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The role of mesenchyme-mediated immune control theory in autoimmunity
The paradigm of autoimmune hepatitis in an animal model

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Ο ρόλος της θεωρίας της ανοσιακής επιτήρησης επαγόμενης από τα μεσεγχυματικά κύτταρα στην αυτοανοσία: Το παράδειγμα του μοντέλου αυτοάνοσης ηπατίτιδας σε πειραματόζωα

Περίληψη στο τέλος του άρθρου

It is well-established that the liver is an organ biased to tolerance. The liver tolerance effect is demonstrated mainly by persistent infection by pathogens such as hepatitis B and C viruses (HBV and HCV), as well as *Plasmodium falciparum*, and establishment of metastatic tumors in the liver. Immune tolerance in the liver can, however, be broken, resulting in robust hepatic immunity against pathogens and sometimes immune-mediated liver damage. Immune tolerance to self-antigens in the liver can also break down, leading to autoimmune liver disease. The tolerogenic properties of the liver are also demonstrated by the spontaneous acceptance of liver transplants in many species without the requirement of immunosuppression. Recently an interaction demonstrated between non-hematopoietic non-parenchymal liver cells and T-effector cells gave birth to the concept of a negative feedback mechanism described under the term mesenchyme-mediated immune control (MMIC). According to this theory, liver mesenchymal cells interact with interferon-gamma generated by alloreactive T-effector cells, resulting in up-regulated B7-H1 expression. The interaction between B7-H1 and its ligand leads to the apoptotic death of T-effector cells. The aim of this experimental study was to investigate whether inadequate expression of interferon-gamma and B7-H1 pathways may eventually lead to inadequate interaction between T-effector cells and mesenchymal cells that will in turn result in deficient MMIC.

Key words

Autoimmune hepatitis
Immunity
Liver tolerance
Rejection

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1. INTRODUCTION

The liver provides a unique immunological environment[1–4] because several cell types residing within the liver have the capacity to act as antigen-presenting cells (APCs). Dendritic cells (DC),[5] Kupffer cells,[6] liver sinusoidal endothelial cells (LSEC),[7] hepatic stellate cells (HSC),[8] and also hepatocytes, all present antigens and activate $CD8^+$ T-cells.[9] It is controversial whether intrahepatic $CD8^+$ T-cell activation results in full effector function,[10,11] tolerance by deletion[12] or induction of memory T-cells.[13] The liver endothelium is unique, consisting of fenestrated endothelial cells lining hepatic sinusoids, allowing hepatocytes to contact immune cells directly. The sinusoids contain endothelial cells, Kupffer cells, stellate cells (important in remodeling and fibrosis) and intrahepatic lymphocytes.

The liver also plays a critical role in the first-line host defense against incoming foreign antigens absorbed through the gut into the portal venous system. It must maintain a balance between tolerance to incoming antigens and generation of an immune response. The liver tolerance effect may facilitate persistent infection by pathogens, such as hepatitis B and C viruses (HBV and HCV), as well as *Plasmodium falciparum*, and support the establishment of metastatic tumors in the liver. Immune tolerance in the liver can be effectively broken however, resulting in robust hepatic immunity against pathogens and sometimes immune-mediated liver damage. Immune tolerance to self-antigens in the liver can also break down, leading to autoimmune liver disease. Tolerance is essential for avoiding food allergy, and it explains graft survival of liver transplants across major histocompatibility complex (MHC) antigen differences. Loss of tolerance or development of a hyper-immune response may lead to autoimmunity.

Autoimmune hepatitis (AIH) is a chronic liver disease of unknown pathogenesis, characterized by elevated trans-

aminases, abundant polyclonal immunoglobulin G (IgG) and specific autoantibodies. Histological findings include infiltration of the liver by lymphocytes, plasma cells and macrophages, and characteristic interface hepatitis.[14,15] Infiltration by T-cells and plasma cells, as well as the genetic association with certain human leukocyte antigen (HLA) alleles[16] suggest that dysregulation of the adaptive immune responses causes the disease. Although circulating autoantibodies are the hallmark of AIH[17] and several antibodies against hepatocyte surface antigens have been identified in the AIH setting,[18,19] whether the autoantibodies are integrally involved in the pathogenesis of AIH, and if so, by what mechanism, have not been completely elucidated.

2. EXPERIMENTAL MODELS OF AUTOIMMUNE HEPATITIS

To date, many experimental models of AIH induction have been described.[20–31] Various murine models of liver inflammation have been developed, including transgenic and non-transgenic models. These models have contributed to the elucidation of the mechanisms of disease development and chronicity. Unfortunately, all of the models have limitations, including a preponderance of T-cell-focused responses. Firstly, murine models do not easily develop fibrosis, a hallmark of AIH in humans.[32] In addition, the various different experimental models may not reach the same conclusions, with differences in the immune responses.[32] This multiplicity of responses does not necessarily imply that these models are inappropriate for the study of liver immunology and autoimmune liver diseases, as different autoantigens may induce different liver responses. Knowledge of how the liver differs from other immune organs is essential to furthering the understanding of liver-specific autoimmunity.

One of the most successful models for studying AIH is the model of ovalbumin (OVA) injection in C57BL/6 mice. Specifically, acute hepatitis with lobular and portal infiltrates, and increased serum alanine transferase (ALT) can be induced by the adoptive transfer of naïve transgenic OVA-specific $CD8^+$ T-cells (OT-I), into transgenic mouse expressing the neo-antigen OVA in hepatocytes.[10,33] This severe hepatitis is mediated only by OT-I cells, mainly activated in the liver, but this autoimmune-mediated hepatitis is short-lived and disappears 12–15 days post-immunization. The adoptive transfer of OVA-specific $CD4^+$ T-cells (OT-II) induces no inflammation, because no migration or activation occurs in the liver. When OT-I and OT-II cells are co-transferred, the hepatitis, although transient, is enhanced compared with OT-I-induced hepatitis. In addition, repeated injections of OT-I and OT-II cells induce chronic AIH with focal areas of lobular and portal inflammation up to 3 months post-immunization.[33]

This experimental setting shows that antigen-specific naïve $CD8^+$ T-cells can be activated within the liver, even in a non-inflammatory microenvironment. Conversely, naïve antigen-specific $CD4^+$ T-cells are much less prone to activation by liver antigens under non-inflammatory conditions and display no autonomous cytotoxic effect in the liver, but these cells can enhance the auto-aggressive capacity of $CD8^+$ T-cells when co-transferred. This synergistic effect could be explained by the production of pro-inflammatory cytokines by activated $CD4^+$ T-cells, secondary to $CD8^+$ T-cell activation.[32] The frequency of the initial inflammatory triggers also appears to be an important factor in breaching liver tolerance. Chronic and progressive AIH is not achieved, however, showing that even inflamed livers maintain their suppressive mechanisms to some degree.

Many lessons learned about the mechanisms of peripheral tolerance came from the in depth study of transplant tolerance, and specifically liver transplant (LT) tolerance.

3. LIVER TRANSPLANT TOLERANCE REQUIRES IFN-γ

IFN-γ is an important pro-inflammatory cytokine secreted mainly by T-effector (T-eff) and natural killer (NK) cells during innate and adoptive immune responses.[34] It acts via the specific receptor (IFN-γR) and is closely linked with MHC expression and DC activation to promote allograft rejection.[35] In contrast, Mele and colleagues found that IFN-γ was essential for spontaneous liver allograft acceptance. In wild type (WT) recipients, an early rejection (infiltration by T-cells) was developed that spontaneously regressed (T-cell elimination), permitting long-term survival of liver allografts, whereas no IFN-$\gamma^{-/-}$ recipients survived beyond 2 weeks.[36] Consistently, LT from IFN-$\gamma R^{-/-}$ mice into WT allogeneic recipients were also acutely rejected.[36] Requirement of IFN-γ implies that LT tolerance may be triggered by the host immune response during rejection.

4. THE ROLE OF LIVER NON-PARENCHYMAL CELLS IN IMMUNE REGULATION

Solid organ transplantation across HLA barriers has been successful for decades, but the outcome of cell transplantation (such as islet and hepatocyte transplants) continues to be poor. This is mirrored in animal models. Despite the fact that liver allografts are spontaneously accepted in mice,[4,37] allogenic hepatocyte transplants are

acutely rejected.[38] The inability of hepatocytes to survive rejection turned the scientific thought to the evaluation of the potential role of organ non-parenchymal cells (NPCs) in determining the fate of the allograft (tolerance or rejection).

5. LIVER TRANSPLANT TOLERANCE IS MEDIATED BY GRAFT MESENCHYMAL NON-PARENCHYMAL CELLS

Comparison of WT (tolerance) and IFN-γR$^{-/-}$ (rejection) liver allografts demonstrated that the graft hematopoietic (CD45^{+}) NPCs were rapidly replaced by cells of recipient origin following transplantation, whereas the CD45^{-} population continued to be of donor origin, even in long-term surviving grafts. In other words, in the IFN-γR$^{-/-}$ graft, the hematopoietic NPCs were quickly replaced by IFN-γR$^{+/+}$ cells, while the mesenchymal (CD45^{-}) NPCs remained IFN-γR$^{-/-}$, suggesting that the fate of liver allograft is unlikely to be determined by graft hematopoietic NPCs, whereas mesenchymal NPCs may play an important role in this IFN-γ-dependent transplant tolerance. This was supported by the finding that mesenchymal NPCs isolated from liver grafts inhibited the T-cell proliferative response to a marked degree.[39]

6. LIVER TRANSPLANT TOLERANCE REQUIRES AN INTACT IFN-γ SIGNALING

CD45^{-} NPCs from IFN-γR$^{-/-}$ grafts largely lose their inhibitory activity, indicating that their immunosuppressive activity requires intact IFN-γ signaling.[39] The direct evidence of liver NPCs being capable of inducing T-eff cell apoptosis was obtained by addition of CD45^{-} liver NPCs into the MLR cultures in which the H2^{b} specific CD8^{+} T-cells were elicited by B6 DC, resulting in marked inhibition of T-cell proliferation, and increase in apoptosis in the dividing CD8^{+} specific T-cells, while these changes were markedly attenuated in the IFN-γR$^{-/-}$ group, indicating the importance of the IFN-γ signaling pathways.[39]

IFN-γ signaling controls many downstream effector molecules such as CD-40, CD-86 and B7-H1. B7-H1 expressed on mesenchymal NPC plays a critical role in immune tolerance via ligation to its receptor, PD-1, which is highly expressed on activated T-cells, resulting in their apoptosis.[40,41] B7-H1$^{-/-}$ liver allograft in WT recipients was acutely rejected despite the replacement of graft CD45^{+} NPCs with recipient origin B7-H1$^{+/+}$ cells.[39] This was further confirmed using a chimeric model in which CD45^{-} NPCs remained B7-H1$^{-/-}$, whereas CD45^{+} NPCs were B7-H1$^{+/+}$. The chimeric liver graft was acutely rejected.[39] Induction of B7-H1 expression on CD45^{-} NPCs is dose-dependent on IFN-γ stimulation, resulting in enhanced inhibition of activated T-cells.[39,41,42] Blockade of PD-1/B7-H1 ligation with anti-B7-H1 or anti-PD-1mAb brakes spontaneous allograft acceptance.[41] These findings highlight the mandatory role of B7-H1 for the induction of LT tolerance.

Overall, the requirement of IFN-γ suggests that the alloreactive response is an absolute requirement for induction of transplant tolerance, and that rejection triggers the process of operational tolerance.

7. THE ROLE OF IMMUNOSUPPRESSOR CELLS IN LIVER TRANSPLANT TOLERANCE

The inflammatory microenvironment elicits the recruitment of MDSCs into the liver allograft, including both granulocyte and monocyte-MDSC populations, which are assumed to contribute to LT tolerance through a variety of mechanisms, such as inhibition of T-cell (both CD4^{+} and CD8^{+} T-cells) proliferation *in vitro* and *in vivo* after interaction with liver stromal cells.[43–45] The generation of Tregs in the liver allograft begins with the action of APCs, with the main player being the HSCs in the presence of IFN-γ.[3] Tregs are increased in liver allografts in both early and prolonged survival grafts.[46,47] They appear to be important in the induction of tolerance since their selective depletion abrogates tolerance by concomitant increases in CD4^{+} and CD8^{+} T-cell responses, with reduced apoptosis of graft-infiltrating T-cells.[46,47] The role of IFN-γ signaling in MDSCs was examined by evaluating the presence and increase of CD11b^{+}Gr^{+} populations in both WT and IFN-γR1$^{-/-}$ liver allografts, compared to syngeneic controls.[39] Both demonstrated an increased suppressive capacity in one-way MLR on both CD4^{+} and CD8^{+} T-cells,[39] a finding that was independent of the origin of the cells (WT or IFN-γR1$^{-/-}$ liver allograft). These data indicate that IFN-γ signaling is not required for enhancement of MDSCs in liver grafts. Moreover, inhibition of MDSC generation in an IFN-γ$^{-/-}$ environment was associated with impaired generation of Tregs,[45] indicating a strong correlation between MDSCs and Tregs expansion.

Comparing the tolerance (WT) with rejection (IFN-γR$^{-/-}$) liver allografts, the number of MDSCs and Tregs were found equally increased in the early postoperative period, while elimination of the graft infiltrating T-eff cells was markedly enhanced in tolerant (WT) grafts compared with rejecting (IFN-γR$^{-/-}$) ones.[39] This highlights the fact that the increase of immune suppressive cells does not necessarily lead to tolerance when it is not combined with elimination of T-eff cells. The enhancement of Tregs and MDSCs alone in the early post-transplant period is not sufficient

to induce LT tolerance, while eliminating the alloreactive T-eff cells is critical.[39] This is supported by the finding that administration of Tregs alone cannot prolong the survival of fully MHC-mismatched islet allografts when administered intravenously.[48]

Recently, the role of Tregs was evaluated in the setting of experimental AIH. Specifically, An Haack and colleagues[20] investigated the impact of Tregs in the OVA-induced model of AIH. Tregs isolated from inflamed livers of HepOVA mice were tested for their functionality *in vitro*. By employing double transgenic (OVA and FoxP3) mice, they analyzed whether Tregs depletion aggravates autoimmune inflammation in the liver *in vivo*. They demonstrated that $CD25^+Foxp3^+$ $CD4^+$ T-cells accumulated in the liver in the course of $CD8^+$ T-cell-mediated hepatitis. Tregs isolated from inflamed livers were functional in suppressing CD8 T-cell proliferation *in vitro*.[20] Moreover, depletion of Tregs dramatically amplified T-cell-mediated hepatitis.[20]

8. MESENCHYME-MEDIATED IMMUNE CONTROL IN TRANSPLANT TOLERANCE

As described above, transplant tolerance can be achieved in many solid organs, such as kidney and heart, with the incidence of the phenomenon prevailing in the liver transplant setting. Liver is an immunoprivileged organ biased towards tolerance. There are many theories for this vital property. First, transplant tolerance could be attributed to continuous exposure to antigens via the portal vein which promotes the expression of a set of cytokines, antigen-presenting molecules and co-stimulatory signals that impose T-cell inactivation, partly via effects on liver APCs.[49–51] This property facilitates the maintenance of liver homeostasis, but with a concomitant price being paid; that of vulnerability to viral infections and autoimmune diseases. Due to its unique architecture and vasculature, liver may be the only organ in which recirculating naïve or activated T-cells come into direct contact with parenchymal and non-parenchymal cells. This could occur in the space of Disse, where lymphocytes circulating in the blood enter via fenestrated endothelial cells and can interact directly with NPCs. The presence of the fenestrations and the low blood flow within them, may offer longer interaction between activated T-cells and NPCs that could be vital for the liver microenvironment to develop homeostatic mechanisms against T-cell-induced tissue injury.

This interaction between non-hematopoietic NPCs and T-eff cells leads to the generation of a negative feedback mechanism well described by the term mesenchyme-mediated immune control (MMIC).[39] According to this mechanism, liver MSCs interact with IFN-γ originating from the alloreactive T-eff cells, via the IFN-γ-IFN-γR complex, resulting in up-regulated B7-H1 expression through the JAK-STAT pathway. The interaction between B7-H1 and PD-1 generates the apoptotic death of T-eff cells. In addition, MSCs induce the generation of MDSCs and Tregs that facilitate tolerance induction by a suppressive effect on T-eff cells.[39] The main principles of this theory are the presence of T-eff cells in liver allograft that initiate a rejection process and produce IFN-γ, the presence of an intact IFN-γ pathway, the appropriate interaction, number and function of liver MSCs, the presence of an intact B7-H1-PD-1 pathway and the efficacy of suppressive cells (MDSCs and Tregs) on T-eff cells.

According to this theory, the difference in the spontaneous tolerance rate between the liver and other solid organs could be attributed to the adequacy of MSCs in liver tissue that, in turn, could contribute to higher MMIC capacity. Additionally, this theory could offer a possible explanation as to why some liver allografts are spontaneously accepted and others are finally rejected. Since both settings begin with rejection, the presence of an intact and functional cascade of MMIC activity would eventually lead to tolerance. As each allograft recipient is a unique case and each allograft is a unique microenvironment, the need to establish biomarkers to identify which recipient/allograft will be spontaneously tolerated or rejected is mandatory, in order to achieve longer allograft survival without the burden of life-time immunosuppression (IS).

A similar scenario appears to apply to cell transplantation, which is known to have poor results probably due to lack of appropriate MSCs to mediate MMIC activity. The improvement of islet transplants by co-transplantation with HSCs[52,53] represents an endeavor to harness MMIC activity. Beyond a role as APCs, HSCs act as bystanders to the activation of MDSCs and Tregs, which both present a suppressive action on T-eff cells.

9. MESENCHYME-MEDIATED IMMUNE CONTROL MAY CONTRIBUTE TO PERIPHERAL TOLERANCE

It is well established that thymic negative selection most effectively deletes T-cell precursors via TCRs with a high affinity for self-antigens (above-threshold affinity).[3] On the other hand, below-threshold or at-threshold affinity antigens do not induce negative selection *in vivo*, escape central tolerance mechanisms and populate the secondary lymphoid organs.[54] These cells have the potential to cause tissue injury unless they are deleted or effectively inactivated in the periphery.[3] A high frequency of just above affinity

threshold self-reactive T-cells in the peripheral repertoire correlate with the susceptibility to develop autoimmune disease.[54] The absolute number of these cells is crucial, since a minimum number of antigen-specific T-cells need to be present to evoke the immune response. In the presence of fewer than the quorum number of above threshold T-cells, it may be extremely difficult to induce an autoimmune disease. Just above affinity threshold T-cells are more likely to exceed the quorum number in the periphery.[54] For this reason, these cells have the highest autoimmune potential.

According to our hypothesis, MMIC theory could possibly explain the cascade of mechanisms that lead to peripheral tolerance, and this could have a wide range of explanations and applications in the field of viral infections, autoimmune disease and tumor microenvironment. When below or just above affinity threshold self-reactive T-cells encounter antigens in the periphery, an interaction with the production of inflammatory cytokines, such as IFN-γ, is generated, that in turn triggers tissue mesenchymal cells, resulting in expression of B7-H1, inducing apoptosis in autoimmune T-eff cells. Finally, the production of soluble factors[45,55] promotes generation of MDSC and Tregs that demonstrate a suppressive effect on these cells. Thus, peripheral tolerance is established.

10. HYPOTHESIS

The aim of this experimental study is to investigate whether inadequate expression of IFN-γR and B7-H1 pathways may eventually lead to inadequate interaction between T-eff cells and MSCs, which in turn will lead to deficient MMIC. Thus, in the HepOVA mouse model of AIH, it is expected greater acute liver damage in HepOVA B7-H1$^{-/-}$ and/or HepOVA IFN-γR$^{-/-}$ mice compared with HepOVA mice in terms of serum ALT level and histologically confirmed tissue damage.

11. MATERIAL AND METHOD

HepOVA mice express OVA under the transferrin promoter in hepatocytes. Transfer of naïve antigen-specific OT-I T-cells into HepOVA mice leads to their activation in the liver and to transient hepatitis.

11.1. Mice and antibodies

HepOVA transgenic mice on the C57BL/6 background, which selectively express membrane-bound OVA on hepatocytes are developed as previously described.[33] Eight- to 12-week male HepOVA mice and age matched OT-I and OT-II mice (Jackson Laboratory, ME) will be used in all studies.

11.2. Induction of autoimmune hepatitis

3×10^6 OT-I and 5×10^6 OT-II T-cells with 1.5×10^6 DC in 0.3 mL will be injected via the penile vein (day 0). Serum for ALT levels will be collected at day 3. At day 5, livers and serum will be collected. Serum ALT levels will be measured by an automatic biochemical analyzer.

11.3. Isolation of liver non-parenchymal cells

Mouse liver NPCs will be isolated by collagenase digestion and centrifugal elutriation. Briefly, the liver is perfused *in situ* via the inferior vena cava with buffered collagenase solution (type IV, 1 mg/mL in HBSS; Sigma Chemical Co, St Louis, MO). The liver will be then removed, diced, and digested with collagenase at 37 °C for 30 min. The liver specimens used will demonstrate normal lobular hepatic architecture, without evidence of fibrosis. Similarly, liver tissue will be meshed and agitated in collagenase IV. Cells will be filtered through a nylon mesh. Parenchymal cells (hepatocytes) will be removed using a low speed centrifugation (50 g). NPC will be further separated from parenchymal cells via Percoll (Sigma) gradient centrifugation. The isolated NPC demonstrate greater than 95% cell viability, estimated by trypan blue exclusion, and less than 5% hepatocyte contamination, determined by morphological examination. CD45$^-$ NPC will be selected using anti-CD45 mAb beads (Miltenyi Biotec, San Diego, CA).

11.4. Mixed leukocyte reaction

One-way mixed leukocyte reaction culture will be performed in triplicate in 96-well round-bottom microculture plates (Corning, NY). Nylon wool-eluted spleen T-cells (2×10^6/well) from OT-I (CD8$^+$, MHC K^b Class I restricted) and OT-II (CD4$^+$ MHC I-A^b Class II restricted) mice will be used as responders. T-cell proliferation will be elicited by DC (B6) at a T:DC ratio of 10:1 or indicated. Cultures will be maintained in RPMI-1640 complete medium, for 3 days in 5% CO_2 in air. T-cell proliferative response will be determined by CFSE dilution assay analyzed by flow cytometry.[56]

11.5. Dendritic cells isolation

BM cells harvested from femurs of B6 mice will be cultured in 24-well plates (2×10^6/well) in 1 mL RPMI 1640 (Life Technologies, Gaithersburg, MD) supplemented with 10 ng/mL mouse GM-CSF+1,000 U/mL rIL-4 (Schering-Plough, Kenilworth, NJ). The selection and purification procedure will be performed at day 3.

11.6. Flow cytometric analysis

Antibodies against CD4, CD8, CD11b, CD11c, CD25, CD31, CD40, CD45 CD86, CD146, Gr-1, H-2Kb, H-2Kk, and I-Ab, IFN-γR or annexin V purchased from BD PharMingen (San Diego, CA), and against B7-H1/FoxP3 from eBioscience (San Diego, CA) will be used. For CFSE labeling, T-cells (10^7/mL) will be incubated with 3 μM CFSE (10 mM concentration, Molecular Probes, Eugene, OR) for 10 min

at room temperature. The isotype and species matched irrelevant mAbs will be used as controls. Flow analysis will be performed with a BD FACS Calibur flow cytometer (BD Biosciences).

11.7. Immunohistochemistry

Immunofluorescence staining protocols will be used for CD4, CD8 and B7-H1 staining in cryostat sections using anti-mouse specific mAb (BD PharMingen). The isotype and species matched irrelevant mAbs will be used as controls. The color will be developed by an enzyme reaction using avidin-biotin-alkaline phosphatase complex (ABC) as the substrate. To detect apoptosis, sections will be stained for TUNEL, using an *in situ* apoptosis detection kit (EMD Millipore, Billerica, MA) according to the manufacturer's instructions. For quantification, the positive cells will be counted on a microscope and a total of 30 high-power fields will be randomly selected in each group.

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ΠΕΡΙΛΗΨΗ

Ο ρόλος της θεωρίας της ανοσιακής επιτήρησης επαγόμενης από τα μεσεγχυματικά κύτταρα στην αυτοανοσία: Το παράδειγμα του μοντέλου αυτοάνοσης ηπατίτιδας σε πειραματόζωα

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Είναι σαφές πλέον στη διεθνή βιβλιογραφία ότι το ήπαρ είναι ένα όργανο προσανατολισμένο στην ανοσιακή ανοχή. Παραδείγματα της εν λόγω ιδιότητας αποτελούν οι χρόνιες λοιμώξεις του ήπατος, όπως οι ηπατίτιδες Β και C, καθώς και ο τροπισμός των μεταστατικών όγκων στο ήπαρ. Διαταραχές αυτής της ανοχής μπορεί να οδηγήσουν σε αδυναμία της ανοσιακής επιτήρησης και στην ανάπτυξη αυτοάνοσων διαταραχών. Οι ιδιότητες ανοχής του ήπατος φαίνονται και από την αυτόματη αποδοχή ηπατικών μοσχευμάτων χωρίς την ανάγκη για ισόβια ανοσοκαταστολή. Πρόσφατα βρέθηκε ότι η αλληλεπίδραση των μη παρεγχυματικών κυττάρων του ήπατος με τα ενεργοποιημένα Τ-λεμφοκύτταρα οδήγησε στη διαμόρφωση μιας θεωρίας παλίνδρομης ρύθμισης, υπό τον όρο ανοσιακή επιτήρηση, επαγόμενης από τα μεσεγχυματικά κύτταρα. Σύμφωνα με τη σχετική θεωρία, τα ηπατικά μεσεγχυματικά κύτταρα αλληλεπιδρούν με την επαγόμενη από τα ενεργοποιημένα Τ-λεμφοκύτταρα, IFN-γ, με συνέπεια την ενεργοποίηση του B7-H1 μονοπατιού. Η ενεργοποίηση του τελευταίου θέτει σε λειτουργία τον προγραμματισμένο κυτταρικό θάνατο των ενεργοποιημένων Τ-λεμφοκυττάρων. Σκοπός του παρόντος πρωτοκόλλου ήταν η μελέτη του ρόλου της ανοσιακής επιτήρησης επαγόμενης από τα μεσεγχυματικά κύτταρα σε πειραματικό μοντέλο αυτοάνοσης ηπατίτιδας.

Λέξεις ευρετηρίου: Ανοσιακή ανοχή, Απόρριψη, Αυτοάνοση ηπατίτιδα, Ηπατική ανοχή

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