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REVIEW

Natural killer cells in liver diseases

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Abstract **The liver has been characterized as a frontline lymphoid organ with complex immunological features such as liver immunity and liver tolerance. Liver tolerance plays an important role in liver diseases including acute inflammation, chronic infection, autoimmune disease, and tumors. The liver contains a large proportion of natural killer (NK) cells, which exhibit heterogeneity in phenotypic and functional characteristics. NK cell activation, well known for its role in the immune surveillance against tumor and pathogen-infected cells, depends on the balance between numerous activating and inhibitory signals. In addition to the innate direct "killer" functions, NK cell activity contributes to regulate innate and adaptive immunity (helper or regulator). Under the setting of liver diseases, NK cells are of great importance for stimulating or inhibiting immune responses, leading to either immune activation or immune tolerance. Here, we focus on the relationship between NK cell biology, such as their phenotypic features and functional diversity, and liver diseases.**

Keywords natural killer cell; phenotype; immune activation; immune tolerance; liver diseases

Introduction

The liver, a central immunological organ in the human body, receives blood from both the arterial system and the portal vein, which originates from the intestine and contains a large number of circulating antigens and microbial products. Notably, the liver maintains immune nonresponsiveness to harmless antigens derived from the gastrointestinal tract [1]. The tolerogenic properties of the liver have also been recognized in liver transplants, in which liver allografts are accepted in spite of mismatched major histocompatibility complex [2]. Follow-up study indicates that tolerance to heart and skin grafts are induced after liver transplantation [3]. There is evidence that liver tolerance contributes to chronic infection and malignant progression in the liver under pathological conditions [4]. Indeed, the exogenous antigens and microbial products derived from the gut can trigger liver immune responses [5]. Moreover, the liver also exhibits robust hepatic immunity in acute viral infection, and sometimes liver immunity leads to liver injury and autoimmune diseases in certain microenvironment. Collectively, it is not surprising that the liver immunology possesses both the properties of liver tolerance and liver immunity; the balance between immune tolerance and immune activation is maintained by the hepatic immune networks under normal circumstances. However, the underlying immune regulation of the balance between liver tolerance and liver immunity remains obscure under pathological conditions, such as important viral infections, parasitic infections, and tumor and autoimmune liver diseases.

Meanwhile, the liver is often considered as an innate immune organ. It is particularly enriched by innate lymphocytes, such as natural killer (NK) cells. Among those immune cells, NK cells constitute approximately 31% of the intrahepatic lymphocyte population [6]. NK cells are important for protection against intracellular bacterial, viral, and parasitic pathogens and malignant cells via natural cytotoxicity and cytokine production [7]. Growing evidences also indicate that regulation by NK cells may shape subsequent immune responses [8,9]. NK cell activity is involved in liver immunology through interaction with innate or adaptive immune cells in liver diseases via their cytokine/chemokine secretion or lytic

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abilities [10–13]. Moreover, NK cells display phenotypic and functional diversities in different liver diseases. According to the immune characteristics of the liver, in which its activation and tolerance are strictly regulated, together with NK cell regulation [14,15], it may be concluded that the liver immunology is very likely influenced by NK cells under pathological conditions.

Here, we focus on recent advances in NK cell biology, including its phenotypic and functional characteristics, and outline emerging evidences of NK cell immunology involved in immune tolerance and immune activation in the liver under pathological conditions, such as viral hepatitis, liver inflammation, and autoimmune and malignant liver diseases, contributing to new immunotherapeutics based on NK cells.

Mechanisms under liver immunity and liver tolerance

The liver is a site of accumulation of abundant adaptive immune cells. It is also rich in hepatocytes, hepatic stellate cells, and dendritic cells (DCs). Among these liver-resident cells, some populations are endowed with antigen-presenting activity, which facilitates liver immunity or liver tolerance. Under appropriate stimulations, these cells are responsible for effective immune responses against viruses, intracellular bacteria, parasites, and malignant cells. Robust immune responses result in immune-mediated liver inflammation with lymphocyte infiltration and may lead to autoimmune liver disease once hepatic self-tolerance is broken. Interestingly, the liver can also provide a local site to prime T cells [16]. In particular, portal-associated lymphoid tissue (PALT) has been induced as a local immunological compartment or pathological niche in inflamed liver, in which myeloid DCs are recruited and modulate T cell immune responses [17,18]. On the other hand, liver-resident cells are implicated in the maintenance of liver tolerance by inducing T cell tolerance [19], demonstrating that local primed T cells result in the inactivation or apoptosis of hepatic T cells [20,21].

In addition, the liver has well-developed lymphatic networks. Liver-draining lymph nodes (LNs), which drain lymphatic fluid from the liver, have been considered for inducing effective immune responses against virus-infected or tumor cells and may also lead to immune tolerance [22,23]. Thus, the liver-draining LNs appear to play a key role in maintaining liver tolerance characteristics and inducing rapid liver immune activation in response to acute infection or autoimmunity. However, it remains unclear how the liver-draining LNs affect the balance between immune tolerance and immune activation in the liver under pathological conditions. Thus, the immune responses that occur in the liver-draining LNs and the hepatic tolerogenic environment could be further compared to consider the differences in the regulation of liver immunology in the context of liver diseases.

NK cell subsets are divided by phenotypic and functional characteristics

Traditionally, human NK cells can be dissected into $CD56^{bright}CD16^{-}$ and $CD56^{dim}CD16^{+}$ NK subsets. The $CD56^{bright}CD16^{-}$ NK cell subpopulation is predominant in the spleen and LNs, which produces a large amount of cytokines; by contrast, the $CD56^{dim}CD16^{+}$ population is predominant in the peripheral blood and exhibits higher cytotoxic activity than the $CD56^{bright}CD16^{-}$ subset [24]. The $CD56^{dim}CD16^{+}$ NK cell population is further subdivided with respect to the surface density of CD94/NKG2A, KIR, CD57, or CD62L [25–28]. Human NK cells have been reported to differentiate into two subpopulations, NK1 and NK2 cells, according to different cytokine production [29]. Four NK subsets are described by their relative surface expressions of CD11b and CD27 in mice [30,31]. The four subsets are shown with different abilities in producing cytokines and cytotoxicity [32]. Previous researches have demonstrated the existence of multiple lineages of NK cells, in different organs, such as the liver, skin, uterus, and kidneys [33–38]. In humans, NK cells are enriched and constitute a large proportion of lymphocytes in the liver, with a higher percentage than those observed in the peripheral blood and the spleen [39,40]. Strikingly, NK cells accumulate largely in the murine liver in contrast to the peripheral blood and spleen. Murine intrahepatic NK cells can be classified into circulating conditional NK cells and liver-resident NK cells based on the relative expression of CD49a and DX5 [41]. Conventional liver NK cells secrete IFN-γ and release perforin and granzymes to mediate cytotoxicity [42]. However, liver-resident NK cells are reported to constitutively express TRAIL or NKG2A and inhibit anti-$CD8^{+}$ T cell immunity [43,44], suggesting their potential regulatory role.

The distinct phenotypic features of NK cells are associated with their functional properties [45]. NK cells were functionally identified in the 1970s based on their distinctive cytotoxicity against allogeneic tumor cells without the need of previous sensitization. Besides cytotoxicity, activated NK cells have been implicated in secreting certain cytokines involved in regulating immune responses [46]. Under pathological conditions, human NK cells exhibit cytotoxic, regulatory, and tolerant functions according to the distinctive activities [30]. Strikingly, the "NK-reg" subset is proposed to have a negative regulatory effect on immune responses, which is similar to that of Treg cells [47]. NK cell exhaustion has been described with high expression of certain inhibitory receptors in

some chronic diseases [48]. In reality, numerous germline-encoded activating and inhibitory receptors transmit signals for NK cell function and dysfunction through sensing infected or malignant cells [49]. For example, NK cells are activated by decreased inhibitory signals or increased activating signals [50]. Activating receptors are involved in NK cell function, including the NCR family; NKG2D; the SLAM-related receptors 2B4, NTB-A, and CRACC; and other receptors such as DNAM-1, NKp80, and CD16 [8]. A number of inhibitory receptors expressed by NK cells are involved in stringent negative regulation of NK cell activation, including the human KIR family; the mouse Ly49 family; the heterodimeric receptor CD94/NKG2A in both humans and mice; and ITIM-containing receptors such as LILR, KLRG1, and NKR-P1 in human NK cells [51].

Although NK cells exhibit unique organ-specific properties, it is still unclear how the phenotype of NK cells is linked to their particular functions under pathogenic conditions. Thus, further studies of certain liver NK cell subsets with specific functions are needed to improve our understanding of liver diseases.

NK cells in liver diseases

As key innate lymphocytes, NK cells are of great importance in early defenses against infected and malignant cells through cytotoxicity or cytokine secretion. In addition, studies have revealed that NK cells can shape innate and adaptive immunity through direct or indirect regulation [47,52], which demonstrates that NK cell activity contributes to either immunosuppression or immunoactivation. Generally, adaptive immunity, especially cellular adaptive immune responses, are considered to play a dominant role in controlling the final outcome of liver diseases [53–55]. Studies on liver diseases have shown that immunoregulatory disorder exists and contributes to the immune tolerance in chronic liver disease and liver cancer and over-reactive immune responses in liver inflammation and autoimmune liver disease [56]. NK cells can amplify anti-viral immune responses with higher IFN-γ production and cytotoxicity to control early viral infection [57,58]; however, evidences also indicate that NK cells are defective in secreting IFN-γ in chronic viral infection [59,60]. Studies have demonstrated that high frequencies and numbers of NK cells with increased expression of IL-8 in the destruction of autologous biliary epithelial cells are observed in patients with primary biliary cirrhosis (PBC), indicating NK cell dysfunction in liver autoimmune disorders [61,62]. On the other hand, dysfunctional NK cells also show decreased levels of IFN-γ secretion and cytotoxic activity in hepatocellular carcinoma (HCC) patients [63]. The above evidences demonstrate that NK cell functional dichotomy exists in liver diseases. However, it still remains unclear how liver NK cell subsets influence the outcome of liver disease. In addition, the ultimate outcome of intrahepatic diseases is largely dependent on antigen-specific T cell immune responses. Thus, it is possible that liver NK cell subsets influence the phenotype and function of numerous immune cell types through diverse immune regulatory mechanisms, which together promote or limit antigen-specific T cell immune responses [64,65] and ultimately affect the outcome of liver diseases.

NK cell effector function in liver immunity

NK cell-associated receptors are observed in liver diseases. Previous studies have highlighted that normalization of NK cell phenotype and function contributes to direct antiviral-mediated clearance of hepatitis C virus (HCV) [66]. During acute hepatitis B virus (HBV) infection, effective NK cell function is displayed by increased NKp46 and decreased NKG2A expressions [67]. NK cells contribute to the inhibition of HCV replication through the cytotoxic ability of NKp30 [68]. NK cells are also reported to protect against HCV infection through the interaction of KIR2DL3 and its ligands [69]. By modulating NKG2D and NKG2A expressions, NK cell cytotoxicity is augmented against HCC [70], and NK cells stimulated by interferons lead to strong antitumor responses after cancer surgery [71]. The over-activated NK cell function could also lead to liver inflammation through a variety of molecular mechanisms [72]. For example, $TRAIL^{+}$-$CD56^{bright}$ and $Perforin^{+}CD56^{dim}$ NK cells contribute to liver injury in chronic hepatitis B (CHB) patients [73]. Moreover, NK cell-derived cytokine milieus are involved in immune-mediated liver damage. Recent studies indicate that activated NK cells with increased expressions of CD69, CD107a, IFN-γ, and TNF-α are positively associated with hepatic inflammation in patients chronically infected with HBV [74]. Additionally, many studies have also indicated that NK cells attenuate liver fibrosis *in vivo* via Toll-like receptor-9 [75] or through TRAIL-, FasL-, and NKG2D-dependent mechanisms [76,77].

Autoimmune liver diseases are induced when self-tolerance in the liver is broken [78,79]. NK cells have been implicated in this kind of disease as well. Increased number of NK cells with perforin expression is found in patients with PBC [80]. Furthermore, hepatic NK cells possess cytotoxic activity via TLR4 ligation in patients with PBC [61]. They are also found to kill cells by TRAIL in patients with PBC [81]. Therefore, NK cell receptors are directly involved in acute liver diseases and autoimmune liver diseases.

As NK cells have shown regulatory effects on multiple aspects of immune responses, T cell immunity is promoted directly or indirectly by NK cells through hepatic

immunity [56]. In particular, NK cells can directly or indirectly enhance T cell responses through cytokine and chemokine secretion, cytotoxicity, or antigen-presenting cell (APC) regulatory functions [46,82]. For instance, NK cells are recruited to the draining LN and promote naïve $CD4^+$ T cell differentiation into TH1 cells [83]. In a mouse model mimicking acute HBV infection, liver conventional NK cells promote anti-HBV $CD8^+$ T cell immunity via secreting IFN-γ [84]. In addition, $CD8^+$ T cells are primed by NK cells even without the requirement of $CD4^+$ T cells [85]. By contrast, the lack of NK cell function results in impaired tumor-specific $CD8^+$ T cell immune responses and tumor progression [86]. In addition, T cell immune responses are enhanced in a NK cell-dependent manner by indirect mechanisms. NK cell-derived IFN-γ contributes to DC accumulation and enhanced T cell recruitment [87,88]. NK cells may affect T cell immunity and control infections through interaction with B cells [89]. They exhibit cytotoxic activity against target cells, and the release of antigens for cross presentation leads to enhanced T cell immune responses [90]. Taken together, the above results demonstrate that the effective NK cell function is often mediated by high expressions of activating receptors and is associated with liver immunity through the positive regulation of T cells in liver diseases.

NK cell dysfunction in liver tolerance

NK cell dysregulation in liver tolerance

Liver tolerance is often induced in chronic hepatic infection and hepatic tumor [91]. Meanwhile, accumulating studies have suggested that the NK cell activity in chronic liver diseases is compromised [92]. A recent study indicated that the $CD11b^-CD27^-$ NK cell subset is associated with NK cell dysfunction and tumor progression in HCC patients [93]. Functional impairment of intrahepatic NK cells, indicated by the decreased production of TNF-α and IFN-γ, was reported in HCC patients [94]. Additionally, numerous studies have shown that the imbalanced NK cell receptors contribute to NK cell dysfunction in chronic viral infection and HCC [95–99]. For example, activating receptors CD16, NKG2D, and NKp30 are downregulated, whereas NK cells show increased expression of NKG2A and Tim-3 in CHB patients [59,100–103]. In patients with chronic hepatitis C (CHC), NK cell function is negatively regulated by KLRG1 [104], whereas the elevated expression of Tim-3 contributes to the increased cytotoxicity of NK cells [105]. Similarly, decreased intrahepatic NK cell cytotoxic activity is observed in CHC infected patients with decreased expression of TRAIL, which leads to impaired intrahepatic NK cell cytotoxicity and virus persistency [96]. On the other hand, NK cell function can be restored after blockade of immunosuppressive cytokines [106]. For instance, a recent study has demonstrated that increased NKG2A expression is observed in HCC patients, and NKG2A blockade facilitates the recovery of immune responses [107]. Collectively, these findings indicate that NK cell dysfunction is often associated with imbalanced NK cell inhibitory and activating receptors in chronic infections and tumor conditions.

Incomplete activation and abortive immune function of hepatic T cells are observed in chronic infections [64]. Several studies highlight that NK cell cytotoxic activity contributes to the cytolysis of T cells [108,109]. In lymphocytic choriomeningitis virus-infected mice mimicking human immunodeficiency virus and HCV infections in humans, NKG2D can mediate regulatory functions of NK cells that affect $CD8^+$ T cell immunity by producing perforin, whereas NK cell depletion triggers strong $CD8^+$ T cell immune responses and viral control [110]. Furthermore, NK cells exhibit cytolytic killing of antiviral $CD8^+$ T cells by upregulating a death receptor in chronic HBV-infected patients [43]. These results have implicated that impaired T cell responses are regulated by NK cells through their cytolytic ability. In line with these findings, several investigations have also pointed out that cytokines secreted by NK cells may trigger regulatory functions of NK cells. A regulatory IL-10-producing NK cell subpopulation is shown with significant inhibitory effect on T cell proliferation [111]. Further studies have demonstrated that the lack of NK cells can restore T cell expansion in *ifnar1*$^{-/-}$ mice [112,113], and type I IFNs protect T cells from attacks by NK cells through down-regulating NCR1 ligands [112]. In addition, NK cell-derived IFN-γ limits T cell proliferation [114] and differentiation [115].

The regulation by NK cells also indirectly contributes to impaired T cell immunity through interaction with APCs [116]. For example, NK cells express highly levels of programmed death ligand 1 to limit DCs activation and reduce their ability to prime $CD8^+$ T cells [117]. In addition, $CD48^-$ mature DCs can also be killed by self-HLA class I specific inhibitory NK receptors defective NK cells [118], which may lead to impaired adaptive immune responses. Interestingly, NK-γδ T cell cocultures also enhance NK cell cytotoxicity against autologous DCs [119]. On the basis of these data, NK cells may diminish DCs, which results in reduced antigen presentation that limits $CD4^+$ T and $CD8^+$ T cell responses, which in turn induce persistent viral infections [120]. As NK cells eliminate antigen presentation of APCs, which results in reduced $CD8^+$ T cell responses in chronic infections, early NK cell depletion can enhance T cell responses and viral control [121]. On behalf of the regulation of the immune responses by NK cells, it is of utmost importance for determining whether there are distinct NK cell subpopulations that exhibit positive and negative regulatory

activities. Therefore, "regulatory NK cells" (NKreg subpopulation) are proposed to exist and show a regulatory effect on innate and adaptive immunity through secreting high levels of regulatory mediators including IL-10 [47]. Collectively, the regulation of T cell responses by NK cells, both directly and indirectly, shows the negative impact on T cell immunity involved in liver tolerance. To validate the regulatory role of NK cells, further studies are required to characterize the specific NK cell phenotype with positive or negative regulatory function at the molecular and cellular levels under liver pathogenic environment.

NK cell exhaustion in liver tolerance

NK cells become functionally exhausted in chronic infections [48]. In SIV-infected nonhuman primate models, continuous NK cell activation leads to the upregulation of Tim-3 and failure to lyse target cells [122]. NK cell exhaustion in tumor and tumor models has been also observed [107,123,124]. Another research has indicated that blockade of Tim-3 reverses exhausted NK cell phenotype in patients with metastatic melanoma [125]. Chronic infection and tumors are also characterized by T cell exhaustion [126]. Further studies have also indicated that IL-10 produced by NK cells promotes T cell exhaustion and peripheral tolerance [127,128]. However, the mechanism underlying T cell exhaustion is currently unknown, and whether there is a relationship between NK cell exhaustion and T cell exhaustion merits further research. Similar to T cell exhaustion, NK cell exhaustion shows increased expression of inhibitory receptors and decreased expression of activating receptors and transcription factors, resulting in impaired control of chronic infection and tumor growth. Generally, NK cell activation is a prelude of $CD8^+$ T cell activation under certain liver diseases. Thus, it is possible that NK cell exhaustion may occur prior to $CD8^+$ T cell exhaustion, suggesting that reversing impaired NK cell function may be considered as a strategy for preventing $CD8^+$ T cell exhaustion (Fig. 1). Further studies that focus on functional exhausted NK cells with specific exhausted phenotype are needed as they will help us to reverse NK cell exhaustion using blockade of the immune checkpoint molecule in chronic liver disease and liver tumor.

More importantly, the human liver also consists of a large number of intrahepatic $CD56^{bright}$ NK cells, which specifically express CD49a, CXCR6, and $Eomes^{high}$ $T\text{-}bet^{low}$ distinct from peripheral blood NK cells [129,130]. Further studies have demonstrated that human liver-resident $CD56^{bright}$ NK cell expression of CD69, CCR5, and CXCR6 is responsible for liver-resident $CD56^{bright}$ NK cell retention within liver sinusoids [131]. A recent study suggested that these liver-resident $CD56^{bright}$ NK cells possess long-lived characteristics [132]. Regarding the functions of liver-resident NK cells, they can induce memory-like immune responses toward virus and haptens [38,133,134]. Moreover, they produce specific cytokines such as TNF and GM-CSF [135]. Therefore, liver-resident NK cells appear to play an important role in regulating liver immunology. However, additional studies are required to determine the role of liver-resident NK cells in liver diseases.

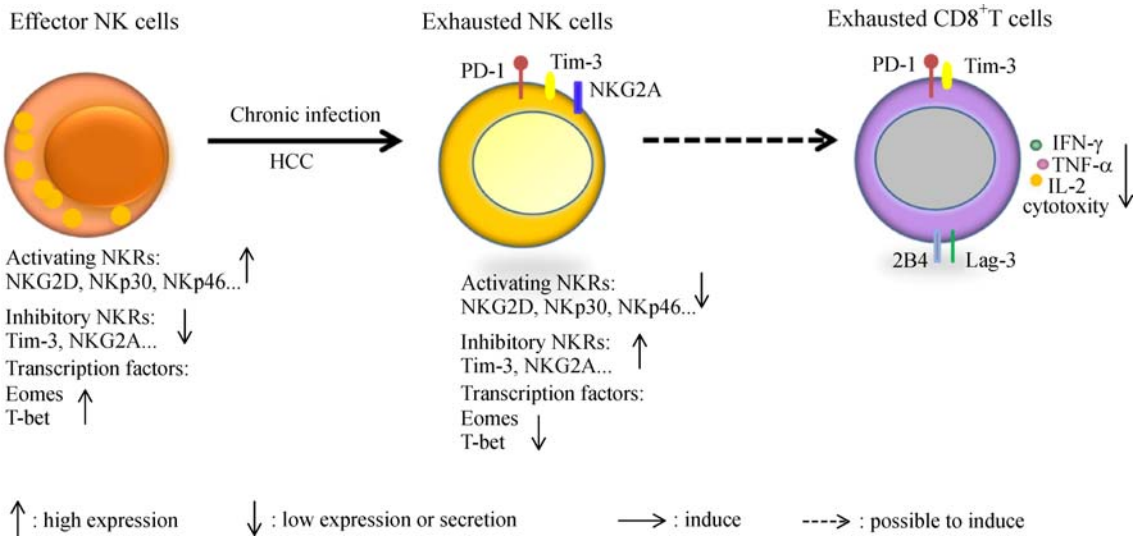

Fig. 1 NK cell exhaustion may be the prelude of $CD8^+$ T cell exhaustion. In chronic infection and HCC, effector NK cells become exhausted with increased expressions of inhibitory receptors, such as Tim-3, NKG2A, and PD-1; decreased expressions of activating receptors including NKG2D and NKp30; and decreased expressions of transcription factors, such as Eomes and T-bet. And exhausted NK cells may lead to $CD8^+$ T cell exhaustion in chronic infection and tumor conditions.

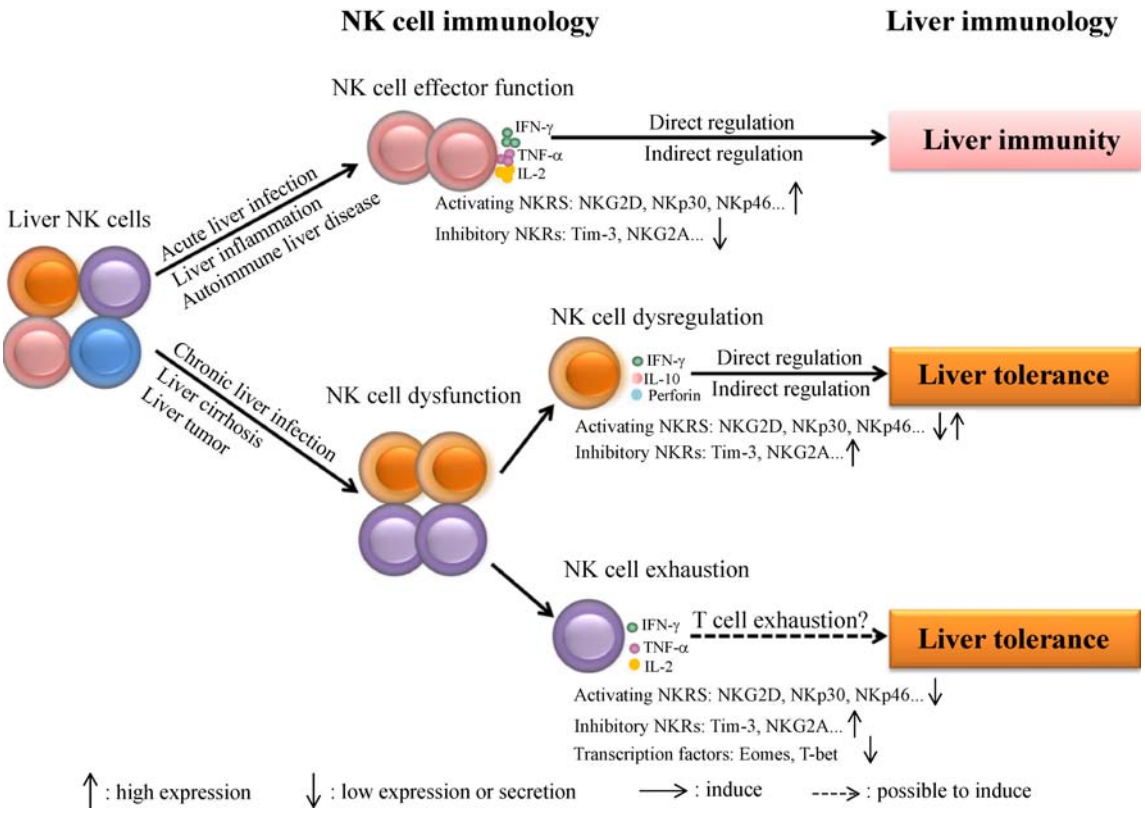

Fig. 2 NK cell activity in liver immunology. NK cells activate T cells through either direct or indirect regulatory mechanisms, leading to liver immunity in acute infection, inflammation, and autoimmune disease. Under chronic infection and tumor conditions, NK cells negatively regulate T cell immunity and induce anergic T cells and Treg cells via direct or indirect mechanisms, which maintain liver tolerance. And NK cell exhaustion may be involved in liver tolerance and associated with exhausted $CD8^+$ T cells in chronic liver disease.

Conclusions

Altogether, given the tremendous data suggesting NK cell activity in orchestrating liver immunology, it is thus possible that NK cells are of great importance in affecting hepatic immunoactivation and immunotolerance. With the increased expression of activating receptors and decreased expression of inhibitory receptors, NK cell activity contributes to T cell activation through direct or indirect regulatory mechanisms, which contribute to liver immunity in acute infection, liver inflammation, and autoimmune liver diseases. However, NK cells are also implicated in liver tolerance by inducing T cell anergy under pathologic conditions, such as chronic infection and liver cancer. In addition, functional exhaustion of NK cells may lead to liver tolerance possibly depending on the induction of T cell exhaustion (Fig. 2).

As upstream regulators of immune responses, NK cells play an important role in controlling chronic infection and cancer and display the potential to be used as new immunotherapeutics [136–138]. For example, functional NK cell responses are associated with the success of antiviral therapies in HCV infection [139]. Through the engagement of their surface receptors, the NKp30/B7-H6 axis could be a target for cancer immunotherapy [140]. However, in the context of liver diseases, NK cell activity appears to exhibit a paradoxical function in influencing the balance between liver tolerance and liver immunity, indicating that heterologous NK cell populations should be considered in liver diseases. Therefore, dissecting NK cell subsets with different phenotypes and functions will help us understand the interplay between immune tolerance and immune activation involved in liver diseases. How to use NK cell biology to target chronic liver infection and tumors or to prevent liver inflammation and autoimmune diseases merits further research and investigations.

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Compliance with ethics guidelines

Meijuan Zheng, Haoyu Sun, and Zhigang Tian declare no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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