REVIEW ARTICLE

Decoding the Natural Killer Cell Enigma: A Review

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ABSTRACT

Background: While the liver's hepatocytes and Kupffer cells are prominent foci of study, the distinct and relatively uncharted roles played by the natural killer cells in liver immunity provide fertile ground for exploration. In this review paper, we have tried to uncover the unique phenotypic and functional attributes of liver-resident natural killer cells, consequently establishing a profound connection between liver immunology and histopathology. ***Objective:*** This review aims to provide an overview of the phenotypic and functional properties of the liver-resident natural killer cells, giving insight on the immunological and histological repercussions of their interactions during liver infections, inflammation, and hepatocellular cancer. ***Methods:*** In this review, published papers in electronic databases comprising PubMed, Scopus, and Google Scholar were retrieved using search themes such as immunological cells, natural killer cell, liver inflammation, and liver cell were examined. ***Results:*** The liver-resident natural killer cells are potent producers of cytokines, including interferon-gamma (IFN-γ) and modulate the phenotype and function of hepatic macrophages, enhancing their antimicrobial activity, as well as influence the activation and cytotoxic function of CD8+ T cells, particularly during chronic liver inflammation. ***Conclusion:*** Our review underscores the undeniable significance of the natural killer cells in the liver defence and highlighted the challenges and constraints researchers encounter when studying the liver natural killer cells. Continued research endeavour are necessary to harness the full capabilities of the natural killer cells, ultimately leading to better insights, innovative therapies, and enhanced protection for the liver, and by extension, the entire body.

Keywords: Liver cell, immune cells, interferon-gamma, cytokines

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INTRODUCTION

The liver is a vital organ that orchestrates complex metabolic activities, detoxification, and immunological surveillance [1]. It tackles an extensive list of obstacles, ranging from viruses to poisons to cancers. While the liver's hepatocytes and Kupffer cells have been prominent subjects of study, the distinct and relatively uncharted roles played by the Natural Killer (NK) cells in liver immunity provide fertile ground for exploration. Moreover, studies have uncovered the unique phenotypic and functional attributes of liver-resident NK cells, consequently establishing a profound connection between liver immunology and histopathology. NK cells in the liver are essential components of the innate immune response against viral infections. They detect virally infected hepatocytes through a delicate balance of inhibitory and activating receptors, such as killer-cell immunoglobulin-like receptors (KIRs) and natural cytotoxicity receptors (NCRs). Activated NK cells release cytotoxic granules containing perforin and granzymes, leading to the destruction of infected cells [2].

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NK cells serve as crucial guardians against hepatocellular carcinoma (HCC) development. They can recognize and eliminate transformed hepatocytes, preventing the progression of liver tumours. This function relies on the detection of abnormal MHC class I expression and stress ligands on the surface of cancerous cells [3]. NK cells participate in immune regulation within the liver by producing cytokines such as interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α). These cytokines influence the activities of other immune cells, enhancing the adaptive immune response and antiviral defence [4].

This article aims to synthesize the findings of these researchers, identifying links between NK cell biology and the histological manifestations of liver health and disease. With an overarching goal of clarifying the intricate cross-connections between immunology and histopathology in the liver, this study seeks to integrate current information about the phenotypic and functional properties of liver-resident NK cells, emphasizing their impact on liver histology and tissue integrity. Secondly, to investigate the dynamic interplay between liver-resident NK cells and other immune cell populations within the microenvironment of the liver, giving insight on the histological repercussions of these interactions during liver infections, inflammation, and hepatocellular cancer. Thirdly, to examine the histopathological implications of liver-resident NK cells in the context of liver disorders, focusing on how their presence and activity affect tissue architecture and disease development

This proceeding review brings together the fields of immunology and histology to examine the crucial function of the Natural Killer cells in liver defence. This review is significant because it offers a chance to explain the immunological foundations of liver histology, bridging the gaps and revealing the complex relationship between the liver immunology and histology.

METHODS

In this review, published papers in electronic databases comprising PubMed, Scopus, and Google Scholar were retrieved using search themes such as "immunological cells", OR "natural killer cell", OR "liver inflammation", OR, and "liver cell" were examined.

RESULTS

Immunological vigilance: While it seems strange to refer to the liver as an organ that plays a pronounced role in the immune response, the liver is very much responsible for a number of events that occur during an immune response. The roles of the liver are past metabolism and detoxification. The liver also possesses characteristic immunological functions which are closely intertwined with its circulatory role which played out in fostering immune surveillance and regulation throughout the body.

1. Within the liver sinusoids are the Kupffer cells which are specialized resident macrophages patrol the bloodstream and phagocytose pathogens and foreign particles serving as the liver's first line of defense against systemic infections [5].
2. Antigen Presentation: Hepatocytes and liver dendritic cells can present antigens to T cells, thus initiating adaptive immune responses and helping to monitor and respond to pathogens [6].
3. Tolerance Induction: The liver plays a pivotal role in inducing immunological tolerance, both to harmless antigens and in controlling autoimmune responses, crucial for immune homeostasis [7].
4. Complement System: The liver is a primary site for the production of complement proteins, which are essential for immune defence mechanisms and opsonization of pathogens [8].
5. Acute-Phase Proteins: Hepatocytes synthesize acute-phase proteins in response to infection or inflammation, contributing to the modulation of immune responses [9].
6. Blood Filtration: The liver effectively filters blood, removing not only pathogens but also cellular debris, toxins, and damaged erythrocytes, further supporting immune functions [10].
7. Regulation of Inflammation: The liver contributes to the fine-tuning of systemic inflammation by producing anti-inflammatory molecules and balancing pro-inflammatory and anti-inflammatory factors [10].
8. Bile Production: Bile produced by the liver contains antimicrobial compounds and assists

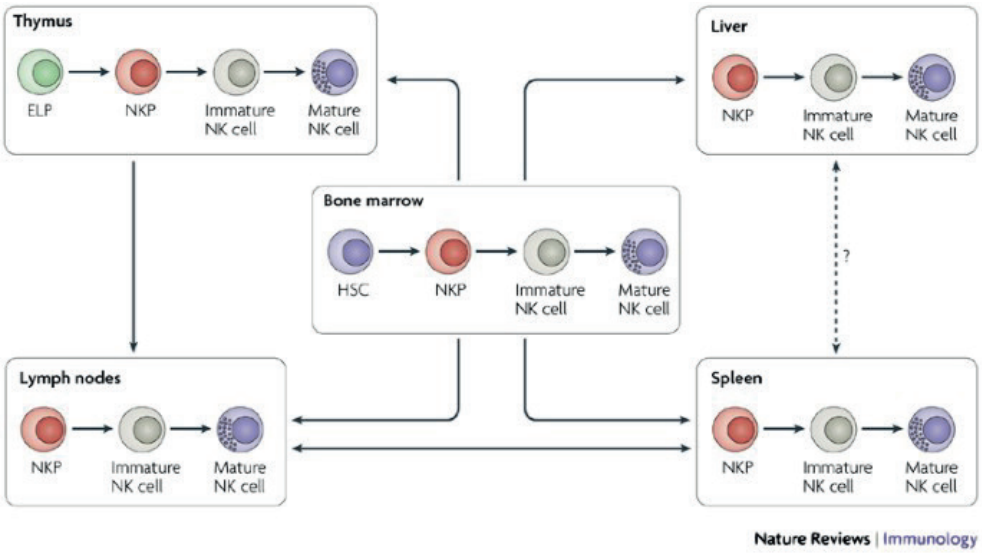

Figure 1. Maturation of NK Cells [12]

in the excretion of waste products and toxins, indirectly contributing to immune defence [11].

Development of the NK Cell: Liver-resident NK cells, like their circulating counterparts, arise from common lymphoid progenitors (CLPs) in the bone marrow. These CLPs differentiate into immature NK cells that subsequently enter the circulation. However, their journey is unique, as a significant fraction of these circulating NK cells preferentially homes to the liver. The liver microenvironment plays a crucial role in shaping their maturation and functional profile.

Studies have shown that liver-resident NK cells have distinct phenotypic and functional characteristics compared to peripheral blood NK cells. For example, they often exhibit a higher expression of tissue-resident markers, such as CD69 and CD49a, reflecting their adaptation to the liver niche [11]. These phenotypic changes are essential for their effective surveillance and defence functions within the liver.

Activation of the Hepatic Micro-environment: NK cells within the liver's unique micro-environment exhibit distinct activation mechanisms, considering the organ's constant exposure to blood borne pathogens and foreign antigens:

1. Balance of Activation and Inhibition: NK cell activity is controlled by a delicate balance between activating and inhibitory signals received through specialized receptors on the surface of the NK cells. These receptors are able to detect various molecules and signals present on the surface of target cells [13].
2. Interplay with Liver Resident Cells: NK cells in the liver interact with other immune cells, such as Kupffer cells and dendritic cells. These interactions modulate NK cell activation and influence the overall immune response [14].
3. Response to Liver Infections: NK cells are crucial in the early defence against viral infections in the liver, such as hepatitis B and C. They detect infected hepatocytes and initiate antiviral responses [15].
4. Tumor Surveillance: Liver resident NK cells play a vital role in detecting and destroying cancerous cells, particularly hepatocellular carcinoma (HCC) and metastatic tumors that may enter the liver via the bloodstream [16].

Liver resident NK cells are integral to the hepatic microenvironment's immune surveillance and regulation. Their unique functionality, including cytotoxicity, cytokine production, and interaction with other immune cells, equips them to respond effectively to pathogens and maintain immune balance within the liver.

NK Cell Defence Mechanisms:

1. Detection and Elimination of Infected or

Transformed Hepatocytes: Liver-resident NK cells are proficient at detecting and eliminating infected or transformed hepatocytes. They possess a unique array of activating and inhibitory receptors, such as NKG2D and NKp46, which allow them to recognize abnormal cells. Upon recognition, they release cytotoxic granules containing perforin and granzymes, leading to the target cell's death. The ability to discriminate between healthy and aberrant cells is crucial in the liver's defence against infections and malignancies [17].

2. Cytokine Production: Liver-resident NK cells are potent producers of cytokines, including interferon-gamma (IFN-γ). IFN-γ is a key player in immune defence against intracellular pathogens and can modulate the function of other immune cells within the liver microenvironment. Liver-resident NK cells, through IFN-γ production, can enhance the antimicrobial activity of macrophages, further contributing to liver defence [18].

3. Interactions with Other Immune Cells: Liver-resident NK cells engage in dynamic interactions with other immune cells, such as macrophages and T cells, within the liver microenvironment. These interactions are pivotal for orchestrating immune responses. They can modulate the phenotype and function of hepatic macrophages, enhancing their antimicrobial activity, as well as influence the activation and cytotoxic function of CD8+ T cells, particularly during chronic liver inflammation [19, 20].

In summary, liver-resident NK cells undergo specific developmental processes and exhibit unique mechanisms to contribute to liver defence. They play a pivotal role in detecting and eliminating infected or transformed hepatocytes, produce critical cytokines, and engage in dynamic interactions with other immune cells. Understanding these mechanisms is fundamental for comprehending the liver's immune defence against infections and malignancies.

Exploring the NK Cell beyond Blood: Liver-resident natural killer (NK) cells are a unique subset of immune cells that play a crucial role in maintaining hepatic homeostasis by participating in immune surveillance and tissue integrity regulation within the liver. This section aims to provide an overview of the phenotypic and functional properties of liver-resident NK cells, emphasising their impact on liver histology and tissue integrity.

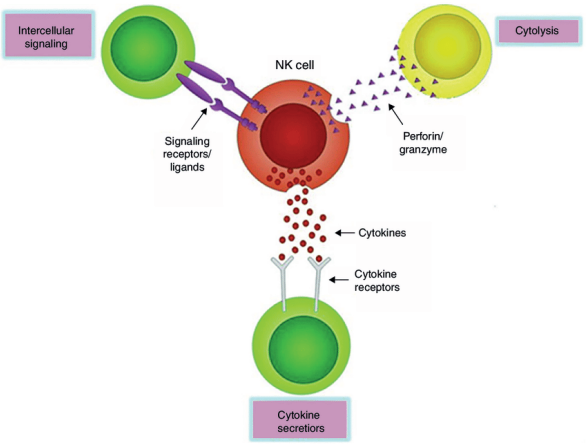

Figure 2. Mechanism of action of Natural Killer cells[21]

Some of the phenotypic characteristics of resident NK Cells include;

1. Surface Markers: Liver-resident NK cells are identified by specific surface markers. They are characterized by the expression of CD49a (integrin α1), CD49b (integrin α2), and CD56 (neural cell adhesion molecule, NCAM). Notably, these cells typically lack CD49d (integrin α4), distinguishing them from circulating NK cells [22].

2. Tissue Residency Markers: Liver-resident NK cells express CD69, CD103, and CXCR6, indicating their tissue-resident nature. CD69 prevents their egress from the liver, while CD103 facilitates their interaction with hepatocytes[23].

Properties of the Resident NK Cell:

1. Cytotoxic Activity: Liver-resident NK cells are highly cytotoxic and can rapidly eliminate infected or transformed hepatocytes. They achieve this through the release of cytotoxic granules containing perforin and granzymes, leading to target cell apoptosis.[24]

2. Cytokine Production: Liver-resident NK cells are potent producers of cytokines such as interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α). These cytokines have both anti-viral and immunomodulatory effects in the liver.[4]

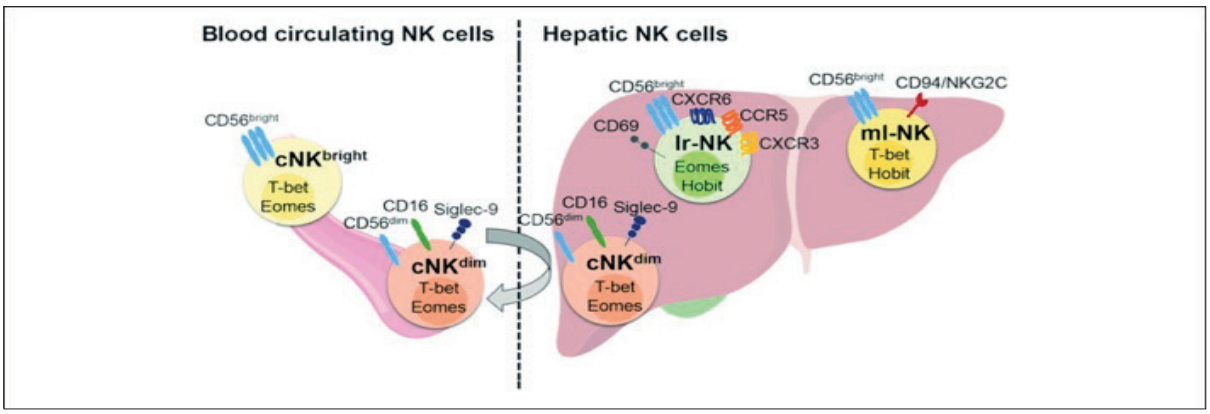

Figure 3. Diagram displaying phenotypic markers of liver resident NK cells[13]

3. Regulation of Fibrosis: Liver-resident NK cells are involved in the regulation of liver fibrosis by interacting with hepatic stellate cells. They can modulate the fibrotic response through the production of transforming growth factor beta (TGF-β) and interferon-lambda (IFN-λ).[17]

Tissue Effect of the NK Cell: The phenotypic and functional properties of liver-resident NK cells have a significant impact on liver histology and tissue integrity. These cells serve as sentinels, continuously surveying the liver for signs of infection or cellular stress. Their rapid cytotoxic response helps to eliminate infected or damaged cells, preventing the spread of infections and contributing to tissue repair.

Moreover, cytokine production by liver-resident NK cells plays a crucial role in regulating the hepatic immune microenvironment. IFN-γ, for example, can enhance the antiviral response and promote the activation of other immune cells. TNF-α contributes to the clearance of pathogens and has anti-tumour effects.

In the context of liver fibrosis, liver-resident NK cells have a dual role. They can limit fibrosis by suppressing the activation of hepatic stellate cells through the production of TGF-β. On the other hand, IFN-λ produced by these NK cells can promote fibrosis resolution [17].

Liver-resident NK cells are a unique subset of immune cells with distinctive phenotypic and functional properties. Their presence and activity in the liver are essential for maintaining hepatic homeostasis, protecting against infections, and regulating liver tissue integrity. Understanding these properties is crucial for advancing our knowledge of liver immunology and exploring therapeutic strategies for liver-related diseases.

Histopathological perspective of the NK cell: Liver-resident NK cells are integral players in the histopathological landscape of liver disorders, exerting substantial influence on tissue architecture and disease development. This section analyzes how the presence and activity of liver-resident NK cells impact histological outcomes and disease progression within the context of liver disorders.

Liver Infections: During liver infections, the presence of liver-resident NK cells can significantly affect tissue architecture. These NK cells infiltrate the liver tissue and form clusters around infected hepatocytes, as observed histologically. These clusters, often termed "immune foci," are indicative of the ongoing immune response against pathogens. Histopathological examination reveals not only the spatial arrangement of NK cells but also their role in shaping the distribution of other immune cells. Furthermore, the presence of NK cells may influence the degree of tissue damage and inflammation, as well as the formation of fibrotic areas [14].

Liver Inflammation: In cases of liver inflammation, the histopathological implications of liver-resident NK cells include the observation of immune cell infiltration into liver tissue. This infiltration, observed histologically, is not limited to NK cells alone but encompasses a variety of immune cell types, including T cells and macrophages. The spatial distribution of these cells provides valuable insights into the immune response's architecture within the liver tissue. Histopathological analysis can reveal localized

regions of immune cell accumulation, providing clues to the areas of the liver that are most affected by inflammation and damage [25].

Hepatocellular Cancer: Liver-resident NK cells play a crucial role in the histological outcomes and disease progression of hepatocellular cancer. Their presence and activity within the tumor microenvironment can be histologically observed. The infiltration of NK cells into the tumor area and their interactions with tumor cells and other immune cells are significant histopathological features. The balance between pro-tumorigenic and anti-tumorigenic signals can be visually assessed in histological sections, providing insights into the potential for tumor progression or regression. This histopathological analysis is valuable not only for diagnosis but also for prognostication and treatment planning [26].

Tissue analysis: Immuno-histopathological analysis of liver tissue is a crucial method for understanding the histological features and immune cell populations in this organ. This examination is essential for diagnosing liver diseases, studying immune responses, and identifying specific immune cell populations, including natural killer (NK) cells. This overview will elucidate the histological techniques commonly employed, emphasizing their role in the detection and characterization of immune cell populations, particularly NK cells, in hepatic tissue.

Histological Techniques: Histopathological analysis reveals the profound implications of liver-resident NK cells in liver disorders. Their presence and activity influence tissue architecture, immune cell distribution, and the degree of tissue damage, providing insights into disease progression and histological outcomes. Understanding these implications is essential for diagnosis, prognosis, and the development of targeted therapeutic strategies for liver disorders.

1. Hematoxylin and Eosin (H&E) Staining: H&E staining is a standard histological method that imparts color to cell nuclei (hematoxylin) and cytoplasm (eosin). It provides a basic overview of liver tissue architecture, helping identify inflammation, fibrosis, and structural abnormalities [27].
2. Immunohistochemistry (IHC): IHC employs specific antibodies to target and label antigens of interest. For immune cell identification, antibodies against cell surface markers are crucial. For NK cell detection, markers such as CD56 and CD16 are commonly used [28].
3. Immunofluorescence (IF): IF allows for the visualization of immune cells by using fluorescently labeled antibodies. It is valuable for colocalization studies and assessing cellular interactions within hepatic tissue [28].
4. In Situ Hybridization (ISH): ISH techniques use labeled RNA or DNA probes to detect specific nucleic acid sequences, such as mRNA for cytokines or specific gene expression in immune cells [29].
5. Electron Microscopy: Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) provide high-resolution images, enabling the visualization of ultrastructural details of cells and tissues, including immune cells [30].

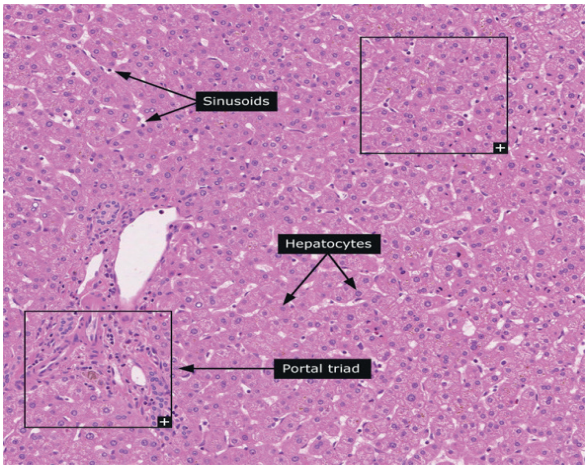

Figure 4: Histological features of liver tissue (H& E staining)[31]

Identifying the NK Cell: Histology plays a critical role in identifying and characterizing immune cell populations within hepatic tissue:

1. NK Cell Detection: NK cells are characterized by their unique markers, including CD56 and CD16. IHC and IF techniques using antibodies against these markers enable the precise identification and localization of NK cells within liver tissue [32].
2. Cellular Distribution: Histological methods allow researchers to assess the distribution of immune cell populations within different liver compartments, including the sinusoids

and portal tracts, providing insights into their spatial relationships [32].

3. Quantification: Quantification of immune cell populations, including NK cells, is possible through histological techniques. This quantification aids in understanding the density and dynamics of immune cell infiltration during liver diseases [8].

4. Functional Insights: Combining histological analysis with functional assays (e.g., cytokine staining) enables the assessment of immune cell activation states and their roles in liver pathology and immune responses [33].

It is highly worthy of note that histological techniques are indispensable for examining liver tissue, identifying immune cell populations, and characterizing their distribution and activation. The precise detection and analysis of NK cells within hepatic tissue, made possible by these techniques, contribute to a comprehensive understanding of liver immunity and pathology

Other Immune Cells:

1. Cross-talk with Dendritic Cells (DCs): NK cells in the liver can interact with DCs, which play a pivotal role in antigen presentation and immune activation. These interactions involve the release of IFN-γ by NK cells, promoting DC maturation and enhancing their antigen-presenting capabilities [34].

2. Collaboration with T Cells: NK cells can influence the adaptive immune response by interacting with CD4+ and CD8+ T cells. They can promote the priming and activation of T cells through cytokine production, particularly IFN-γ, which is involved in enhancing T-cell responses against liver pathogens and tumors [3].

3. Regulation of Liver-Resident Immune Cells: Liver-resident NK cells are known to interact with other immune populations, such as liver-resident T cells and macrophages. These interactions contribute to the overall orchestration of immune responses within the liver, ensuring a balanced defense against threats [23].

NK cells are central players in liver defense, acting as a first line of defense against viral infections and malignancies. Their intricate mechanisms of action, which involve cytotoxicity, cytokine production, and interactions with various immune cells, make them indispensable in maintaining hepatic homeostasis. Pivotal studies have shed light on the dynamic and multifaceted role of NK cells in liver immunity, further emphasizing their significance in safeguarding this vital organ.

Overview of the NK Cell Functionality: NK cells are innate immune cells known for their rapid and effective response against infected or transformed cells, particularly in the context of viral infections and cancer. They are characterized by their ability to recognize and eliminate target cells without the need for prior sensitization [35].

1. Cytotoxicity: NK cells release cytotoxic granules containing perforin and granzymes, which induce apoptosis in target cells [36].

2. Cytokine Production: NK cells produce cytokines, such as interferon-gamma (IFN-γ), which play a crucial role in regulating the immune response [17].

3. Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC): NK cells can also kill antibody-coated target cells, linking the innate and adaptive immune responses [37].

Vivacious Role of the NK Cell: NK (Natural Killer) cells, a subset of lymphocytes, are known for their potent cytotoxicity against virus-infected cells and tumours. In the liver, NK cells play a vital role in defending against invading pathogens and preventing malignant transformations of hepatocytes. NK (natural killer) cells comprise 10%-15% of peripheral blood mononuclear cells and have morphology of large, granular lymphocytes with the central role of killing the virus-infected and malignantly transformed cells, without prior sensitization. NK cells participate in hematopoiesis regulation, reproduction processes, as well as in numerous immune system reactions in vivo[38]. This section explores the multifaceted functions and intricate mechanisms underlying NK cell participation in liver defense, drawing on pivotal studies that highlight their dynamic role and interactions with other immune cells.

Significance of the Resident NK Cell: The liver, a multifunctional organ nestled within the human abdominal cavity, plays an indispensable role in a wide array of physiological processes. Beyond its well-recognized functions in metabolism, digestion, and detoxification, the liver also serves as a formidable guardian of the body's

immune defences. Within this intricate realm of immunological function, liver-resident immune cells, particularly natural killer cells, emerged as the key sentinels in the liver's constant vigilance against threats. This article delves into the unique immunological role of the liver, with a special emphasis on the significance of liver resident NK cells. By exploring their specialized functions and interactions within the liver's distinctive microenvironment, we illuminate their critical contributions to immune surveillance, response to infections, tumour surveillance, and immune tolerance in this vital organ.

1. Unique Microenvironment: The liver provides a distinct microenvironment that influences the function of resident immune cells. NK cells are well-adapted to this environment due to the liver's constant exposure to blood borne pathogens and foreign antigens [34].
2. Surveillance against Infections: Liver resident NK cells are crucial for early defence against viral infections. They are able to quickly recognize and eliminate infected cells, limiting the spread of viruses within the liver and to other organs [17].
3. Tumour Surveillance: NK cells in the liver also play a vital role in detecting and destroying cancerous cells. They are particularly effective against liver tumours and metastatic cancer cells that may enter the liver through the bloodstream [39].
4. Immune Tolerance: Liver resident NK cells contribute to immune tolerance and the prevention of autoimmune responses. They help maintain a delicate balance between immune activation and suppression within the liver [18].
5. Interaction with Other Immune Cells: Liver NK cells interact with other immune cells, such as Kupffer cells, dendritic cells, and T cells, influencing the overall immune response in the liver [15].
6. Hepatitis and Liver Diseases: Dysfunction of liver resident NK cells has been associated with chronic liver diseases, particularly viral hepatitis [15].
7. Potential Therapeutic Targets: Harnessing the unique properties of liver resident NK cells holds promise for future immunotherapies against liver diseases and cancers [39].

Creating New Pathways: There have been notable developments in the field of immunohistopathological evaluation; nonetheless, there are still difficulties in the study of liver NK cells. It is critical to recognise the current gaps in our knowledge of hepatic NK cell dynamics and provide potential solutions in order to address these issues and map out future research directions.

Limitations

Immunohistopathological examination of liver NK cells face several limitations and constraints, including:

1. Inhibitory ligands and cytokines: Suppressive cells in the tumor microenvironment (TME) pose a direct threat to therapeutic NK cells through presentation of inhibitory ligands and secretion of suppressive cytokines and metabolites
2. Access to the tumor: Prior to these challenges, NK cells must find their way into and persist in the tumor itself.
3. Immunosuppression: Immunosuppression often results from chemotherapy or radiation administered alongside allogeneic NK cells.

Future Research

To overcome these obstacles, promising avenues for future research include:

1. Immunometabolic inhibition: Immunometabolic inhibition is critical for designing a new cohort of effective natural killer cell immunotherapies against solid tumors such as HCC.
2. NK cell engineering: Recent developments in the manufacturing and genetic or metabolic engineering of NK cells to have robust and prolonged antitumor responses in preclinical and clinical settings.
3. Off-the-shelf NK cells: Various sources of NK cells for cellular immunotherapy are being developed, including transfer of cytokine-activated autologous NK cells and mismatched inhibitory receptors and ligands from allogeneic NK cells.

Technological innovations that may surmount these obstacles include:

1. Therapeutic antibodies: Therapeutic antibodies that drive antibody-dependent

cellular cytotoxicity.

2. Chimeric antigen receptors: Chimeric antigen receptors that increase targeting of therapeutic NK cells toward cancer.
3. Magnetic manipulation: Magnetic-manipulated NK cell proliferation and activation that enhance immunotherapy of orthotopic liver cancer.

While challenges persist in the immunohistopathological examination of liver NK cells, promising avenues for future research and technological innovations may surmount these obstacles, fostering a deeper understanding of liver NK cell dynamics.

CONCLUSION

Our review underscores the undeniable significance of NK cells in liver defence. The promising avenues for future research, including single-cell analysis, immunotherapeutic strategies, and biomarker discovery, hold the potential to unravel the full spectrum of NK cell functions within the liver. Continued research endeavour is necessary to harness the full capabilities of NK cells, ultimately leading to better insights, innovative therapies, and enhanced protection for the liver, and by extension, the entire body. The study also explored the challenges researchers encounter when studying liver NK cells.

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