement of regulatory T-cells[18,19] (Figure 1), and induction of MDSCs[20]. The role of MDSCs is vital to induction of immune tolerance, and this process occurs by skewing the differentiation and effector function of T cells.

Chou et al[20] demonstrated that HpSCs promoted the generation of MDSCs both in vitro and in vivo. Induction of MDSCs is dependent on an intact interferon gamma (IFN-γ) signaling pathway in HpSCs and is mediated by soluble factors, suggesting that the specific tissue stromal cells play a crucial role in regulating immune responses via inflammation-induced generation of MDSCs. One of the effective soluble factors secreted by HpSCs is complement component 3 (C3). C3 deficient HpSCs lose their ability to induce MDSCs and, consequently, fail to protect the cotransplanted islet allografts. HpSCs produce complement activation factor B and factor D, which then enhances C3 cleavage into the activation products iC3b and C3d. Addition of exogenous iC3b leads to differentiation of MDSCs with potent immune-inhibitory function[21]. HpSCs are a major source of the immunoregulatory metabolite all-trans retinoic acid (ATRA) in the liver, which may contribute to the generation of tolerogenic DCs in that location. ATRA has been shown to enhance both Arginine 1 and iNOS expression in DCs, resulting in a tolerogenic phenotype[22]. MDSCs induced by HpSCs express B7-H1 and secrete iNOS, which leads to the protection of islet allografts from rejection when MDSCs are cotransplanted with allogeneic islets. This process is associated with attenuation of CD8 T cells in grafts and marked expansion of regulatory T (Treg) cells, which contribute to MDSC-induced T cell hyporesponsiveness[23,24]. These findings provide novel
mechanistic insights into influence of local tissue cells on the differentiation of myeloid cells and may assist in the development of MDSC-based therapy in clinical settings.

**IMMUNOTHERAPY**

Li et al.\(^{[25]}\) showed that adoptive transfer of HpSC-induced MDSCs successfully reversed disease progression in experimental autoimmune myasthenia gravis (EAMG), a T cell-dependent and B cell-mediated model for myasthenia gravis. In addition to ameliorating the disease severity, MDSC-treated EAMG mice showed suppressed acetylcholine receptor (AChR)-specific T cell responses, decreased levels of serum anti-AChR IgGs, and reduced complement activation at the neuromuscular junctions. MDSCs directly inhibited B cells through multiple mechanisms, including PGE2, inducible NO synthase, and arginase. These results demonstrated that HpSCs induce MDSCs concurrently suppress both T and B cell autoimmunity, leading to effective treatment of established EAMG. Another MDSC-based immunotherapy was performed in hemophilia A mice (factor VIII deficiency)\(^{[26]}\). An adverse effect of factor VIII infusion therapies used for the treatment of hemophilia A is the production of antibodies (inhibitors) against factor VIII, which is a T cell-dependent and B cell-mediated process. HpSC mediated MDSCs, propagated from hemophilia A mice, can also inhibit the proliferation and activation of B cells stimulated by IgM and interleukin-4 (IL-4). Administration of MDSCs, mediated by HpSCs, induced CD4\(^+\) T cell and B220\(^+\) B cell hyporesponsiveness to factor VIII and reduced inhibitor formation in hemophilia A mice.

A recent study by Dusabineza et al.\(^{[27]}\) revealed that cotransplantation of hepatocytes with HpSCs could improve hepatocyte engraftment in vivo. Four weeks after human hepatocytes were cotransplanted with human HpSCs into mouse livers, human albumin positive (huAlb\(^+\)) hepatocytes formed clusters and were more numerous, occupying 2 to 5.9-fold more surface area on the tissue section than in livers transplanted with hepatocytes alone. Increased huAlb mRNA expression in livers transplanted with the cell mixtures confirmed these results. The presence of HpSCs increased the number of hepatocytes entrapped in the host liver at an early time point post-transplantation but not their proliferation in situ as assessed by the cumulative incorporation of BrdU. Additionally, no accumulation of \(\alpha\)SMA\(^+\) activated HpSCs or collagen deposition at 4 wk post-transplantation was found. Engrafted hepatocytes also formed E-cadherin\(^+\) adherent junctions with adjacent
donor or mouse hepatocytes. Cotransplantation of hepatocytes with HpSCs into a healthy liver recipient does not generate fibrosis but significantly improves the engraftment of hepatocytes, probably by ameliorating cell homing.

Taken together, HpSC-based cell therapy has been successfully conducted based on the above studies, and the results increase the therapeutic potential of this technique.

**HPSCS AND T CELLS**

HpSCs play an important role in the regulation of sinusoidal blood flow (contractility), maintenance of hepatic architecture (extracellular matrix synthesis), and production of various growth factors. During liver injury, HpSCs transform into myofibroblast-like cells and deposit extracellular matrix, causing liver fibrosis. Activated HpSCs also recruit lymphocytes by producing chemokines [28-30], and they produce numerous cytokines with either proinflammatory or anti-inflammatory activity [30-31].

HpSCs have been reported to be non-professional antigen-presenting cells (APCs) that do not constitutively express the MHC class II proteins required for interaction with naïve T cells; these are expressed only upon stimulation by certain cytokines such as IFN-γ.

HpSCs stimulated by IFN-γ express MHC class I and costimulatory molecules and upregulate the expression of IL-6, transforming growth factor-β, and migration inhibitory factor. Activated HpSCs markedly expresses B7-H1 and then induce the T-cell hyporesponsiveness associated with enhanced T cells apoptosis. Blockade of B7-H1/PD-1 ligation significantly reduces HpSC immunomodulatory activity in mice and humans [5,32].

The in vitro evidence of immune modulatory activity of HpSCs was validated in vivo in an islet transplantation model. Cotransplanted HpSCs that effectively protected islet allografts from rejection formed a multi-layered capsule, which reduced allograft immunocyte infiltrates by enhancement of apoptotic death [33]. Yang et al. [33] noted that expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), an apoptosis-inducing ligand, on HpSCs was crucial in the protection of islet allografts because HpSCs derived from TRAIL knockout mice demonstrated less inhibitory activity towards T cell proliferative responses and substantially lost their capacity to protect cotransplanted islet allografts from rejection. This finding may reflect an intrinsic mechanism of immune inhibition mediated by liver-derived tissue cells. Jiang et al. demonstrated that HpSCs selectively expanded regulatory T cells (CD4+CD25+FoxP3+) in an interleukin-2-dependent manner [26]. These expanded regulatory T cells successfully inhibited T cell proliferation in responses to an anti-CD3 monoclonal antibody or alloantigens in a non-specific major histocompatibility complex manner.

The relationship between HpSCs and B cells is not fully understood. Brandão et al. [35] conducted a study to verify the relationship between plasma cells and HpSCs in human autoimmune hepatitis. They found a significant correlation between HpSCs, the score of fibrosis and the number of plasma cells. Additionally, they found a co-localization of plasma cells and HpSCs. Patients who had successfully been treated were found to have a reduced number of both cells. The result suggests a direct interaction between the HpSCs and plasma cells, but the exact mechanism is still unknown.

**CONCLUSION**

It is not surprising that the liver, as an immune privileged organ, contains cells that exhibit powerful immune regulatory activity [36]. Due to its anatomical location and function, the liver is continuously exposed to various antigens, including dietary and commensal antigens. In the long journey of evolution, the liver has acquired the ability to control inappropriate immune responses to those harmless antigens. HpSCs possess weak antigen-presenting ability and function as immunological bystander cells in regulating immune responses via the induction of effector T cell apoptosis and generation of MDSCs and Treg cells [5,18-20]. The combination of these mechanisms indicates that HpSCs are a potent immunoregulatory entity capable of modulating immune responses in the liver (Figure 2).

Liver sinusoidal endothelial cells (LSECs) are another abundant NPC population in the liver and line the hepatic sinusoids. LSECs represent the unique characteristics of APCs and have an increased scavenger ability that is different from HpSCs. LSECs can also restrain inflammation by induction of Treg cells [37], as evidenced by in vivo studies in a mouse model of multiple sclerosis and experimental autoimmune encephalomyelitis [38]. LSECs are capable
of cross-presenting circulating tumor antigens, thereby inducing non-responsive antigen-specific CD8+ T cells through the PD-1/PD-L1 pathway. LSECs can also negatively regulate the APC function of neighboring DCs, which lose their ability to prime naïve T cells by downregulating DC costimulatory signals. However, HpSCs are potentially more beneficial for conducting immunotherapy than LSECs because HpSCs can produce large amounts of MDCs that are broadly distributed to primary and secondary lymphoid organs to exert their immune-modulatory ability and induce immune tolerance.

Organ transplantation has been widely applied for decades, but cellular transplants, including islets and hepatocytes, remain largely experimental because the side effects of immunosuppression often outweigh the benefits. Therefore, it is crucial to develop a protocol to reduce or avoid immunosuppression. The recent studies related to allogeneic islets cotransplanted with HpSCs or MDCs mediated by HpSCs show that these cells achieve long-term survival without immunosuppressive medications in mice and offer a promising future for clinical application.

In summary, activated HpSCs can orchestrate both innate immunity and adaptive immunity to build a negative immune network that leads to immune tolerance. Further understanding of hepatic immune tolerance will provide the basis for developing new immunotherapies that target transplant rejection, chronic viral infection and cancer.

REFERENCES

1. Calne RY, Sells RA, Pena JR, Davis DR, Millard PR, Herbertson BM, Binnis RM, Davies DA. Induction of immunological tolerance by porcine liver allografts. Nature 1969; 223: 472-476 [PMID: 4894426 DOI: 10.1038/223472a0]
2. Kamada N, Brons G, Davies HS. Fully allogeneic liver grafting in rats induces a state of systemic nonreactivity to donor transplantation antigens. Transplantation 1980; 29: 429-431 [PMID: 6990572 DOI: 10.1097/00007890-198005000-00021]
3. Qian S, Demetris AJ, Murase N, Rao AS, Fung JJ, Starzl TE. Murine liver allograft transplantation: tolerance and donor cell chimerism. Hepatology 1994; 19: 916-924 [PMID: 8138266 DOI: 10.1002/hep.1840190418]
4. Bumgardner GL, Heininger M, Li J, Xia D, Parker-Thornburg WJG. Liver sinusoidal endothelial cells veto CD8 T cell activation by antigen-presenting dendritic cells. Eur J Immunol 2008; 38: 957-967 [PMID: 18338043 DOI: 10.1002/eji.200738060]
5. Giampieri MP, Jezequel AM, Orlandi F. The lipocytes in normal human liver. A quantitative study. Digestion 1981; 22: 165-169 [PMID: 7308589 DOI: 10.1159/0001098640]
6. Jezequel AM, Novelli G, Venturini C, Orlandi F. Quantitative analysis of the perisinusoidal cells in human liver; the lipocytes. Front Gastroenterol Res 1984; 8: 85-90 [DOI: 10.1159/0000408420]
7. Friedman SL. Hepatic stellate cells: protein, multifunctional, and enigmatic cells of the liver. Physiol Rev 2008; 88: 125-172 [DOI: 18195085 DOI: 10.1152/physrev.00013.2007]
8. Schölzel K, Schildberg FA, Welz M, Börner C, Geiger S, Korts C, Heikenwälder M, Knoll A, Wohlräber D. Transfer of MHC-class-I molecules among liver sinusoidal cells facilitates hepatic immune surveillance. J Hepatology 2014; 61: 600-608 [PMID: 24798625 DOI: 10.1016/j.jhep.2014.04.028]
9. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009; 9: 162-174 [PMID: 19197294 DOI: 10.1038/nri2506]
10. Almand B, Clark JJ, Nikitina E, van Beynen J, English NR, Knight SC, Carbone DP, Gabrilovich DI. Increased production of immature myeloid cells in cancer patients: a mechanism of immunosuppression in cancer. J Immunol 2001; 166: 678-689 [PMID: 11123353 DOI: 10.4049/jimmunol.166.1.678]
11. Ochoa AC, Zea AH, Hernandez C, Rodriguez PC, Arginase, prostaglandins, and myeloid-derived suppressor cells in renal cell carcinoma. Clin Cancer Res 2007; 13: 721s-726s [PMID: 17255300 DOI: 10.1158/1078-0432.CCR-06-1979]
12. Schmelian J, Finn OJ. Activated granulocytes and granulocyte-derived hydrogen peroxide are the underlying mechanism of suppression of T-cell function in advanced cancer patients. Cancer Res 2001; 61: 4756-4760 [PMID: 11046548]
13. Ugell S, Delpozzo F, Desantis G, Papalini F, Simonato F, Sonda N, Zilbo S, Bronte V. Therapeutic targeting of myeloid-derived suppressor cells. Curr Opin Pharmacol 2009; 9: 470-481 [PMID: 19616472 DOI: 10.1016/j.coph.2009.06.014]
14. Chen CH, Kuo LM, Chang Y, Wu W, Goldbach C, Ross MA, Stolz DB, Chen L, Fung JJ, Lu L, Qian S. In vivo immune modulatory activity of hepatic stellate cells in mice. Hepatology 2006; 44: 1171-1181 [PMID: 17058227 DOI: 10.1002/hep.21379]
15. Yang HR, Chou HS, Gu X, Wang L, Brown KE, Fung JJ, Lu L, Qian S. Mechanistic insights into immunomodulation by hepatic stellate cells in mice: a critical role of interferon-gamma signaling. Hepatology 2009; 50: 1981-1991 [PMID: 19821484 DOI: 10.1002/hep.23202]
16. Chou HS, Hsieh CC, Yang HR, Wang L, Arakawa Y, Brown K, Wu Q, Lin F, Peters M, Fung JJ, Lu L, Qian S. Hepatic stellate cells regulate immune response by way of induction of myeloid suppressor cells in mice. Hepatology 2011; 53: 1007-1019 [PMID: 21374665 DOI: 10.1002/hep.24162]
17. Hsieh CC, Chou HS, Yang HR, Lin F, Bhatt S, Qin J, Wang L, Fung JJ, Qian S, Lu L. The role of complement component 3 (C3) in differentiation of myeloid-derived suppressor cells. Blood 2013; 121: 1760-1768 [PMID: 23299310 DOI: 10.1182/blood-2012-06-440214]
18. Bhatt S, Qin J, Bennett C, Qian S, Fung JJ, Hamilton TA, Lu L. All-trans retinoic acid induces arginase-1 and inducible nitric oxide synthase-producing dendritic cells with T cell inhibitory function. J Immunol 2014; 192: 5098-5108 [PMID: 24790153 DOI: 10.4049/jimmunol.1303073]
19. Chou HS, Hsieh CC, Charles R, Wang L, Wagner T, Fung JJ, Qian S, Lu L. Myeloid-derived suppressor cells protect islet transplants by B7-H1-mediated enhancement of T regulatory cells. Transplantation 2012; 93: 272-282 [PMID: 22179405 DOI: 10.1097/TP.0b013e3182f83b39]
20. Arakawa Y, Qin J, Chou HS, Bhatt S, Wang L, Stuehr D, Ghosh A, Fung JJ, Lu L, Qian S. Cotransplantation with myeloid-derived suppressor cells protects transplant recipients: a crucial role of inducible nitric oxide synthase. Transplantation 2014; 97: 740-747 [PMID: 24642866 DOI: 10.1097/TP.0b013e3182f83857]
21. Li Y, Tu Z, Qian S, Fung JJ, Markowitz SD, Kusner LL, Kaminski

Hsieh CC et al. Hepatic immune tolerance
Hsieh CC et al. Hepatic immune tolerance

HJ, Lu L, Lin F. Myeloid-derived suppressor cells as a potential therapy for experimental autoimmune myasthenia gravis. *J Immunol* 2014; 193: 2127-2134 [PMID: 25057008 DOI: 10.4049/jimmunol.1400857]

Bhatt S, Shen GQ, Li Y, Qian S, Ragni MV, Lu L. Hepatic stellate cell-conditioned myeloid cells provide a novel therapy for Prevention of factor VIII antibody formation in mice. *Exp Hematol* 2015; 43: 277-285 [PMID: 25534204 DOI: 10.1016/j.exphem.2014.12.001]

Dusabineza AC, Najimi M, van Grunsven LA, Sokal E, Leclercq IA. Hepatic stellate cells improve engraftment of human primary hepatocytes: A pre-clinical transplantation study in animal model. *Cell Transplant* 2015; Epub ahead of print [PMID: 25706818 DOI: 10.3727/096368915X686788]

Marra F, DeFranco R, Grappone C, Parola M, Milani S, Leonardiuzzi G, Pastacaldi S, Wenzel UO, Pinzani M, Dianzani MU, Laffi G, Gentilini P. Expression of monocyte chemotactic protein-1 precedes monocyte recruitment in a rat model of acute liver injury, and is modulated by vitamin E. *J Invest Med* 1999; 47: 66-75 [PMID: 10071483]

Lu L, Qian S, Hershberger PA, Rudert WA, Lynch DH, Thomson AW. Fas ligand (CD95L) and B7 expression on dendritic cells provide counter-regulatory signals for T cell survival and proliferation. *J Immunol* 1997; 158: 5676-5684 [PMID: 9190916]

Lu L, Woo J, Rao AS, Li Y, Watkins SC, Qian S, Starzl TE, Demetriss AJ, Thomson AW. Propagation of dendritic cell progenitors from normal mouse liver using granulocyte/macrophage colony-stimulating factor and their maturational development in the presence of type-I collagen. *J Exp Med* 1994; 179: 1823-1834 [PMID: 8195710 DOI: 10.1084/jem.179.6.1823]

Friedman SL. Seminars in medicine of the Beth Israel Hospital, Boston. The cellular basis of hepatic fibrosis. Mechanisms and treatment strategies. *N Engl J Med* 1993; 328: 1828-1835 [PMID: 8502273 DOI: 10.1056/NEJM199306243282508]

Charles R, Chou HS, Wang L, Fung JJ, Lu L, Qian S. Human hepatic stellate cells inhibit T-cell response through B7-H1 pathway. *Transplantation* 2013; 96: 17-24 [PMID: 23756770 DOI: 10.1097/TP.0b013e318294caee]

Yang HR, Hsieh CC, Wang L, Fung JJ, Lu L, Qian S. A critical role of TRAIL expressed on cotransplanted hepatic stellate cells in prevention of islet allograft rejection. *Microsurgery* 2010; 30: 332-337 [PMID: 19774615 DOI: 10.1002/micr.20697]

Jiang G, Yang HR, Wang L, Wildey GM, Fung J, Qian S, Lu L. Hepatic stellate cells preferentially expand allogeneic CD4+ CD25+ Foxp3+ regulatory T cells in an IL-2-dependent manner. *Transplantation* 2008; 86: 1492-1502 [PMID: 19077880 DOI: 10.1097/TP.0b013e318188d13]

Brandão DF, Ramalho FS, Martinelli AL, Zucoloto S, Ramalho LN. Relationship between plasma cells and hepatic stellate cells in autoimmune hepatitis. *Pathol Res Pract* 2010; 206: 800-804 [PMID: 20926203 DOI: 10.1016/j.prp.2010.08.002]

Orlando G, Soker S, Wood K. Operational tolerance after liver transplantation. *J Hepatol* 2009; 50: 1247-1257 [PMID: 19394103 DOI: 10.1016/j.jhep.2009.03.006]

Kruste N, Neumann K, Schrage A, Derkow K, Schott E, Erben U, Kühn A, Loddenkemper C, Zeitz M, Hamann A, Klugewitz K. Priming of CD4+ T cells by liver sinusoidal endothelial cells induces CD25low forkhead box protein 3+ regulatory T cells suppressing autoimmune hepatitis. *Hepatology* 2009; 50: 1904-1913 [PMID: 19787806 DOI: 10.1002/hep.23191]

Carambia A, Freund B, Schwinge D, Heine M, Laschowitz A, Huber S, Wraith DC, Korn T, Schramm C, Lohse AW, Heeren J, Herkel J. TGF-β-dependent induction of CD4+ CD25 Foxp3+ Tregs by liver sinusoidal endothelial cells. *J Hepatol* 2014; 61: 594-599 [PMID: 24798620 DOI: 10.1016/j.jhep.2014.04.027]

Höchst B, Schildberg FA, Böttcher J, Metzger C, Huss S, Türler A, Overhaus M, Knoblich A, Schneider B, Pantelis D, Kurts C, Kalff JC, Knolle P, Diehl L. Liver sinusoidal endothelial cells contribute to CD8 T cell tolerance toward circulating carcinoembryonic antigen in mice. *Hepatology* 2012; 56: 1924-1933 [PMID: 22610745 DOI: 10.1002/hep.23844]
