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Review

Transplant Immunology in Liver Transplant, Rejection, and Tolerance

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Abstract: Liver transplantation is the most effective treatment for end-stage liver disease. Despite improvements in surgical techniques, transplant rejection remains a significant concern. The liver is considered an immune-privileged organ due to its unique microenvironment and complex interactions among various cell types. Alloimmune responses mediated by T cells and antigen-presenting cells (APCs) play crucial roles in transplant rejection. The liver's dual blood supply and unique composition of its sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), hepatocytes, and hepatic stellate cells (HSCs) contribute to its immune privilege. Alloantigen recognition by T cells occurs through direct, indirect, and semidirect pathways, leading to acute cellular rejection (ACR) and chronic rejection. ACR is a T cell-mediated process that typically occurs within the first few weeks to months after transplantation. Chronic rejection, on the other hand, is a gradual process characterized by progressive fibrosis and graft dysfunction, often leading to graft loss. Acute antibody-mediated rejection (AMR) is less common following surgery compared to other solid organ transplants due to the liver's unique anatomy and immune privilege. However, when it does occur, AMR can be aggressive and lead to rapid graft dysfunction. Despite improvements in immunosuppression, rejection remains a challenge, particularly chronic rejection. Understanding the mechanisms of rejection and immune tolerance, including the roles of regulatory T cells (Tregs) and hepatic dendritic cells (DCs), is crucial for improving transplant outcomes. Strategies to induce immune tolerance, such as modulating DC function or promoting Treg activity, hold promise for reducing rejection and improving long-term graft survival. This review focuses on the liver's unique predisposition to rejection and tolerance, highlighting the roles of individual cell types in these processes. Continued research into the mechanisms of alloimmune responses and immune tolerance in liver transplantation is essential for developing more effective therapies and improving long-term outcomes for patients with end-stage liver disease.

Keywords: liver transplant; transplant immunology; rejection and tolerance

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Citation: Yokoyama, M.; Imai, D.; Wolfe, S.; George, L.; Sambommatsu, Y.; Khan, A.A.; Lee, S.D.; Saeed, M.I.; Sharma, A.; Kumaran, V.; et al. Transplant Immunology in Liver Transplant, Rejection, and Tolerance. *Livers* **2024**, *4*, 420–434. https://doi.org/10.3390/livers4030031

Academic Editor: George Therapondos

Received: 1 May 2024
Revised: 9 August 2024
Accepted: 2 September 2024
Published: 9 September 2024

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1. Introduction

Liver transplantation remains the most effective treatment for end-stage liver disease. However, despite advances in surgical techniques, the risk of transplant rejection persists as a significant challenge [1].

The liver's immune-privileged status, arising from its distinctive microenvironment and intricate cellular interactions, contributes to this complexity. Alloimmune reactions orchestrated by T cells and antigen-presenting cells (APCs) play pivotal roles in rejection phenomena. The liver's dual vascular supply and the presence of specialized cells, including liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), hepatocytes, and hepatic stellate cells (HSCs), contribute to its immune privilege [2]. T cell recognition of alloantigen occurs via direct, indirect, and semidirect pathways, leading to acute cellular

rejection (ACR) and chronic rejection. While acute antibody-mediated rejection (AMR) is less common due to the liver's unique anatomy and immune-privileged status, it can manifest aggressively. Despite improvements in immunosuppressive strategies, rejection remains a formidable obstacle, particularly chronic rejection, which can precipitate graft loss [3–7].

A comprehensive understanding of rejection mechanisms and immune tolerance, including the roles of regulatory T cells (Tregs) and hepatic dendritic cells (DCs), is crucial for enhancing transplant outcomes. Strategies aimed at inducing immune tolerance, such as modulating DC function or augmenting Treg activity, hold promise in reducing rejection occurrences and improving long-term graft viability.

This review delineates the liver's unique predisposition to rejection and tolerance, highlighting the roles of individual cell types in these processes. Continued research in this field is essential for developing more effective therapies and improving long-term outcomes for patients with end-stage liver disease.

2. Types of Rejection

Allograft rejection can lead to permanent liver damage, ultimately resulting in graft failure. Rejection can manifest in various clinical forms, such as hyperacute rejection, acute cellular rejection (ACR), acute antibody-mediated rejection (AMR), and chronic rejection. Hyperacute rejection represents an exceedingly aggressive form of antibody-mediated graft injury, typically occurring immediately following ABO-incompatible liver transplantation [7]. While hyperacute antibody-mediated rejection, which occurs due to recipient antibodies against the donor's major histocompatibility complex (MHC), has been documented, it is considered rare in the context of liver transplantation. The frequency of acute and chronic rejection has decreased due to advancements in immunosuppression therapies for liver transplant recipients. ACR is the most common type of allograft injury, typically occurring within the initial 3 months post-liver transplantation. It impacts 15–25% of liver transplant recipients receiving tacrolimus-based immunosuppression and often responds well to steroid treatment [3–6]. ACR occurs when recipient T cells identify and react against donor alloantigens. The transplantation of MHC-incompatible tissues triggers a T cell-mediated immune response that can damage the donor tissues. After being internalized by donor and recipient antigen-presenting cells (APCs), donor MHC molecules are processed and presented to T cells as MHC peptide fragments following intracellular processing. APCs also deliver a second signal that can activate the T cell or induce anergy if inhibitory. On the other hand, viral infections (e.g., CMV) can disrupt this state of anergy. T cells can recognize alloantigens through various pathways. In the direct pathway, recipient T cells identify allogeneic MHC molecules on the surface of donor APCs. In the indirect pathway, recipient APCs process and present MHC peptides shed by donor cells to recipient T cells. Additionally, in the semi-direct pathway, recipient APCs acquire intact MHC molecules through direct contact with donor APCs and present them to T cells via T cell receptors [8–10]. ACR is characterized by a rapid decline in allograft function, and biopsy typically shows infiltration of T cells and other leukocytes, along with signs of ductular injury and endothelial inflammation [11]. Inadequate adherence to immunosuppressive medications is a major cause of late rejection [12]. Banff Classification [13] has been used for histological diagnosis and grading of T cell-mediated rejection (TCMR), which assesses three primary histological dimensions. The rejection activity index grades the histological severity of TCMR through a semiquantitative evaluation of these features [14,15]. Effective combinations and high doses of immunosuppressive medications could potentially diminish the window of opportunity for immune recognition of the liver graft, especially in the early stages of transplant surgery. This approach might eventually result in tolerance or the minimal long-term immunosuppression requirement. However, TCMR can occasionally manifest in the later phases, and it tends to be more severe and less responsive to steroid treatment. Acute AMR, previously referred to as humoral rejection, is rare, occurring in less than 1% of liver transplant recipients [16,17].

This finding is attributed to numerous factors, including the liver's dual blood supply, which lowers the sinusoidal flow rate and expression of human leukocyte antigen (HLA) class II antigens. In addition, certain cells maintain a network to negatively modulate the immune system through variations in gene expression, microenvironment, and surface markers [16–18]. The presence of ABO incompatibility or a positive cross-match does not necessarily rule out liver transplantation, as the liver can effectively eliminate donor-specific antibodies (DSAs). Although the risk of AMR may be higher in the settings of extremely high levels of pre-existing DSAs (with a mean fluorescence intensity exceeding 15,000), the majority of liver transplant recipients in such situations do not experience graft injury [19]. Even though routine screening for donor-specific antibodies (DSAs) is generally not recommended before liver transplant, it may be considered in specific situations, such as women with a history of prior pregnancies, retransplantation, or before proceeding with aggressive minimization of immunosuppression [20]. It is essential for the diagnosis of AMR to have high mean fluorescence intensity of DSAs and to exclude other causes of graft dysfunction. According to a retrospective study, acute AMR was found in 20% of these highly selected cases if they tested positive for DSAs [16]. In 2016, the Banff Working Group announced four diagnostic criteria for AMR [21]. Those included histopathologic disruption consistent with acute AMR, positive serum DSA, dispersed C4d deposits in microvasculature, and exclusion of other pathologies with a similar presentation. However, some cases do not include all four criteria, especially when co-present with TCMR [22], making identification difficult. Thus, the criteria should be developed to link allograft dysfunction with histological findings in order to correlate with both the frequency and severity of rejection injuries in addition to predicting therapeutic efficacy [18]. Acute AMR that includes severe allograft injury is usually challenging to treat, rarely responding to steroids. In addition, the determination of HLA class I and II molecules through DSA analysis is another important step in making a diagnosis. Most of the time, the focus is on anti-HLAs, but DSAs can target class I or II HLA or non-HLA antigens, such as the angiotensin II type 1 receptor [23]. While there are no official criteria for the mean fluorescence intensity (MFI) during rejection, some consensus shows an MFI of >3000–5000 to be predictive [22]. While chronic rejection (CR) is characterized as a long-term process that typically develops months to years after liver transplantation, its definition does not specify a particular timeframe. CR can manifest within a few months post-transplant and has the potential to cause graft failure within the initial year following liver transplantation [21,24,25]. CR can arise due to insufficient treatment of recurrent episodes of TCMR or from a single severe episode of AMR [26]. It typically manifests as a gradual onset of cholestatic graft dysfunction and can ultimately lead to graft failure [24]. Most consensus confirms that the rate of chronic AMR following transplant is unknown. Most patients have regular liver function following surgery, albeit some grafts are damaged [27,28]. In order to predict a likely chronic AMR, four criteria are used, including corresponding histology (see "Mechanism of Rejection"), the presence of serum DSA before 3 months post-biopsy, local C4d (>10% in portal tracts, unlike the widespread deposits of C4d in acute AMR), and exclusion of similar pathologies [21]. Even with these standards, some cases are complicated by the presence of TCMR. TCMR is often accompanied by DSA, making the diagnosis of chronic AMR more challenging [22]. The frequency of CR in liver transplant patients varies from 3 to 17%. Compared to earlier cyclosporin-based regimens, several studies reported that tacrolimus-based protocols reduced the occurrence of CR [21,24]. Chronic rejection represents an irreversible state [24]. Potent immunosuppressive therapy might decelerate the disease's natural course, underscoring the critical need for early detection to forestall advancing fibrosis and graft failure [26].

3. Mechanism of Rejection

Upon the receipt of donor liver tissue following a liver transplant, new surface molecules including major histocompatibility complex (MHC) or human leukocyte antigens (HLA) are introduced to the recipient immune system. These molecules are then displayed in a variety of locations by antigen-presenting cells (APCs). Thus, a primary trigger of graft rejection in liver transplants includes improper HLA or MHC matches.

Upon encountering an alloantigen, activated helper T cells (Th) secrete cytokines such as TNF-α, IFN-γ, and IL-2, amplifying the innate immune responses. Concurrently, they activate effector CD4 T cells and cytotoxic CD8 T cells, inducing the expression of granzyme and perforin, which in turn target the liver graft (Figure 1). In addition to cell-mediated acute rejection, the humoral immune response mediated by donor-specific antibodies (DSA) plays a pivotal role in hyperacute and chronic rejections. DSA-mediated rejection is instigated by and acts in concert with T cell-mediated alloimmunity [2,29,30]. Multiple studies have shown that either allograft rejection or graft-versus-host disease (GvHD) are associated with elevated levels of memory T cells or stem-like memory T cells in both human and animal models. Stem-like memory T cells possess the ability not only to regenerate the complete spectrum of memory and effector T cell populations but also to sustain their pool size through self-renewal [31–33]. Hence, donor antigen-specific memory T cells pose a significant barrier to inducing tolerance successfully. Tissue-resident memory (TRM) T cells are recently identified lymphocyte lineage that occupies tissues without recirculating. They provide a first response against pathogens or antigens reencountered in peripheral non-lymphoid tissues such as the liver, gut, and skin. Since TRM cells are absent from peripheral blood, they remain poorly characterized. However, they exhibit unique transcriptional, phenotypic, and functional profiles, distinguishing them from recirculating central and effector memory T cells [34]. Studies have indicated the presence of donor-derived TRM cells in liver allografts, with their abundance potentially linked to organ survival and decreased rejection rates [35–37]. Specifically, the prolonged presence of donor-derived TRM cells in lung tissue is associated with a lower occurrence of clinical events leading to allograft injury, such as primary graft dysfunction (PGD) and acute cellular rejection (ACR) [38]. Yet, the association between liver donor-derived TRM cells and the occurrence of rejection requires further investigation [36]. In liver allograft tissues, around 2–6% of CD8+ T cells exhibited a donor-derived TRM phenotype at 11 years post-transplantation [39], indicating the long-term persistence of human liver TRM cells. In the transplant setting, the development of adaptive immunity to allografts hinges on the formation of immune memory, which is triggered by recognizing alloantigens and eliciting responses from alloreactive T cells [40]. It is important to note that the alloimmune response differs from the immune response to classical pathogenic antigens due to the high diversity of the alloreactive repertoire, particularly within the naïve T cell subpopulation, as demonstrated previously using next-generation sequencing (NGS) technology [41]. Each T cell clone possesses a distinctive identity conferred by the T cell receptor (TCR), with approximately 2.5×10^7 TCRs present in human naïve T cells in each individual. It is estimated that the TCR repertoire specific to a particular allogeneic major histocompatibility complex (MHC) haplotype constitutes less than 10% of the total TCR repertoire [40]. Consequently, the initial recognition of the alloantigen is a crucial first step that determines the subsequent immune response or tolerance induction in the context of transplantation. Recognition of the alloantigen by host T cell receptors (TCRs) can occur through three major pathways: direct, indirect, and semidirect (Figure 2), which involves the cross-dressing of graft major histocompatibility complex (MHC) molecules by host DCs [40]. The semidirect pathway is discussed separately. Direct recognition occurs when allograft APCs present the alloantigen directly to host CD8 T cells using their own MHC class I molecules and to host CD4 T cells using allograft MHC class II molecules. This form of recognition proceeds as direct recognition of intact antigens (proteins) without the need for antigen processing. Direct recognition of the alloantigen is considered the primary pathway leading to transplant rejection and is associated with the passenger

leukocyte theory. The term 'passenger leukocytes' encompasses all graft-derived immune cells that are transferred to the recipient's secondary lymphoid tissue, initiating allograft rejection through the direct recognition of alloantigens [42–44]. However, the precise role of passenger leukocytes in either allograft rejection or tolerance induction remains unclear. In rodent models, irradiation of the allograft before operation leads to the destruction of graft lymphocytes and subsequent transplant rejection in recipients that would otherwise be tolerant. This indicates a potential role for donor-derived graft-resident lymphocytes in inducing tolerance [45–47]. However, within months following liver transplantation, the majority of donor lymphocytes are replaced by hematolymphoid cells derived from the recipient's bone marrow [48–50]. Despite this replacement, direct recognition of the alloantigen by CD4 T cells existed during the early stages post-transplantation and was strongly associated with the lifespan of DCs [51]. The indirect recognition of alloantigens is associated with both acute and chronic transplant rejection. In this process, host APCs internalize and convert the alloantigen into peptide fragments. These fragments are then displayed with host MHC molecules and identified by the TCR repertoire of host T cells. In solid organ transplantation, CD4 T cell responses resulting from the indirect recognition pathway are considered more relevant to allograft rejection than CD8 T cell responses. This is because the expression of host MHC class I antigen epitopes in vascularized allografts is relatively low [52,53]. The indirect pathway plays a primary role in CD4 T cell responses, predominantly involving self-restricted, processed alloantigens. This pathway is believed to be particularly relevant in the late phase of transplant rejection, providing assistance for cytotoxic T cells and humoral immunity [54–57]. T cell-mediated rejection (CMR) is prevalent in the majority of AMR cases [58]. The mechanism underlying AMR of liver allografts has been proposed as a "two-hit" hypothesis. An initial attack on the allograft, such as T cell-mediated rejection (TCMR), viral hepatitis, hepatic ischemia, or ischemic reperfusion injury, leads to an upregulation of HLA class II expression. This facilitates the binding of donor-specific antibodies (DSA) and activates the classical complement cascade through the binding of the C1 complex [59]. The complement system can play a role in liver graft injury by opsonizing liver cells. During this process, C4d and C3d attach to the cells, signaling them for removal by the innate immune response. Furthermore, anaphylatoxins such as C3a and C5a serve as strong chemotactic signals, drawing inflammatory cells that contribute to tissue damage. The membrane attack complex (MAC), composed of C5b-9, disrupts cell membranes, resulting in cell injury (Figure 3). Moreover, DSAs can bind to MHC molecules. This process promotes the recruitment of innate immune cells such as neutrophils, macrophages, and NK cells [22,60].

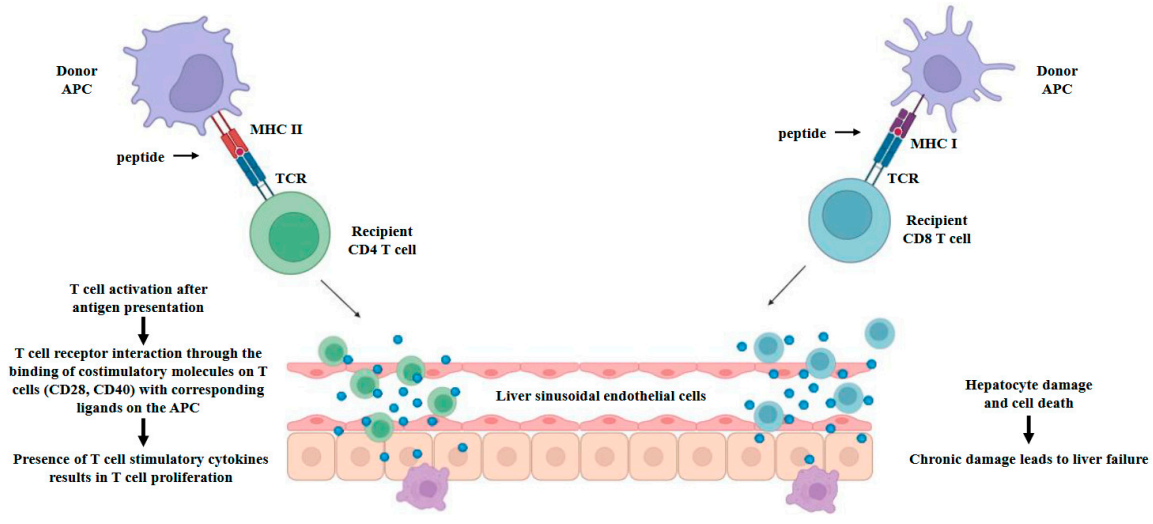

Figure 1. Immunological basis of T cell-mediated rejection.

The complement activation in antibody-mediated rejection is the activation of the classical pathway starting from C1q after DSA binds to donor antigens on the endothelial cell membrane. The complement system can harm the liver graft via multiple mechanisms: (a) opsonization, where C4d and C3d attach to liver cells, marking them for destruction by the innate immune system; (b) anaphylatoxin production, where C3a and C5a act as potent chemotactic agents, attracting inflammatory cells and causing tissue damage; (c) the membrane attack complex (MAC), where C5b-9 creates pores in cell membranes, leading to cellular injury.

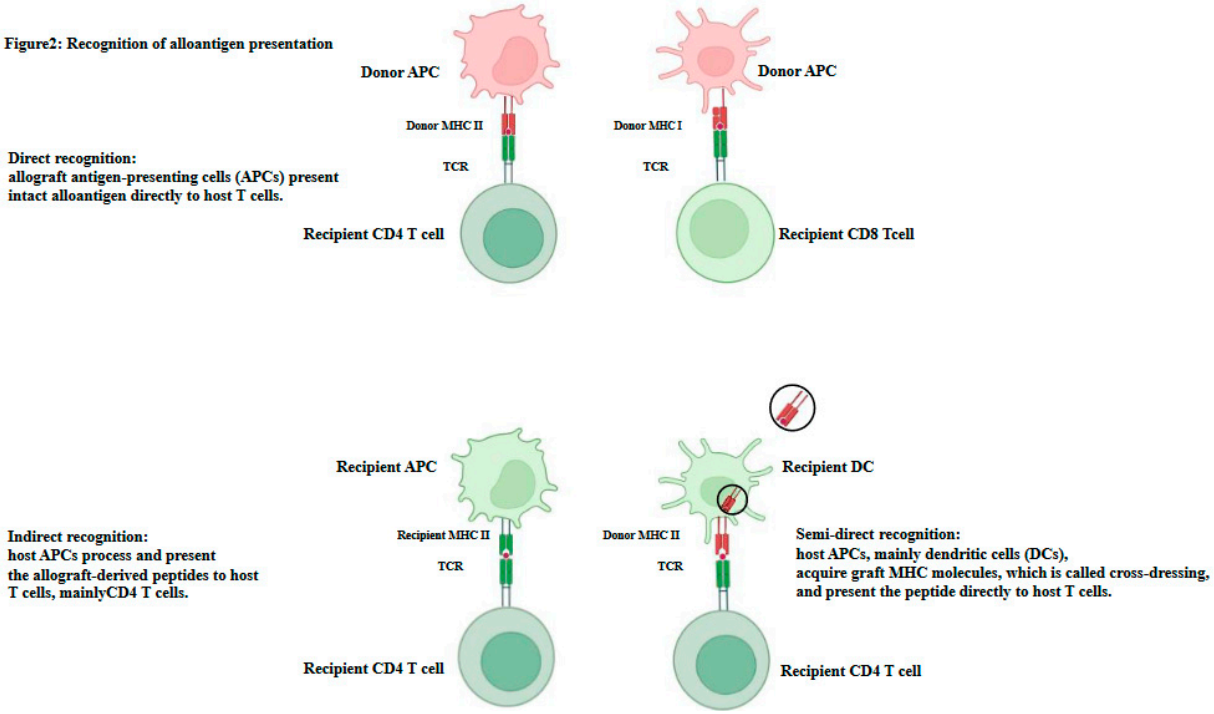

Figure 2. Recognition of alloantigen presentation.

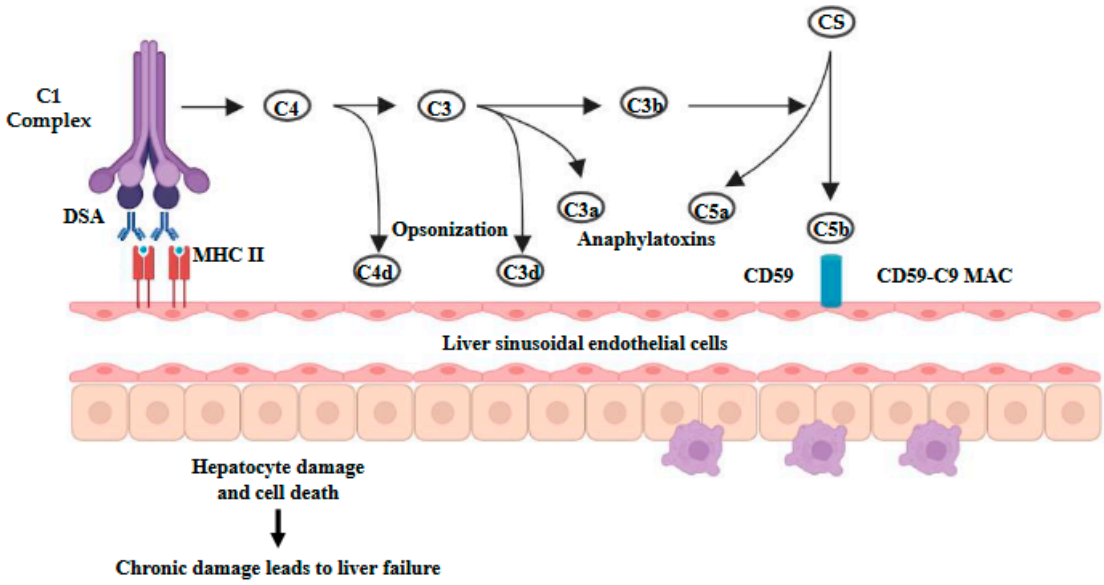

Figure 3. Pathways of antibody-mediated rejection.

4. Tolerance

Consensus in research reveals the significant roles of immune cells in immune tolerance. Up to 75% of the liver's blood supply flows from the portal vein, which collects flow from both the gastrointestinal tract and spleen. Hence, portal blood flow is rich in microbe-related products and antigens. The remaining 25% comes from the hepatic artery, which supplies oxygenated blood [61]. This contributes to the tight control and regulation of the unique hepatic immune system under physiological conditions. Alongside leukocytes from the bloodstream, the liver contains hepatocytes, hepatic stellate cells (HSCs), liver sinusoidal endothelial cells (LSECs), cholangiocytes, and various immune cells that reside in or migrate to the liver [62]. Communication between these liver cells and immune cells is crucial for maintaining the balance between immunity and tolerance. Typically, innate immune cells such as DCs and liver-resident DCs (Kupffer cells) function as professional antigen-presenting cells (APCs) to T cells, playing a role in mediating hepatic immunity. In solid organ transplant, a specific class of CD4 T cells known as regulatory T cells (Tregs) heavily influence the maintenance of tolerance following the reduction of immunosuppressive drugs. Regulatory T cells are identified by the expression of transcription factor FoxP3. Memory Tregs, however, have been shown to function even more productively compared to naïve Tregs. These cells are often differentiated by various molecules including increased CD25 expression (the α chain of the IL-2 receptor), CTLA-4, and CD39 [41,63]. Belatacept is a CTLA4 immunoglobulin used for immunosuppression in kidney grafts that has been investigated for liver transplant procedures. However, previous clinical trials were terminated due to occurrences of graft damage and acute rejection near 10 weeks post-transplant [64]. In addition, a phase II trial in adult liver recipients showed that patients on belatacept had higher incidences of acute rejection and graft failure [65]. Besides utilizing the inhibitory receptor CTLA-4, Treg cells suppress immune responses by expressing IL-10 and TGF-β. Notably, CD4+ Treg cells, which make up about 10% of peripheral lymphocytes in humans, exhibit a CD25highFOXP3+ phenotype [66]. Tregs play a crucial role in regulating the hepatic immune balance toward tolerance through alloantigen recognition [67]. Consequently, the interaction between alloreactive T cells and APCs represents the initial and pivotal step in regulating the outcome of liver transplantation. Multiple animal models have utilized experimental natural killer T cells (NKT), natural killer cells (NK), and dendritic cells (DCs) to limit immune reactivity. Experimental studies in rats have indicated that NKT cells, which are abundant in the liver, may contribute significantly to liver transplant tolerance by inducing a shift from a Th-1 to a Th-2 response. Mice that received α-galactosylceramide, a synthetic glycolipid known to activate NKT cells, exhibited significantly prolonged allograft survival. This effect was associated with elevated IL-10 levels and reduced IFN-γ levels [68]. The presence of donor liver NK cells, which can act as "passenger leukocytes" circulating in the recipient's body, is thought to play a role in allograft acceptance [69]. Interestingly, livers from donor rats treated with IL-4 showed decreased rejection rates. IL-4 treatment led to a robust inflammatory response in the donor liver, characterized by the presence of alternatively activated macrophages and NK cells expressing indoleamine 2,3-dioxygenase (IDO). These IDO-expressing NK cells may possess immunosuppressive properties and are believed to migrate to the recipient's spleen [70]. Yokota et al. reported that in a mouse liver transplantation model, grafts depleted of DCs resulted in early rejection [71], suggesting that donor-derived hepatic dendritic cells play a crucial role in inducing immune tolerance after liver transplantation. On the other hand, inducing an increase in dendritic cells and activating them, along with administering the hematopoietic cytokine fms-like tyrosine kinase 3 ligand (Flt3L) to the recipient to increase IL-12 production, leads to rejection. Graft survival has been reported to be prolonged by neutralizing IL-12, indicating that DCs have a dual function of inducing either rejection or tolerance depending on their activation state [72–74]. The DNAX-activating protein of 12 kDa (DAP12) is strongly expressed in hepatic dendritic cells DCs and controls their activation. In DAP12 knockout mice, hepatic DCs show enhanced production of inflammatory cytokines and increased alloreactivity of T cells. In a mouse liver transplantation

model, grafts from DAP12 knockout mice have been reported to significantly reduce the duration of graft survival [75,76]. CD39 is a cell membrane enzyme that hydrolyzes ATP to adenosine, controlling the activation of immune cells and strongly expressed in DCs. In a mouse liver transplantation model, grafts from CD39 knockout mice have been reported to significantly reduce graft survival duration, while the administration of CD39 extends graft survival duration [77]. From this, it is deducted that DAP12 and CD39 expressed in hepatic DCs are important molecules in inducing immune tolerance after liver transplantation. Via a semi-direct recognition pathway, host dendritic cells (DCs) acquire the expression of graft major histocompatibility complex (MHC) molecules, a phenomenon known as cross-dressing of the host DCs. Subsequently, they present the intact alloantigen to host T cells without the need for further processing. This process was observed in a mouse liver transplant model analyzed by Ono [78], where interstitial DCs from the graft rapidly decreased post-transplant and were then replaced by host DCs. The host DC population peaked on day 7 and persisted indefinitely. Approximately 60% of the host DCs in the liver graft expressed graft MHC-I, indicating cross-dressing, and effectively regulated the proliferation of anti-graft host T cells. In contrast, DCs that were not cross-dressed were unable to inhibit the anti-graft T cell response [79–81]. The semi-direct pathway enables linked help to be provided by allowing indirect pathway recognition of CD4 T cells to activate alloreactive CD8 T cells. These CD8 T cells then target the cells within the graft that express MHC-I alloantigens after activation, leading to their cytotoxic activity through the expression and secretion of granzyme and perforin [81–83]. Additionally, antigen-specific regulatory T cells (Tregs) can reduce the antigen-presenting ability of DCs by removing antigens and MHC class II complexes from the surface of DCs. The induction of immune tolerance through the interaction between DCs and regulatory T cells (Tregs) has also been reported [84]. The interaction between liver cells and alloreactive T cells plays a crucial role in the outcome of liver transplantation. Several cells were discussed in this section, both in vitro and in vivo. The liver allograft contains numerous antigen-presenting cells (APCs), including DCs expressing low levels of MHC antigens along with co-stimulatory molecules, as well as KCs engaged in phagocytosis of pathogens. These cells also secrete cytokines and participate in antigen processing and presentation [85,86]. Liver sinusoidal endothelial cells (LSECs), which make up 50% of the liver's non-parenchymal cells, form a distinctive vascular network in the liver. These cells feature fenestrae arranged in sieve plates and lack a basal membrane. LSECs have direct interactions with immune cells and antigens present in the bloodstream, taking advantage of the liver's abundant blood supply and its unique sinusoidal structure. As a result, LSECs are often referred to as the 'gatekeepers' of hepatic immunity [87]. Immune cells within the liver microenvironment possess surveillance capabilities due to their broad expression of pattern recognition receptors (PRRs). These include scavenger receptors, carbohydrate receptors (lectins), Toll-like receptors (TLRs), and cytoplasmic receptors, which enable them to detect antigens from the blood and gut. Evidence suggests that antigens entering the liver can induce a natural tendency toward tolerance, facilitated by the production of anti-inflammatory mediators and the expression of inhibitory cell surface ligands [88]. Liver tolerance is upheld by various hepatic cell types, including KCs [89,90]. These KCs constitute about 20–35% of the liver's nonparenchymal cells. Additionally, the liver houses diverse DC subsets, such as plasmacytoid DCs (pDCs), and lymphocytes, each exhibiting unique phenotypes based on their origins [91]. KCs are situated within the lumens of hepatic sinusoids, which are fenestrated blood vessels lined by LSECs [92]. KCs display major histocompatibility complex (MHC)-I and MHC-II as well as costimulatory molecules B7.1, B7.2, and CD40, albeit at lower levels compared to hepatic dendritic cells (HDCs). In a stable state, KCs release transforming growth factor-beta (TGF-β), prostaglandin E2 (PGE2), and interleukin-10 (IL-10) [93]. Additionally, KCs exhibit Fas ligand (Fas-L) and programmed cell death ligand 1 (PD-L1) are expressed on KCs, which are powerful inhibitors of immune responses. PD-L1 also reduce T lymphocyte activity by interacting with programmed cell death protein 1 (PD-1) on the T cells [94]. This repertoire of secreted and surface-bound molecules promotes the differentiation of

hepatic regulatory T (Treg) cells. In vivo, KCs trigger apoptosis in neutrophils and other polymorphonuclear cells (PMNCs) via the Fas/Fas-L pathway [95,96]. The interaction between phosphatidylserine (PS) on apoptotic cells and the PS receptor on KCs has been shown to increase the secretion of TGF-β, IL-10, and PGE2. Furthermore, this interaction decreases the production of proinflammatory cytokines by KCs in inflammatory conditions, thereby supporting the maintenance of liver tolerance [97]. Hepatic dendritic cells (HDCs) in the liver are a highly diverse group, fulfilling various roles both under normal circumstances and following transplantation [98]. Certain cytokines in the liver, including FMS-like tyrosine kinase 3 ligand (Flt3L) and granulocyte-macrophage colony-stimulating factor (GM-CSF), can attract conventional dendritic cells (cDCs) that originate from bone marrow progenitors [98]. In the liver, monocyte differentiation into HDCs results in a subset that promotes Th2 responses due to the intrahepatic environment [99]. Certain anti-inflammatory and immunosuppressive medications, such as aspirin, corticosteroids, calcineurin inhibitors, and rapamycin, can influence the recruitment, maturation, and function of HDCs [98]. HDCs comprise subsets such as pDCs and cDCs, which are further divided into cDC1s (CD8+ lymphoid) and cDC2s (CD11b+) [100]. Compared to extrahepatic dendritic cells, HDCs generally produce lower levels of IFN-γ and higher levels of IL-10 than IL-12, thereby promoting Th2 responses [101,102]. Typically, hepatic pDCs have limited endocytic abilities and reduced expression of MHC-II and costimulatory molecules such as CD40, B7.1, and B7.2, which are fairly immature APCs [103–105]. Conversely, other subsets of hepatic DCs show elevated levels of these markers. Nevertheless, hepatic dendritic cells (HDCs) can exhibit increased levels of PD-L1, TGF-β, PGE2, and various other immunosuppressive molecules, thereby supporting hepatic immune tolerance [106]. By interacting with liver sinusoidal endothelial cells (LSECs) and engaging in the adhesion cascade within the hepatic sinusoids, lymphocytes that evade LSEC immune surveillance can traverse the LSEC barrier. This migration, facilitated by chemokines and adhesion molecules, occurs through various pathways—paracellular, transcellular, or intracellular—to communicate with hepatocytes [87]. Paracrine factors secreted by hepatocytes enhance the recruitment of lymphocytes. This interaction between hepatocytes and immune cells is vital for promoting liver transplant tolerance. Generally, hepatocytes act as non-professional antigen-presenting cells (APCs), expressing MHC-I to interact with CD8 T cells under normal conditions. During inflammation, particularly in the presence of IFN-γ, they can also induce MHC-II expression. Nevertheless, the low expression of co-stimulatory molecules on hepatocytes causes apoptosis in alloreactive T cells [107]. For tolerance induction, the direct recognition of MHC-I alloantigen expressed by hepatocytes (cross-presentation) is necessary. Indirect recognition, where CD4 T cells identify the processed allogeneic peptide presented on MHC-II, is not sufficient for inducing tolerance. However, this indirect recognition can extend graft survival and produce regulatory T cells (Tregs), which aid in promoting transplant tolerance [108,109]. Hepatic stellate cells (HSCs) are primarily recognized for storing vitamin A and retinyl esters [110]. However, they also function as antigen-presenting cells (APCs) in the liver. In cultured conditions, HSCs express HLA family members (HLA-I and HLA-II) and lipid-presenting molecules (CD1b and CD1c), and its accessory molecules play a role in T-lymphocyte activation (CD40 and B7.1) [111]. Furthermore, incubation with proinflammatory cytokines such as IL-1 and IFN-γ has been shown to enhance these characteristics. Under these conditions, the cells can efficiently present antigens to T lymphocytes that are restricted by CD1d, MHC-I, and MHC-II [112]. Conversely, HSCs have been shown to suppress T cell responses through PD-L1-mediated apoptosis. While HSCs alone do not appear to present antigens to naïve CD4+ T lymphocytes, they preferentially induce FOXP3+ Treg cells when HDCs and TGF-β are present [113]. Additionally, HSCs are crucial in the development of fibrosis from various causes [114], and fibrosis can be observed post-liver transplant. There are several ways to achieve tolerance. One strategy is immunosuppression withdrawal. This occurrence has been reported in several instances in both adults and children [115,116]. While some recipients experienced instances of graft rejection when tapering immunosuppressants, the

episodes were both manageable and mild. Furthermore, graft rejection did not occur in any case. Donor-specific antibodies (DSAs) are a major factor to monitor when tapering immunosuppressive drugs. However, no markers of histological damage were identified in adult or pediatric patients in the presence of DSA [115,116]. When discontinuing immunosuppressants, patient selection, timing, and rejection risk, in addition to complete or partial withdrawal, must be considered.

5. Conclusions

The liver is a privileged organ in terms of alloreactivity. Alloimmune responses mediated by T cells and their interactions with antigen-presenting cells play a crucial role in transplant rejection. The unique cellular interactions of alloreactive T cells with innate immune cells and specialized liver cells, including hepatocytes, liver sinusoidal endothelial cells (LSECs), and hepatic stellate cells (HSCs), significantly contribute to the transplant outcome, immunosurveillance, and modulation of immune tolerance within the liver microenvironment.

The liver's distinctive anatomy, vascular supply, and cellular composition create a unique immunological milieu that predisposes it to both rejection and tolerance mechanisms. A comprehensive understanding of these intricate cellular interactions and their roles in shaping alloimmune responses is paramount for improving long-term graft survival and developing strategies to induce transplant tolerance.

Author Contributions: Conceptualization, M.Y. and D.I.; original draft preparation, M.Y.; writing, M.Y. and D.I.; review and editing, D.I., S.W., L.G., Y.S., A.A.K., S.D.L., M.I.S., A.S., V.K., A.H.C. and M.F.L.; supervision, D.A.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

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

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