ChinaRxiv

AI translation · View original & related papers at
chinarxiv.org/items/chinaxiv-202308.00216

Advances in Complement Receptor Immunoglobulin Superfamily Molecules in Regulating Liver Immune Responses

Authors: Yang Shusen, Li Jingtao, Yan Shuguang, Jiao Junzhe, Yang Shusen

Date: 2023-08-20T00:00:00+00:00

Abstract

Kupffer cells (KCs) constitute an important component of hepatic immune cells and are crucial for maintaining tissue homeostasis and mounting rapid responses to liver injury. Complement receptor of the immunoglobulin superfamily (CRIg) is a receptor protein on the KC membrane that can capture pathogenic microorganisms flowing through hepatic blood via complement binding and mediate hepatic immune responses by regulating immune cells within the liver. Recent studies on CRIg have further established its key role in regulating liver immunity. This review primarily summarizes the mechanisms of CRIg action and the latest research advances in its regulation of hepatic immune responses.

Full Text

Research Progress of Complement Receptor of Immunoglobulin Superfamily in Regulating Liver Immunity

YANG Shu-sen[1], LI Jing-tao[2], YAN Shu-guang[1], JIAO Jun-zhe[2]*

[1]School of Basic Medical Sciences, Shaanxi University of Chinese Medicine, Xianyang 712046, China
[2]Department of Hepatology, Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, China

Abstract

Kupffer cells (KCs) constitute a crucial component of the hepatic immune system, playing a vital role in maintaining tissue homeostasis and mounting rapid responses to liver injury. Complement receptor of immunoglobulin superfamily (CRIg) is a receptor protein expressed on the KC membrane that captures

pathogenic microorganisms from hepatic blood flow through complement binding while also mediating hepatic immune responses by regulating immune cells within the liver. Recent studies have further established the pivotal role of CRIg in modulating liver immunity. This review summarizes the mechanisms of CRIg action and the latest research progress in its regulation of hepatic immune responses.

Keywords: CRIg; Kupffer cells; hepatic immunity; pathogenic microorganisms

The liver serves as a critical immune organ in the human body, and Kupffer cells (KCs), as liver-resident macrophages, are key regulators of hepatic immune responses. KCs are widely distributed within hepatic sinusoids, where they not only phagocytose pathogens entering through portal venous or arterial circulation but also activate other immune cells in the blood to eliminate pathogenic microorganisms. Blood flow increases the difficulty of capturing pathogens, necessitating complement assistance for KCs to rapidly seize microorganisms. While complement can recognize and bind pathogens, nearly all complement receptors fail to fully engage their ligands under shear flow conditions. Currently, only CRIg, specifically expressed on macrophage surfaces, can bind pathogens under such dynamic conditions. Recent research on CRIg has further confirmed its essential role in clearing pathogenic microorganisms and regulating immune cells. This article reviews recent findings on CRIg' s mechanisms in hepatic immune modulation to provide a theoretical foundation for future investigations.

1 Overview of CRIg

CRIg, also known as V-set and immunoglobulin domain-containing protein 4 (VSIG4), is a 399-amino-acid protein encoded by a gene spanning 18.3 kb with eight exons, located in the border region between markers DXS1213 and DXS1194 on the human X chromosome. As a type 1 transmembrane immunoglobulin superfamily member belonging to the B7 family-related proteins, CRIg exhibits functional similarities to both B7 family co-inhibitory molecules and complement receptors. It possesses the capacity to inhibit T cell proliferation and differentiation characteristic of the B7 family, while also maintaining complement receptor functions for pathogen clearance. Structurally, CRIg comprises either IgV and IgC2 domains (huCRIg(L)) or a single IgV-type immunoglobulin domain (huCRIg(S)) and muCRIg. In terms of distribution, CRIg is primarily expressed on subsets of tissue-resident macrophages, with KCs representing the largest population, making the liver the principal site for CRIg-mediated immune regulation. Beyond macrophages, CRIg is also present on dendritic cells, and its expression pattern partially determines its immunological properties. As an essential component of the innate immune system, CRIg plays important roles in maintaining immune tolerance, host defense, and other immunomodulatory functions.

2 Mechanism of Action of CRIg

CRIg participates in hepatic immune responses primarily through complement binding. The complement system comprises serum proteins and cell surface receptors, with the liver serving as the main production site for complement proteins. As part of the innate immune system, complement can utilize pre-existing IgM antibodies as recognition mechanisms while also directly binding and killing pathogenic microorganisms. Complement integrates with adaptive immunity by promoting B cell-mediated antibody responses during early immune reactions, thereby regulating adaptive immune defense. Complement C3 contains eight macroglobulin-like domains (MG1-MG8). Upon pathogen contact, C3 undergoes continuous structural changes [Figure 1: see original paper]. The TED domain masks most binding surfaces for other complement components, whereas in C3b, the CUB and TED domains undergo substantial movement, exposing the thioester site for covalent binding to pathogens while simultaneously unfolding the B factor binding site, which drives C3 conversion and initiates activation. Following CRIg binding to C3b, only the variable region MG6 exhibits minor loop movements. Moreover, the CRIg binding site and TED domain are located on opposite sides of the β-chain, enabling macrophage-expressed CRIg to readily bind C3b covalently attached to pathogens. Additionally, research indicates that complement enables platelet binding to pathogens, expanding the size of viral complexes and facilitating CRIg-mediated pathogen capture, although this pathway contributes more significantly to splenic immunity. Beyond complement-mediated binding, CRIg can also directly bind and clear bacteria. To avoid degradation, CRIg is actively transferred from phagosomes to recycling endosomal pools before lysosomal fusion, after which it is recruited back to the plasma membrane to ensure continued participation in phagocytic activity. Since macrophages are the most important effector cells for CRIg, regulating macrophages represents its primary mechanism of participating in hepatic immunity.

Figure 1. Structural changes from C3 to C3b and CRIg binding sites

3 Unique Immune Environment of the Liver

The liver serves as the primary surveillance organ for intravascular infections, with approximately 30% of total blood volume passing through the liver each minute. Hepatic blood supply originates mainly from the portal vein and hepatic artery, with nearly 70% of blood coming from the portal vein. As the first extra-intestinal organ connected to venous blood from the small and large intestines via the portal vein, the liver is uniquely susceptible to bacterial products translocated from the intestinal lumen into the portal circulation. While some pathogens flow through lymphatic vessels into mesenteric lymph nodes to initiate adaptive immune responses, most bypass splenic and lymph node immune surveillance and travel via the portal vein to the liver. Portal venous blood enters hepatic sinusoids, where pathogens and antigens activate various immune cells including KCs, T cells, and natural killer T cells within the sinusoidal

space. Although rapid blood flow hinders immune cell-pathogen binding, the slowed blood flow within hepatic sinusoids prolongs the interaction time between immune cells and pathogens. Despite reduced flow velocity, pathogen capture remains challenging. KCs account for 90% of all tissue-resident macrophages in the body, and as the principal immune cells in the liver, they are crucial for intercepting bacterial pathogens and maintaining blood sterility. Functionally, KCs primarily adhere to the surface of hepatic sinusoidal endothelial cells, and this unique positioning brings KCs into close proximity with pathogens, creating favorable conditions for CRIg-mediated pathogen capture. Overall, the liver' s unique immune environment is characterized by two key features: first, the liver is the primary organ mediating intravascular immunity, with surveillance and clearance of blood-borne pathogens representing a critical task for hepatic immune cells; second, Kupffer cells constitute the largest population of resident macrophages in the body, which partially determines their central role in hepatic immunity. Consequently, CRIg, which is both KC-associated and participates in blood immunity, may represent a key regulator of hepatic immune responses.

4 Role of CRIg in Hepatic Immunity

The liver' s unique physiological structure creates a distinctive immune environment. As the "right-hand man" for KCs in grasping pathogenic microorganisms, CRIg is currently the primary complement receptor capable of binding pathogen-complement complexes under shear flow conditions. Furthermore, CRIg can mediate the activation of KCs and other immune cells. The specific functions of CRIg are discussed below.

4.1 CRIg: The "Best Catcher" of Pathogenic Microorganisms

Fungal dissemination into the bloodstream can cause invasive fungal infections, with the liver being a key organ for fungal clearance. Clinical studies have observed that patients with liver cirrhosis or end-stage liver disease are more susceptible to *Cryptococcus neoformans* brain infections. Following intravenous injection of *C. neoformans*, CRIg knockout mice show significantly reduced fungal burden in the liver but increased burden in other organs. CRIg deficiency impairs KC phagocytic capacity and increases the probability of fungal escape, suggesting that loss of CRIg clearance function may elevate disease risk in other organs. Bacteria possess immune evasion capabilities; *Staphylococcus aureus* produces complement inhibitors and extracellular fibrinogen-binding proteins that inhibit C3b deposition on its surface, thereby blocking complement-mediated clearance. Bacterial lipoteichoic acid (LTA) is a critical molecule for bacterial growth and cell division. CRIg can directly recognize bacterial LTA, reducing the time required for KCs to capture Gram-positive bacteria, thus functioning as a pattern recognition receptor. Blood-borne parasites have complex survival mechanisms in blood. Research demonstrates that antibody-activated complement is essential for CRIg-mediated KC capture of circulating parasites.

However, this study also observed that CRIg cannot act as a pattern recognition receptor for direct binding of circulating African trypanosomes by KCs, suggesting limitations of the direct binding mechanism. CRIg also plays an important role in mediating viral invasion immunity. One study showed that complement C3b covalently binds to adenovirus, and CRIg mediates KC binding to C3b. After adenovirus phagocytosis, the capsid releases membrane-lytic protein VI, inducing KC death. Blocking CRIg prevents KC death following low-dose adenovirus inoculation, confirming that CRIg is an important protein involved in adenovirus capture. Overall, complement receptor function represents the primary mechanism by which CRIg mediates pathogen clearance. Although direct binding can capture pathogens more rapidly, this pathway requires further investigation [Figure 2: see original paper].

Figure 2. CRIg capture of pathogenic microorganisms within hepatic sinusoids

4.2 CRIg: The "Inhibitor" of Immune Cells

CRIg can respond to inflammatory stimuli and regulate macrophage activation. CRIg transmits feedback signals to activate the PI3K-Akt-STAT3 signaling axis, which upregulates pyruvate dehydrogenase kinase 2 and inhibits mitochondrial pyruvate metabolism, inducing PDH phosphorylation and suppressing mitochondrial reactive oxygen species (ROS) secretion and M1-like gene expression, thereby inhibiting macrophage activation. Additionally, antibody stimulation of CRIg induces recruitment of the adaptor protein MS4A6D in surface inhibitory signal complexes, subsequently activating the JAK2-STAT3-A20 signaling cascade to inhibit nuclear factor- B, which reduces expression of NOD-like receptor thermal protein domain associated protein 3 and interleukin-1β. Thus, CRIg plays an important role in suppressing macrophage activation and negatively regulating macrophage-driven intracellular inflammation. Beyond macrophage regulation, CRIg can inhibit proliferation of both mouse and human T cells. Programmed death-ligand 1 (PD-L1) effectively inhibits T cell activation, and in vitro experiments show that CRIg inhibition is similar to PD-L1. In vivo studies demonstrate that CRIg-Ig fusion molecules can suppress induction of cytotoxic T lymphocyte responses and development of T helper cell-dependent IgG responses, while blocking Th cell cytokine production simultaneously inhibits B cell activation. Subsequent research also shows that CRIg blocks T helper cell-dependent isotype switching by inhibiting activation and differentiation of helper T cells as well as isotype switching-induced cytokines produced by helper T cells, establishing CRIg as an effective negative regulator of T cell and Th cell responses. Notably, a recent study revealed that CRIg transmits direct co-inhibitory signals to $CD8^+$ T cells through an unknown counter-receptor on activated $CD8^+$ T cells, providing compelling evidence for CRIg regulation of T cell activation despite requiring further validation. Animal experiments show that CRIg-deficient mice fail to induce tolerance of liver T cells and natural killer T cells to their cognate antigens, demonstrating that CRIg inhibition also manifests in hepatic immune tolerance. Therefore, CRIg participates in hepatic

immune responses by regulating multiple immune cell types including T cells and B cells, primarily acting as an "inhibitor" to prevent excessive immune cell activation, thereby reducing excessive inflammatory and autoimmune responses in the liver [Figure 3: see original paper].

Figure 3. CRIg regulation of immune cells (All figures created with BioRender)

4.3 CRIg: A Potential Therapeutic Target for Liver Diseases

CRIg plays an important role in ameliorating liver diseases. Studies show that alcohol-related liver injury alters hepatic macrophage composition and phenotype, and reduced numbers of CRIg-expressing KCs impair pathogen clearance capacity. CRIg deficiency further exacerbates ethanol-induced liver disease in mice, while CRIg-Ig injection improves liver injury and excessive inflammatory responses. Additionally, reports indicate that in high-fat diet-induced nonalcoholic fatty liver disease (NAFLD), CRIg expression is significantly downregulated in both NAFLD patients and obese mice with fatty liver, which enhances the pro-inflammatory state of macrophages and activates nuclear factor- B signaling to accelerate inflammatory responses. CRIg knockout also accelerates insulin resistance and lipid deposition metabolic dysfunction in HFD mice, but both metabolic and inflammatory abnormalities return to normal upon CRIg restoration. In nonalcoholic steatohepatitis (NASH), single-cell RNA sequencing shows that the lipotoxic environment significantly reduces the number of CRIg-expressing KCs. In NASH mouse liver tissue, CRIg-expressing KCs are concentrated primarily in the central venous zone, while overall hepatic CRIg is markedly reduced, with CRIg expression negatively correlating with NASH severity. In hepatocellular carcinoma, CRIg expression is also significantly downregulated in pathological tissues, which may be closely associated with poor prognosis in hepatitis B virus-positive patients or hepatocellular carcinoma patients, further supporting the link between CRIg and liver-related diseases. From initial hepatic inflammation and injury to liver cancer, CRIg is generally in a suppressed state, which both exacerbates excessive inflammatory responses in the liver and impairs pathogen clearance mechanisms. Therefore, restoring normal CRIg function holds promise as a potential therapeutic target for multiple types of liver diseases.

5 Summary and Outlook

In summary, the liver' s unique structure determines the distinctiveness of hepatic immunity. Activating innate hepatic immunity and regulating adaptive immune responses are crucial for maintaining systemic immune homeostasis. CRIg plays important roles in clearing pathogens flowing through hepatic sinusoids, regulating the activity of intrahepatic immune cells, and modulating autoimmune diseases. CRIg primarily participates in pathogen clearance within hepatic sinusoids in the form of a complement receptor. Regarding immune cell regulation, CRIg functions predominantly as an immunosuppressive agent, alleviating excessive inflammatory responses and autoimmunity in the liver. As

KCs are the main participants in hepatic immunity, stabilizing CRIg levels as a key "pathogen-fighting" receptor on KCs is beneficial for maintaining hepatic immune homeostasis.

Only two decades have passed since CRIg' s discovery, and its mechanisms in regulating hepatic immunity remain incompletely elucidated. Notably, CRIg primarily intervenes in immune responses through immunosuppression, which mitigates excessive inflammatory reactions. However, its role remains controversial in diseases such as cancer that require moderate immune cell activation to block disease progression, with studies suggesting its potential to promote tumor growth. Therefore, research on CRIg must clarify its mechanisms in cancer and determine whether CRIg activation produces other adverse effects. Future studies should first elucidate the precise mechanisms through which CRIg functions in known immune environments and validate how to better exploit its immunosuppressive effects. Second, its role in adaptive immunity should be explored, such as whether it can directly bind Gram-negative bacteria or other pathogens. Finally, the safety of CRIg activation must be verified. Although the mechanisms of CRIg action remain to be fully defined, advances in detection technology and subsequent research will hopefully provide new directions for treating hepatic immune diseases.

References

[1] DBERNSMEIER C, VAN DER MERWE S, PÉRIANIN A. 2020. Innate immune cells in cirrhosis[J]. J Hepatol, 73(1): 186-201. DOI:10.1016/j.jhep.2020.03.027
[2] KULLE A, THANABALASURIAR A, COHEN T S, et al. 2022. Resident macrophages of the lung and liver: The guardians of our tissues[J]. Front Immunol, 13: 1029085. DOI:10.3389/fimmu.2022.1029085
[3] KRENKEL O, TACKE F. 2017. Liver macrophages in tissue homeostasis and disease[J]. Nat Rev Immunol, 17(5): 306-321. DOI:10.1038/nri.2017.11
[4] KUBES P, JENNE C. 2018. Immune responses in the liver[J]. Annu Rev Immunol, 36(1): 247-277. DOI:10.1146/annurev-immunol-051116-052415
[5] LEE M Y, KIM W J, KANG Y J, et al. 2006. Z39Ig is expressed on macrophages and may mediate inflammatory reactions in arthritis and atherosclerosis[J]. J Leukoc Biol, 80(4): 922-928. DOI:10.1189/jlb.0306160
[6] LI Y, WANG Q, LI J, et al. 2023. Therapeutic modulation of V Set and Ig domain-containing 4 (VSIG4) signaling in immune and inflammatory diseases[J]. Cytotherapy, 25(6): 561-572. DOI:10.1016/j.jcyt.2022.12.004
[7] HELMY K Y, KATSCHKE K J, GORGANI N N, et al. 2006. CRIg: a macrophage complement receptor required for phagocytosis of circulating pathogens[J]. Cell, 124(5): 915-927. DOI:10.1016/j.cell.2005.12.039
[8] ZHAO D, YANG F, WANG Y, et al. 2022. ALK1 signaling is required for the homeostasis of Kupffer cells and prevention of bacterial infection[J]. J Clin Invest, 132(3): e150489. DOI:10.1172/JCI150489
[9] MUNAWARA U, PERVEEN K, SMALL A G, et al. 2019. Human dendritic cells express the complement receptor immunoglobulin which regulates T cell

responses[J]. Front Immunol, 10: 2892. DOI:10.3389/fimmu.2019.02892
[10] GARRED P, TENNER A J, MOLLNES T E. 2021. Therapeutic targeting of the complement system: from rare diseases pandemics[J]. Pharmacol Rev, 73(2): DOI:10.1124/pharmrev.120.000072
[11] THORGERSEN E B, BARRATT-DUE A, HAUGAA H, et al. 2019. The role of complement in liver injury, regeneration, and transplantation[J]. Hepatology, 70(2): 725-736. DOI:10.1002/hep.30508
[12] GEISBRECHT B V, LAMBRIS J D, GROS P. 2022. Complement component C3: A structural perspective and potential therapeutic implications[J]. Semin Immunol 59: 101627. DOI:10.1016/j.smim.2022.101627
[13] ALCORLO M, LÓPEZ-PERROTE A, DELGADO S, et al. 2015. Structural insights on complement activation[J]. FEBS J, 282(20): 3883-3891. DOI:10.1111/febs.13399
[14] WIESMANN C, KATSCHKE K J, YIN J, et al. 2006. Structure of C3b in complex with CRIg gives insights into regulation of complement activation[J]. Nature, 444(7116): 217-220. DOI:10.1038/nature05263
[15] BROADLEY S P, PLAUMANN A, COLETTI R, et al. 2016. Dual-track clearance of circulating bacteria balances rapid restoration of blood sterility with induction of adaptive immunity[J]. Cell Host Microbe, 20(1): 36-48. DOI:10.1016/j.chom.2016.05.023
[16] VAN LOOKEREN CAMPAGNE M, VERSCHOOR A. 2018. Pathogen clearance and immune adherence "revisited" : Immuno-regulatory roles for CRIg[J]. Semin Immunol, 37: 4-11. DOI:10.1016/j.smim.2018.02.007
[17] MIKULAK J, BRUNI E, ORIOLO F, et al. 2019. Hepatic natural killer cells: organ-specific sentinels of liver immune homeostasis and physiopathology[J]. Front Immunol, 10: 946. DOI:10.3389/fimmu.2019.00946
[18] SEKI E, SCHNABL B. 2012. Role of innate immunity and the microbiota in liver fibrosis: crosstalk between the liver and gut: Toll-like receptors, microbiota and liver fibrosis[J]. J Physiol, 590(3): 447-458. DOI:10.1113/jphysiol.2011.219691
[19] PABST O, HORNEF M W, SCHAAP F G, et al. 2023. Gut-liver axis: barriers and functional circuits[J]. Gastroenterol Hepatol, 20(7): DOI:10.1038/s41575-023-00771-6
[20] YANG X, LU D, ZHUO J, et al. 2020. The gut-liver axis in immune remodeling: new insight into liver diseases[J]. Int J Biol Sci, 16(13): 2357-2366. DOI:10.7150/ijbs.46405
[21] TSOI K M, MACPARLAND S A, MA X Z, et al. 2016. Mechanism of hard-nanomaterial clearance by the liver[J]. Nat Mater, 15(11): 1212-1221. DOI:10.1038/nmat4718
[22] JU C, TACKE F. 2016. Hepatic macrophages in homeostasis and liver diseases: from pathogenesis to novel therapeutic strategies[J]. Cell Mol Immunol, 13(3): 316-327. DOI: 10.1038/cmi.2015.104.
[23] GUILLIAMS M, SCOTT C L. 2022. Liver macrophages in health and disease[J]. Immunity, 55(9): 1515-1529. DOI:10.1016/j.immuni.2022.08.002
[24] SINGH N, SIFRI C D, SILVEIRA F P, et al. 2015. Cryptococcosis in patients with cirrhosis liver and posttransplant outcomes[J]. Transplantation,

99(10): 2132-2141. DOI:10.1097/TP.0000000000000690
[25] SUN D, SUN P, LI H, et al. 2019. Fungal dissemination is limited by liver macrophage filtration of the blood[J]. Nat Commun, 10(1): 4566. DOI:10.1038/s41467-019-12381-5
[26] ZENG Z, SUREWAARD B G J, WONG C H Y, et al. 2016. CRIg functions as a macrophage pattern recognition receptor to directly bind and capture blood-borne gram-positive bacteria[J]. Cell Host Microbe, 20(1): 99-106. DOI:10.1016/j.chom.2016.06.002
[27] LIU G, FU Y, YOSRI M, et al. 2019. CRIg plays an essential role in intravascular clearance of bloodborne parasites by interacting with complement[J]. Proc Natl Acad Sci U S A, 116(48): 24214-24220. DOI:10.1073/pnas.1913443116
[28] HE J Q, KATSCHKE K J, GRIBLING P, et al. 2013. CRIg mediates early Kupffer cell responses to adenovirus[J]. J Leukoc Biol, 93(2): 301-306. DOI:10.1189/jlb.0612311
[29] LI J, DIAO B, GUO S, et al. 2017. VSIG4 inhibits proinflammatory macrophage activation by reprogramming mitochondrial pyruvate metabolism[J]. Nat Commun, 8(1): 1322. DOI:10.1038/s41467-017-01327-4
[30] HUANG X, FENG Z, JIANG Y, et al. 2019. VSIG4 mediates transcriptional inhibition of Nlrp3 and Il-1β in macrophages[J]. Sci Adv, 5(1): eaau7426. DOI:10.1126/sciadv.aau7426
[31] VOGT L, SCHMITZ N, KURRER M O, et al. 2006. VSIG4, a B7 family-related protein, is a negative regulator of T cell activation[J]. J Clin Invest, 116(10): 2817-2826. DOI:10.1172/JCI25673
[32] JUNG K, SEO S K, CHOI I. 2015. Endogenous VSIG4 negatively regulates the helper T cell-mediated antibody response[J]. Immunol Lett, 165(2): DOI:10.1016/j.imlet.2015.04.004
[33] WIDYAGARINI A, NISHII N, KAWANO Y, et al. 2022. VSIG4/CRIg directly regulates early CD8+ T cell activation through its counter-receptor in a narrow window[J]. Biochem Biophys Res Commun, 614: 100-106. DOI:10.1016/j.bbrc.2022.04.120
[34] JUNG K, KANG M, PARK C, et al. 2012. Protective role of V-set and immunoglobulin domain-containing 4 expressed on kupffer cells during immune-mediated liver injury by inducing tolerance of liver T- and natural killer T-cells[J]. Hepatology, 56(5): 1838-1848. DOI:10.1002/hep.25906
[35] DUAN Y, CHU H, BRANDL K, et al. 2021. CRIg on liver macrophages clears pathobionts protects against alcoholic liver disease[J]. Nat Commun, 12(1): DOI:10.1038/s41467-021-27385-3
[36] LI Y, SUN J P, WANG J, et al. 2019. Expression of Vsig4 attenuates macrophage-mediated hepatic inflammation and fibrosis in high fat diet (HFD)-induced mice[J]. Biochem Biophys Res Commun, 516(3): 858-865. DOI:10.1016/j.bbrc.2019.06.045
[37] LUO Z, JI Y, ZHANG D, et al. 2022. Microbial DNA enrichment promotes liver steatosis and fibrosis in the course of non-alcoholic steatohepatitis[J]. Acta Physiol (Oxf), 235(3): e13827. DOI:10.1111/apha.13827
[38] LI H Y, FU S W, WU J C, et al. 2023. Vsig4+ resident single-Kupffer cells improve hepatic inflammation fibrosis NASH[J]. Inflamm Res, 72(4):

DOI:10.1007/s00011-023-01696-1
[39] ZHU S, TAN W, LI W, et al. 2018. Low expression of VSIG4 is associated with poor prognosis in hepatocellular carcinoma patients with hepatitis B infection[J]. Cancer Manag Res, 10: 3697-3705. DOI:10.2147/CMAR.S165822
[40] JUNG K, JEON Y K, JEONG D H, et al. 2022. VSIG4-expressing tumor-associated macrophages impair anti-tumor immunity[J]. Biochem Biophys Res Commun, 628: 18-24. DOI:10.1016/j.bbrc.2022.08.055
[41] SMALL A G, AL-BAGHDADI M, QUACH A, et al. 2016. Complement receptor immunoglobulin: a control point in infection and immunity, inflammation and cancer[J]. Swiss Med Wkly, 146: w14301. DOI:10.4414/smw.2016.14301

Note: Figure translations are in progress. See original paper for figures.

Source: ChinaXiv —Machine translation. Verify with original.