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Review

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Review

The comprehensive role of apoptosis inhibitor of macrophage (AIM) in pathological conditions

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Summary

CD5L/AIM (apoptosis inhibitor of macrophage), as an important component in maintaining tissue homeostasis and inflammation, is mainly produced and secreted by macrophages but partially dissociated and released from blood AIM-IgM. AIM plays a regulatory role in intracellular physiological mechanisms, including lipid metabolism and apoptosis. AIM not only increases in autoimmune diseases, directly targets liver cells in liver cancer and promotes cell clearance in acute kidney injury, but also causes arteriosclerosis and cardiovascular events, and aggravates inflammatory reactions in lung diseases and sepsis. Obviously, AIM plays a pleiotropic role in the body. However, to date, studies have failed to decipher the mechanisms behind its different roles (beneficial or harmful) in inflammatory regulation. The inflammatory response is a "double-edged sword," and maintaining balance is critical for effective host defense while minimizing the adverse side effects of acute inflammation. Enhancing the understanding of AIM function could provide the theoretical basis for new therapies in these pathological settings. In this review, we discuss recent studies on the roles of AIM in lipid metabolism, autoimmune diseases and organic tissues, such as liver cancer, myocardial infarction, and kidney disease.

Keywords: AIM; immunoregulation; inflammation; disease

Abbreviations: CLF: acute and chronic liver failure; AD: atopic dermatitis; AIM: apoptosis inhibitor of macrophage; AKI: Acute kidney injury; AKT: protein kinase B; ALS: Amyotrophic Lateral Sclerosis; anti-dsDNA: anti-double stranded DNA antibody; APAP: acetaminophen; ARDS: acute respiratory distress syndrome; BD: Behcet's disease; C3: complement 3; CAP: community-acquired pneumonia; CCL2/MCP-1: monocyte chemoattractant protein-1; CD: Crohn's disease; CD5L: CD5 antigen-like; CDC: complement dependent cytotoxicity; CRP: C-reactive protein; CXCL1: Chemokine (C-X-C motif) ligand 1; ECM: extracellular matrix; ERK: extracellular regulated protein kinases; ESR: erythrocyte sedimentation; EV: extracellular vesicles; FFA: free fatty acid; GM-CSF: granulocyte-macrophage colony stimulating factor; GSK3: Glycogen synthase kinase 3; HBV: Hepatitis B virus; HCC: hepatocellular carcinoma; HFD: high-fat diet; HSPN: Henoch-Schönlein purpura nephritis; IFN-γ: Interferon-gamma; IgAN: IgA nephropathy; IL-23: interleukin 23; iNOS: inductible Nitric Oxide Synthase; KIM-1: kidney injury molecule 1; LDL: low density lipoprotein; LXR/RXR: nuclear receptor liver X receptor/retinoid X receptor; LXRE: liver X receptor elements; MARE: Maf recognition elements; MMPs: matrix metalloproteinases; MRSA: Methicillin-resistant Staphylococcus aureus; NASH: non-alcoholic steatohepatitis; NF-κB: nuclear factor-κB; OA: Osteoarthritis; PLI: acute lung parenchyma injury; RA: Rheumatoid arthritis; ROS: reactive oxygen species; SCARB1: scavenger receptor SR-B1; SLE: Systemic lupus erythematosus; SNP: single nucleotide polymorphism; SOFA: sequential organ failure assessment; SPMS: secondary progressive multiple sclerosis; SRCR: scavenger receptor cysteine-rich; SREBP: Sterol regulatory element binding protein; STAT3: signal transducer and activator of transcription 3; TGFβ1: transforming growth factor β1; TLR: Toll-like receptor; TNF: tumor necrosis factor; UC: ulcerative colitis; WT: wild-type

Introduction

Apoptosis inhibitor of macrophage (AIM, also called CD5L and Api6; encoded by cd5l gene) is a 40 kDa soluble protein produced mainly by tissue-resident macrophages through transcriptional activation of nuclear receptor liver X receptor/retinoid X receptor (LXR/RXR) heterodimer and/or transcription factor MafB [1–3] (Fig. 1A). AIM belongs to the scavenger receptor cysteine-rich (SRCR) superfamily, which consists of three SRCR domains in series with about 100 amino acids [1]. In serum, AIM binds to the IgM pentamer of the Fc region, protecting AIM from renal excretion and maintaining high levels of circulating AIM (approximately 5 μg/ml in humans and mice) [4, 5]. Although AIM bound to IgM is functionally inactive, AIM is isolated from IgM during different diseases locally or throughout the body to perform its function of promoting disease repair [5, 6]. However, the binding mode of AIM to the IgM-Fc pentamer remains unclear.

Hiramoto *et al.* [7] speculated that AIM-IgM binding was most likely to occur through the disulfide bond between Cys414 in the Fc-Cμ3 domain of IgM and Cys194 in the SRCR2 domain of AIM(figure 1A). AIM-Fc binding was comparable to that of antibody–antigen interaction, but the affinity was relatively low. In mice lacking natural IgM, the synthesis of IgM-Fc enhanced endogenous blood AIM, and this treatment did not induce any unwanted immune response [8].

Glycogen synthase kinase 3 (GSK3) is a serine/threonine kinase originally identified for its ability to phosphorylate and inhibit glycogen synthase [9]. Wang *et al.* [10]. found

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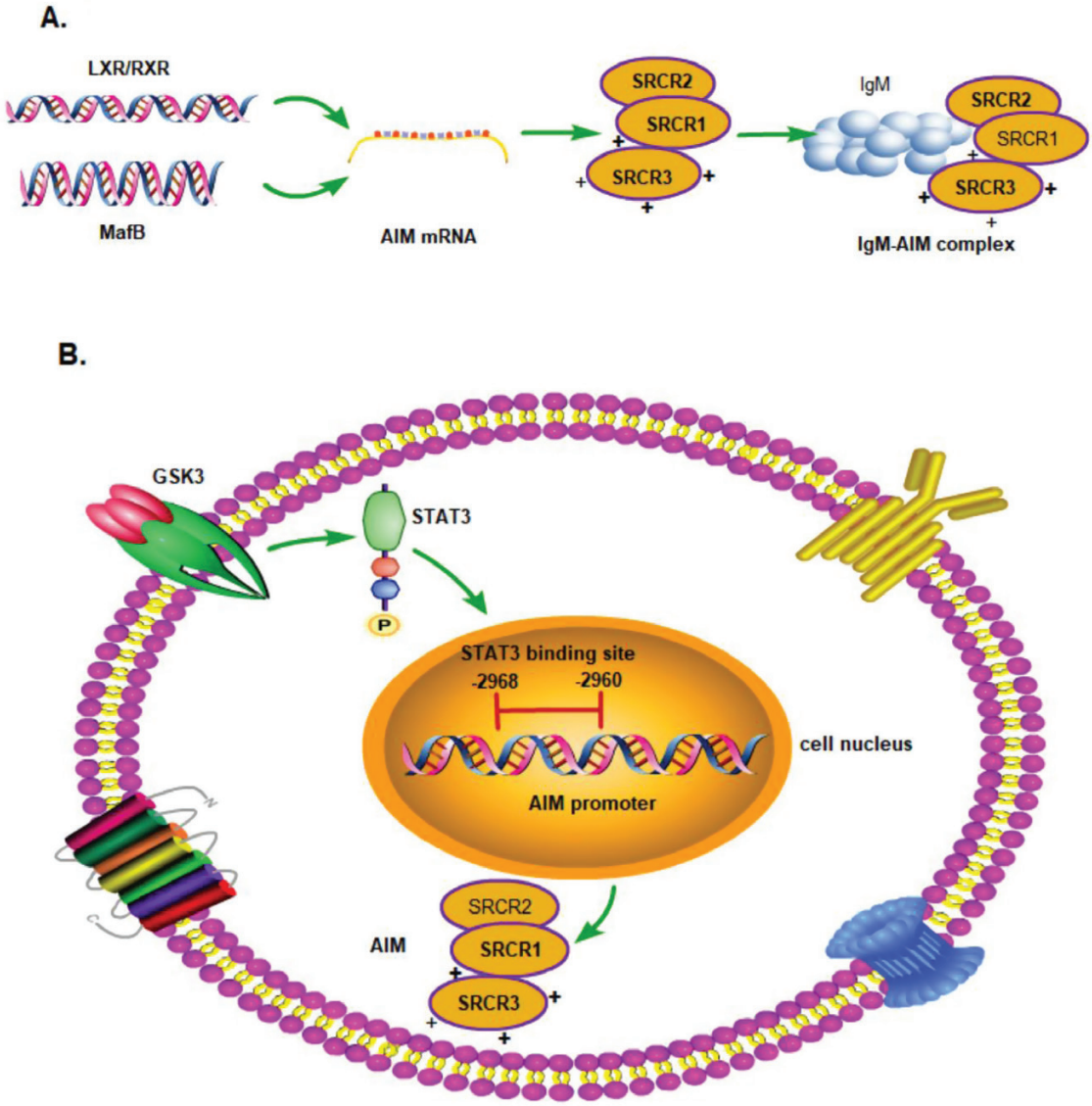

Figure 1: Transcriptional activation and IgM binding of AIM. A.AIM is activated by LXR/RXR or MafB transcription and bound with IgM. The three AIM domains play different properties when AIM-IgM is bound. Specifically, The binding of the two is most likely to occur through the disulfide bond between Cys414 in the Fc-Cμ3 domain of IgM and Cys194 in the SRCR2 domain of AIM; the SRCR1 domain may contribute to protein production efficiency and/or protein stability, but does not affect binding to IgM; the SRCR3 domain may interact with the Fc-Cμ4 domain. It may be mediated by the charge distribution of amino acids, because the SRCR3 domain has a surface cluster of positively charged amino acids and the Fc-Cμ4 domain is negatively charged [7]. B. AIM expression is activated by glycogen GSK3. GSK3 activation of STAT3, which affectes the promoter activity of AIM. AIM promoter sequences contained between -2968 and -2960 contained the putative STAT3 binding site [10].

that GSK3 regulated the expression of AIM through activated STAT3, and further analysis found that AIM promoter sequences contained between –2968 and –2960 contained the putative STAT3 binding site, suggesting that STAT3 may regulate the expression of AIM by affecting the promoter activity of AIM (Fig. 1B). In Th17 cells, AIM regulated the fatty acid composition of polyunsaturated fatty acids with saturated and monounsaturated fatty acids. AIM inhibited cholesterol synthesis by regulating key enzymes sc4mol and cyp51 pathways. IL-23 inhibited AIM, and AIM inhibited the pathogenicity of Th17 cells. Sustained AIM expression antagonized the pathogenicity driven by IL-23 [11].

As for the receptor of AIM, in the current study, the specific receptor of AIM is not clear. AIM can bind with a wide range of molecules, one of which is CD36. CD36 is a membrane glycoprotein presenting on platelets, mononuclear phagocytes, adipocytes, liver cells, muscle cells and some epithelial cells. In phagocytes, CD36 participated in apoptosis, internalization of certain bacterial and fungal pathogens as well as modified low density lipoprotein through its function as a scavenger receptor that recognized specific oxidized phospholipids and lipoproteins, which led to inflammatory responses and atherosclerotic thrombotic disease [12].

Immunological roles of AIM

AIM levels in serum are IgM dependent under physiological conditions, and the significance of the circulating AIM–IgM complex may lie in the storage function of AIM molecules. The mechanism for responding to inflammatory stimuli

may involve an increase in free-form AIM levels, thus providing a buffer for the sudden onset of pathological processes in the initial stages of inflammation. The level of free form AIM may be increased by [13]: (1) free form AIM released from the AIM-IgM complex by enzymatic decomposition or other dissociation mechanisms; (2) free-form AIM is released from storage sites in some body compartments, such as the cytoplasm of macrophages or other cell populations (Fig. 2A). This delayed increase in AIM production was a compensatory mechanism to prevent AIM shortages caused by the acute phase of inflammation. In addition, AIM bound to p19 to form a new p19/AIM complex heterodimer [14], which can induce cell proliferation, STAT5 phosphorylation, and enhance GM-CSF expression(figure 2A). Phosphorylated STAT3 translocated to the nucleus after IL-10 stimulation and bound directly to the AIM promoter [15], resulting in increased AIM promoter activity and subsequently induced enhanced AIM mRNA and protein expression.

Sanjurjo *et al.* [16] reported a novel role of AIM in regulating macrophages homeostasis. AIM activated autophagy mediated regulation of TLR activation in macrophages through CD36 receptors, and AIM blocked TLR-induced secretion of TNF and IL-1β while increasing IL-10 levels, thereby downregulating macrophages inflammation (Fig. 2B). *In vitro* and *in vivo* studies of gene-targeted mice have shown that AIM was involved in regulating the apoptosis of developing CD4/CD8 double-positive thymocytes [1]. However, its high expression in tissue macrophages, including those in the liver, abdominal cavity, and red pulp of the spleen, as well as its binding to LDL and other cholesterol-containing antigens [1], suggests that the molecule has additional functions that require further investigation.

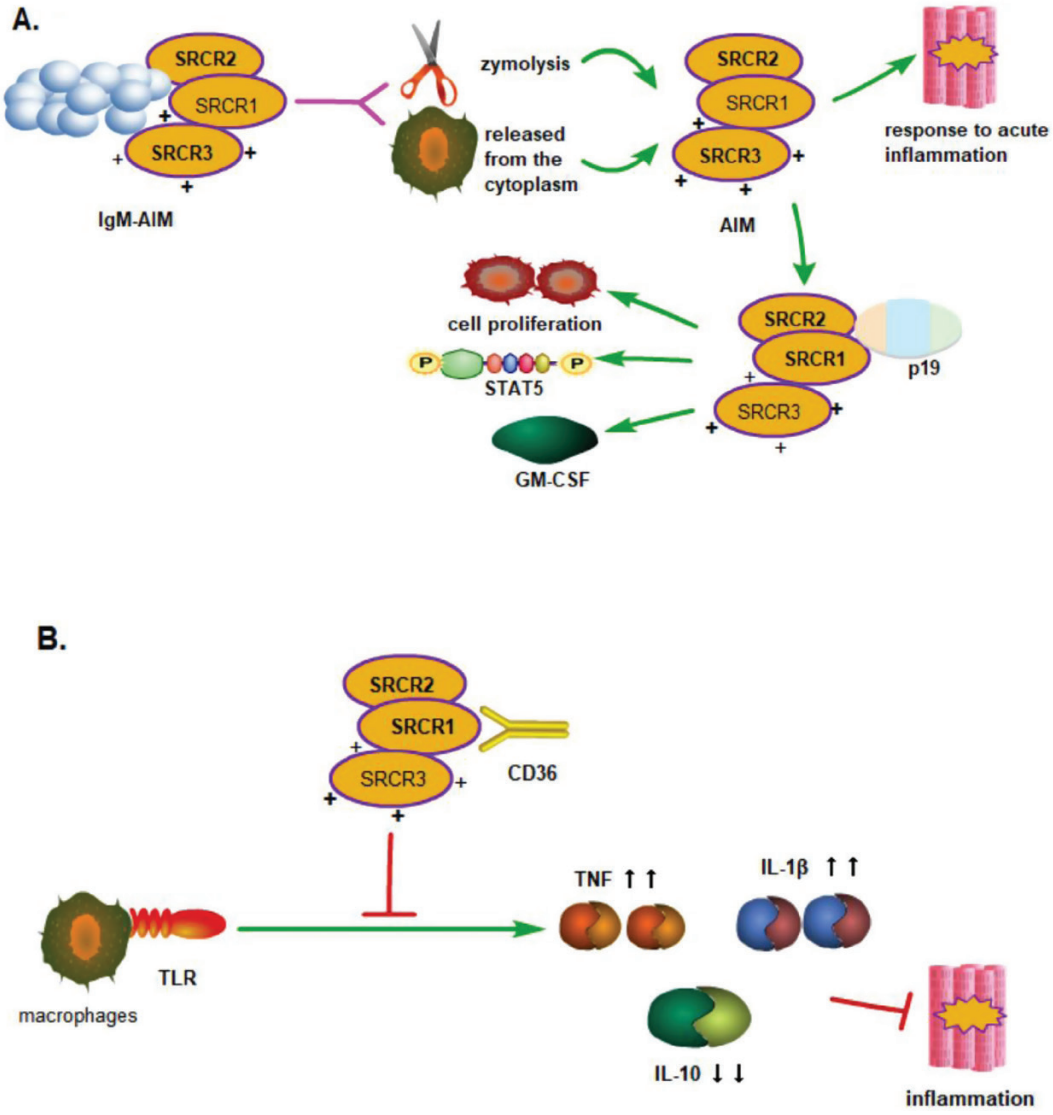

Figure 2: Immunological effects of AIM in cells. A.AIM dissociation mechanism and subsequent immune function. The level of free form AIM may be increased by [13] enzymatic decomposition or releasing from storage sites such as the cytoplasm. Free AIM not only responds to acute inflammation [13], but also binds to p19 to form a new p19/AIM complex heterodimer [14], which can induce cell proliferation, STAT5 phosphorylation, and enhance GM-CSF expression. B.A novel role of AIM in regulating macrophages homeostasis. AIM activates autophagy mediated regulation of TLR activation in macrophages through CD36 receptors, and AIM blocks TLR-induced secretion of TNF and IL-1β while increasing IL-10 levels, thereby down-regulating macrophages inflammation [16]. symbolize promotion; symbolize inhibtion.

Table 1: Effect of AIM in different diseases

Types of diseases	main function	references
lipid metabolism	AIM was an atherogenic protein involved in several events of macrophage homeostasis, including macrophage survival, adhesion to endothelial cells, and oxidized LDL uptake and subsequent foam cell formation.	[17–19]
	AIM in the blood increased obesity induced adipocytes' lipolysis and triggered the efflux of saturated FFA to stimulate the TLR4 pathway, which triggered adipocytes to produce pro-inflammatory chemokines.	[20–22]
	Compared with $AIM^{+/+}$ mice, HFD caused an increase in fat cell size and fat weight in $AIM^{-/-}$ mice, and injection of recombinant AIM inhibited HFD-induced increase in fat mass.The mRNA levels of pro-inflammatory cytokines such as TNFα, IL-6 and IL-1β in adipose tissue and liver of $AIM^{-/-}$ mice fed with HFD for 12 weeks were significantly lower than those of $AIM^{+/+}$ mice.	[20]
	Many $AIM^{-/-}$ mice developed HCC tumors after treatment with a high fructose diet.	[23]
hepatic disease	AIM protein played a protective role on fibrosis through a variety of mechanisms, including prevention of injury, prevention of fibrosis and immune cell infiltration, and AIM changed the phenotype of recruited macrophages from $Ly6C^{hi}$ to $Ly6C^{low}$.	[24]
	The HCC incidence of AIM-felinized mice was significantly lower than that of $AIM^{-/-}$ mice after 1 year of HFD.	[25]
	AIM levels were elevated in liver tumors compared with surrounding non-tumor tissues, and was associated with the characteristics of aggressive tumors enhanced proliferation and poor clinical outcomes, and AIM even could protect HCC cells from cisplatin-induced apoptosis.	[26]
	Increment of AIM expression in the liver of mice treated with excessive APAP may contribute to the promotion of mitochondrial oxidative stress in liver cells.	[27]
	Sanchez-rodriguez et al reported that circulating AIM lacked in acute and chronic liver failure (ACLF) significantly associated with circulatory, cerebral, and respiratory failure.	[28]
renal disease	IgM-free AIM crossed the glomerular membrane and accumulates on debris of dead cells in the lumen associated with AKI, thereby blocking the proximal renal tubules, and deposited AIM promoted phagocytosis and clearance of debris, contributing to overall renal tissue repair.	[29]
	In the IgAN animal model, the mRNA expression level of glomerular inflammation and fibrosis gene in $AIM^{-/-}$ mice was significantly lower than that in WT mice. Recombinant AIM can restore $AIM^{-/-}$ mouse glomerular IgM/IgG co-deposition and glomerular damage, suggesting that abnormal accumulation of AIM can lead to kidney damage.	[30]
cardiovascular disease	AIM was a key factor in the initiation of obesity-related chronic inflammation, leading to insulin resistance, which led to the progression of atherosclerosis and future cardiovascular events.	[21], [22]
	AIM was highly expressed in foam macrophages collected from atherosclerotic plaques and supported macrophage survival by inhibiting apoptosis and its subsequent accumulation, leading to inflammatory responses within the lesion and ultimately to disease progression.	[2]
	The $AIM^{-/-}$ mice increased survival rate, reduced heart rupture rate, more M1 macrophages, lower levels of M1 markers (iNOS and IL-6) and MMP-2 and 9 in acute stage after myocardial infarction than WT mice.	[31]
	In the context of atherosclerosis, the loss of AIM in $LDLr^{-/-}$ mice led to a sharp increase in the number of apoptotic macrophages in the lesions, resulting in a decrease in foam macrophage content and significantly reduced plaque growth.	[2]
	AIM was secreted by epicardial adipose tissue in patients with heart failure after isoproterenol treatment, which may activate the TLR4/NF-κB pathway on adjacent cells to produce pro-inflammatory cytokines.	[32]
	In experimental stroke models, AIM-deficient mice showed severe neurological damage and higher mortality compared to wild-type mice.	[33]
	AIM was the only independent predictor of cardiac rejection.	[34]
pulmonary disease	Serum AIM had important value in differentiating bacterial infection from viral infection and predicting 30-day mortality in adult patients with pneumonia.	[35]
	AIM was also an independent risk factor for trauma-related acute lung parenchyma injury (PLI) or acute respiratory distress syndrome (ARDS) within 24 hours after trauma.	[36]
	AIM can enhance the uptake of macrophages and neutrophils on S. aureus. Blocking AIM with anti-AIM antibodies improve bacterial clearance, such as a reduction in bacterial load in the lungs and blood, which provided lower inflammatory stimulation.	[37]
	AIM may be a potential biomarker for non-invasive diagnosis of lung cancer.	[38]

Table 1. Continued

Types of diseases	main function	references
autoimmune disease	AIM levels were elevated in patients with ALS, SPMS, RA, OA, SLE and psoriatic disease. AIM can be used as a new sensitive biomarker to assist in the evaluation of disease activity.	[39–42],[43],[44]
	AIM levels were high only in patients with CD and not in patients with UC or intestinal Behcet's disease (BD), assessing AIM levels may help distinguish CD from other chronic intestinal diseases.	[45]
	AIM was a potential plasma biomarker for predicting pre-eclampsia, and elevated in prostate cancer, atopic dermatitis (AD) and age-related macular degeneration.	[46–49]
tuberculosis bacterium disease	AIM induced the increase of ROS production and antimicrobial peptide synthesis in infected mice, and accompanied by the increase of autophagy mechanism, enhanced the killing activity of macrophages.	[16]
peritonitis	Lack or insufficiency of AIM may result in persistent inflammation of the peritoneum. The pro-inflammatory cytokines released in the early stages; In the late stage, mesenchymal cells were redistributed on the peritoneal surface of $AIM^{+/+}$ mice. Mesenchymal cells were non-professional phagocytes, and AIM enhanced the phagocytosis of mesenchymal cells to dead cell fragments.	[50]
sepsis	In sepsis mouse models, AIM down-regulated production of inflammatory cytokines TNF-α, IL-6 and chemokine CCL2, as well as leukocyte infiltration in alveolar lavage fluid, including macrophages, neutrophils and lymphocytes, were blocked. AIM disrupted immune homeostasis by inducing abnormal IL-10 production, leading to failure to eradicate invading pathogens in the immunosuppression stage, which may lead to long-term inflammation after sepsis.	[51]

The role of AIM in different diseases

AIM is released from the IgM-AIM complex and participates in the compensatory regulation of the body. Timely removing the damaged cell and debris generated in the body, avoiding the excessive generation of inflammation, so as to maintain the normal homeostasis and function of the body. However, the performance of AIM in pathological state is not so uniform. Table 1 summarizes the important role of AIM in various diseases.

AIM: crosstalk between lipid metabolism and inflammatory response

Although AIM was originally found to inhibit macrophage apoptosis, it was widely studied for its important role in lipid metabolism through CD36 receptors. Apparently, AIM levels were negatively associated with various metabolic index such as body mass index, obesity index, percentage of fat mass, waist circumference, low-density lipoprotein (LDL), and fasting blood glucose [52]. AIM was an atherogenic protein involved in several events of macrophage homeostasis, including macrophage survival, adhesion to endothelial cells, and oxidized LDL uptake and subsequent foam cell formation. Diet-induced obesity caused adipose tissue macrophages to shift from the M2 polarized state to the M1 pro-inflammatory state, which impaired insulin signaling and secreted pro-inflammatory cytokines such as TNFα, IL-1β, and IL-6 [17–19].

However, how obesity stimulated the infiltration and activation of pro-inflammatory cells, most importantly inflammatory macrophages and the M2-to-M1 transition, was largely unknown. Recently, it has been reported that AIM was one of the molecules mediating the crosslysis between adipocytes and macrophages (Fig. 3). Compared with $AIM^{+/+}$ mice, high fat diet (HFD) caused an increase in fat cell size and fat weight in $AIM^{-/-}$ mice, and injection of recombinant AIM inhibited HFD-induced increase in fat mass [20].The mRNA levels of pro-inflammatory cytokines such as TNFα, IL-6, and IL-1β in adipose tissue and liver of $AIM^{-/-}$ mice fed with HFD for 12 weeks were significantly lower than those of $AIM^{+/+}$ mice [20]. The reasons for this phenomenon were as follows, increased AIM level in blood may induce severe lipolysis in obese adipose tissue, resulting in the outflow of saturated fatty acids from adipose cells, including palmitic acid and stearic acid, which stimulated the production of chemokines in adipose cells and resident macrophages through activation of toll-like receptor 4 (TLR4), leading to the migration of M1 macrophages [21].Crosstalk between macrophages and fat cells formed a vicious cycle that accelerates inflammation, leading to further progress in inflammation, fat decomposition, and macrophage recruitment. AIM was involved in two different obesity-related pathological immune responses, namely chronic inflammation based on innate immunity and autoantibody production based on humoral immunity [4]. Therefore, AIM inhibition may be used as a treatment to prevent not only insulin resistance and metabolic disorders but also autoimmunity in obesity conditions.

Liver steatosis and inflammation/fibrosis induced by a high fructose diet were much milder than those fed on an HFD, but many $AIM^{-/-}$ mice developed hepatocellular carcinoma (HCC) after treatment with a high fructose diet [23]. Chronic inflammation with macrophage polarity biased toward M1 phenotype was a key event to induce steatosis associated with HCC [23]. Therefore, a high fructose diet was likely to induce HCC in an independent manner and not necessarily required an inflammation-fibrosis process, and it may be reasonable that the cytotoxicity produced by fructose itself and fructose metabolites activated the carcinogenic cascade. Further studies are needed to clarify the pathway regulating AIM expression.

Transcriptome studies have shown that, LXR/RXR induced the expression of MafB, a transcription factor that induces the differentiation of bone marrow monocytes, by conservative LXRE in the upstream regulatory region of MafB gene in macrophages. MafB regulated the expression of AIM gene by directly binding to the highly conservative MARE element in the AIM promoter region. LXR/RXR mediated AIM induction was not detected in MafB deficient macrophages [3].

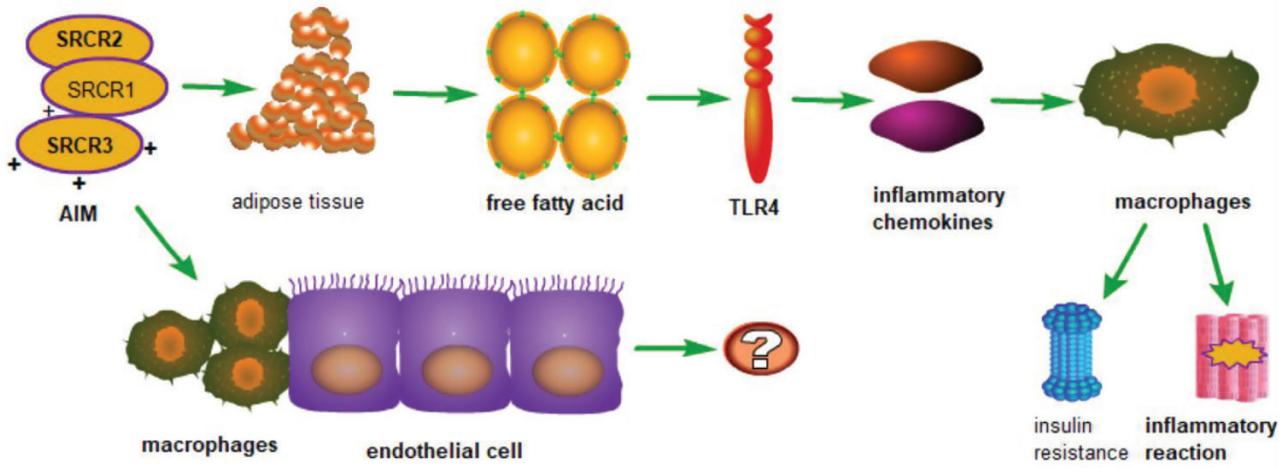

Figure 3: AIM causes crosstalk between lipid metabolism and inflammatory response. AIM in the blood increased obesity induced adipocytes' lipolysis and triggers the efflux of saturated FFA to stimulate the TLR4 pathway, which triggers adipocytes to produce pro-inflammatory chemokines. For example, MCP-1 induces recruitment of M1 macrophages/monocytes into adipose tissue, ultimately leading to adipose inflammation and insulin resistance [20–22].The human AIM may contribute to macrophage-endothelial cell adhesion, which is an unprecedented function of this protein, requiring further investigation of this phenomenon [55]. symbolize promotion.

Sterol regulatory element binding protein (SREBP) transcription factor activated lipid metabolism genes. There are three major mammalian SREBP, 1a isotype is specifically expressed at a very high level in macrophages. Macrophages lacking SREBP-1a express AIM at a lower level and were more prone to apoptosis [53]. In addition, the modification status of AIM also profoundly affected the secretion efficiency and lipolysis function of AIM. The absence of N-glycan significantly enhanced the lipolysis function of mouse AIM, which seemed to be mainly caused by the increased level of endocytosis mediated by scavenger receptor CD36 on the cell surface. Unlike mice AIM, the lipolysis function of human AIM was not affected by the addition of N-glycan [54]. Amezaga *et al.* [55] proposed that human AIM may contribute to macrophage-endothelial cell adhesion, which was an unprecedented function of this protein, requiring further investigation of this phenomenon (Figure 3).

AIM plays a dual role in liver inflammatory damage

In lipid metabolism, AIM contributed to lipolysis, which in turn aggravated lipolysis related inflammation. In the liver microenvironment, TGFβ1 was one of the most effective pro-fibrotic cytokines and played a central role in the process of liver fibrosis [56]. Therefore, the elevation of AIM during liver disease was an adaptive response to liver injury and fibrosis, aiming to counteract inflammatory signaling and the pro-fibrosis effect of TGFβ [24]. In a mouse model of liver injury, AIM protein played a protective role on fibrosis through a variety of mechanisms [24], including prevention of injury, prevention of fibrosis and immune cell infiltration, and AIM changed the phenotype of recruited macrophages from $Ly6C^{hi}$ to $Ly6C^{low}$. Liver fibrosis is a dynamic process in which chronic damage of any etiology, including viral infection, alcohol consumption and steatosis, leading to persistent inflammation and accumulation of ECM [24]. Eventually, liver fibrosis progresses to cirrhosis or even liver cancer (Fig. 4).

In fact, AIM produced by macrophages in the liver, rather than the blood, played an indispensable role in liver cancer. Relevant research can prove this. On the one hand, dissociation of AIM from IgM enhanced the activation of AIM in HCC associated with non-alcoholic steatohepatitis (NASH), significantly elevated AIM without increasing AIM production [6]. Further studies are needed to elucidate the exact mechanism by which IgM releases AIM. On the other hand, when mice AIM were replaced with cat AIM (AIM-felinized mice), due to the high binding affinity of cat AIM to IgM, it was rarely isolated from IgM, and the HCC incidence of AIM-felinized mice was significantly lower than that of $AIM^{-/-}$ mice after 1 year of HFD. This suggested that AIM produced by hepatic Kupffer macrophages may directly target cancerous liver cells without passing through the bloodstream and promote cell elimination [25]. Furthermore, the presence of high concentration of blood AIM in HFD-fed wild-type mice did not prevent the development of HCC [57]. Thus, circulating AIM released from IgM into the bloodstream helped to inhibit obesity and fatty liver, while macrophage-derived non-circulating AIM mainly blocked the development of HCC.

When cells express CD36 and/or other scavenger receptors that mediated AIM endocytosis, AIM may accumulate on their cell surface and trigger complement-dependent cytotoxicity (CDC), inducing tumor cell death [20](figure 4). Most complement were highly produced by hepatocytes, and local AIM concentrations in the liver may be higher than in other organs, as Kupffer macrophages were the main producers of AIM [57]. Therefore, AIM-induced tumor killing may be most effective in the liver. However, it may be worth asking whether AIM can eliminate different types of cancer cells. In the study of Aran *et al.* [26], AIM levels were elevated in liver tumors compared with surrounding non-tumor tissues, and was associated with the characteristics of aggressive tumors enhanced proliferation and poor clinical outcomes, and AIM even could protect HCC cells from cisplatin-induced apoptosis (Fig. 4). The differences found can be explained by: (1) differences in AIM function and expression between humans and mice; (2) different etiologies of HCC, such as HCV or HBV infection or non-alcoholic steatohepatitis associated HCC, may trigger different mechanisms of AIM; (3) types of

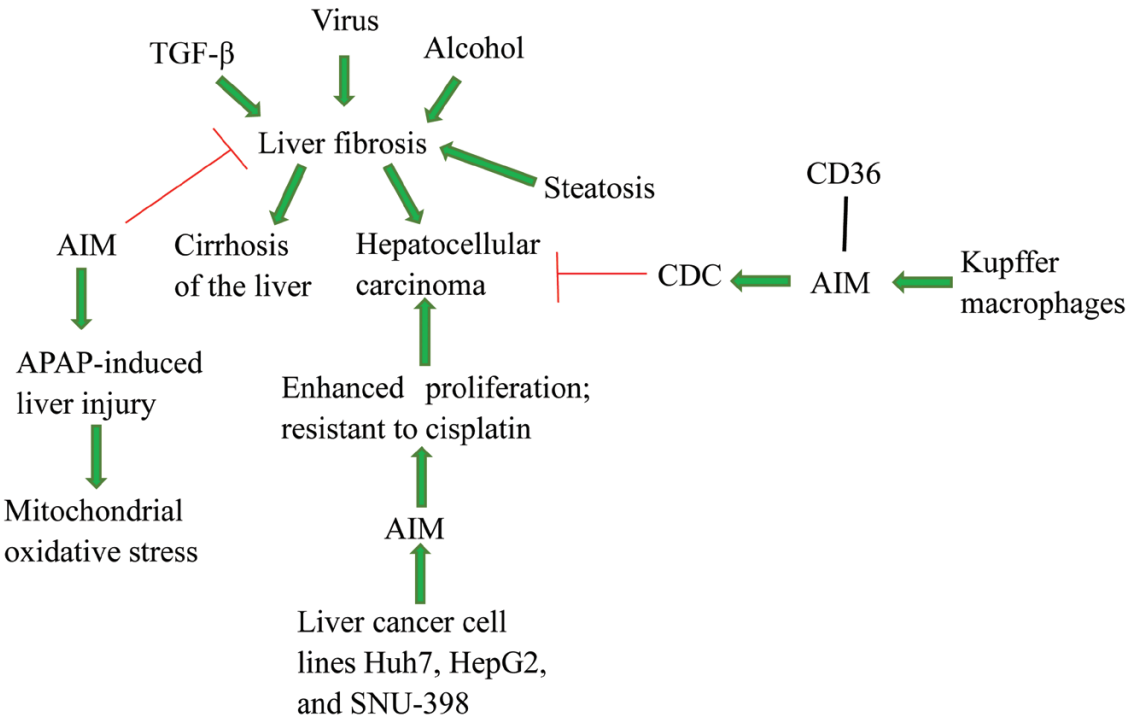

Figure 4: AIM plays a dual role in liver inflammatory damage. Chronic damage of any etiology, including viral infection, alcohol consumption and steatosis, leads to persistent inflammation and accumulation of extracellular matrix [24]. Eventually, liver fibrosis progresses to cirrhosis or even HCC. AIM produced by Kupffer macrophages triggers complement dependent cytotoxicity (CDC), inducing tumor cell death [20, 57]. However, the high expression of AIM in HCC was associated with the characteristics of aggressive tumors enhanced proliferation and poor clinical outcomes, such as protecting HCC cells from cisplatin-induced apoptosis. AIM silencing inhibited colony formation and proliferation in the liver cancer cell lines Huh7, HepG2, and SNU-398 [26]. In addition, increased AIM expression in the liver of mice treated with excessive APAP may contribute to the promotion of mitochondrial oxidative stress in liver cells [27]. symbolize promotion; symbolize inhibtion; symbolize binding.

AIM producing cells. It is necessary and significant to further explore the mechanism of AIM action in HCC cells.

In the study of drug-induced liver injury [27], increased AIM expression in the liver of mice treated with excessive acetaminophen (APAP) may contribute to the promotion of mitochondrial oxidative stress in liver cells (Fig. 4). Sanchez-Rodriguez *et al.* [28] reported for the first time that circulating AIM loss in acute and chronic liver failure (ACLF) significantly associated with circulatory, cerebral, and respiratory failure, and the exact molecular events associated with this association remain unclear. Patients with ACLF showed significantly higher levels of pro-inflammatory cytokines/chemokines, including TNF-α, MCP-1, IL-8 and IFN-γ, as well as anti-inflammatory IL-10 [58]. Further studies are needed to uncover the relationship between AIM and these specific cytokines/chemokines in systemic inflammation.

AIM removes debris deposited in the kidney and contributes to tissue repair

In serum, AIM was released from the IgM pentamer and used for different diseases, including acute kidney injury(AKI) [29, 59]. IgM-free AIM crossed the glomerular membrane and accumulated on debris of dead cells in the lumen associated with AKI, thereby blocking the proximal renal tubules, and deposited AIM promoted phagocytosis and clearance of debris, contributing to overall renal tissue repair [29]. In clinical settings, hyperchloremia was considered by most researchers to be a risk factor for AKI and was usually caused by fluid containing super-physiological chloride concentrations [60, 61]. A high salt load interfered with the dissociation of AIM from the IgM pentamer, resulting in a reduced removal efficiency of lumen debris and further exacerbating AKI [62] (Fig. 5). However, the exact physiological mechanisms that promote AIM dissociation remain unknown, so it is difficult to specify how high salt load inhibits AIM dissociation. Although there is a clear clinical association between hyperchloremia and AKI, the underlying mechanisms linking the two problems remain unknown. There were no significant differences in mRNA expression of inflammatory and fibrosis genes in ischemia-reperfusion mice with and without high salt [62]. Thus, at least for the exacerbation of renal tubular injury, the adverse effect of high salt load appeared to be primarily due to reduced AIM dissociation from IgM pentamer, and clinical studies of AIM levels without IgM in patients with AKI receiving hyperchlorinated fluids are needed to test this idea. AIM without IgM was rapidly cleaved in the blood and preferentially excreted into the urine, preventing a continuous increase in blood AIM levels, especially the functional AIM without IgM. Therefore, therapeutic administration of AIM is unlikely to lead to excessive accumulation of AIM in the blood, and the exact mechanism of how sera AIM is selectively filtered by the glomerulus remains unknown, possibly only through molecular size selection, and the protease that causes AIM cleavage in the blood remains unknown. There are many proteases in blood, such as clotting factors and complement. In particular, clotting factors II, VII, IX, XI, and XII were constitutionally active serine proteases on vascular walls and may be involved in proteolytic cleavage of AIM in blood [63](figure 5).

IgA deposited in the glomeruli can lead to chronic inflammation and kidney damage. In the IgA nephropathy (IgAN) animal model [30], recombinant AIM can restore $AIM^{-/-}$ mouse glomerular IgM/IgG co-deposition and glomerular damage, suggesting that abnormal accumulation of AIM can lead to kidney damage (Fig. 5), similar to the accumulation of AIM on HCC cells that can lead to cancer cell injury [57]. The deposition of AIM on HCC cells activated complement cascade reaction, thus inhibiting the function of complement inhibitors expressed on cells by direct binding. Hence, in cancer cells, AIM deposition led to a beneficial outcome (i.e. prevention of HCC), whereas in normal cells, it led to a harmful outcome (i.e., initiation of IgAN). AIM levels in urine were positively correlated with the histological severity of proteinuria and hematuria, as well as urinary β2 microglobulin and urinary N-acetyl-β-D-glucosamino glycosidase levels, which can reflect active renal inflammation, and infiltrating macrophages can lead to immune-mediated glomerulonephritis damage [64]. With the increase of the pathological grade of IgA nephropathy, the infiltration of M2 macrophages and the expression of AIM and TGF-β1 also increased, which was closely related to clinical indicators such as 24-h urinary protein, serum creatinine and eGFR in IgAN patients, and closely related to the fibrosis process of IgAN [65]. Therefore, serum-free AIM may not be the only major source of urinary AIM in children with IgAN and Henoch-Schönlein purpura nephritis (HSPN), and infiltrating macrophages may be considered as an additional cell source of urinary AIM [64]. Although the role of AIM in the pathogenesis of IgAN and HSPN is unclear, AIM may have a multifaceted function in the kidney.

AIM may induce rapid clearance of harmful immune complexes or damaged mesangial cells, which may play an important role in the repair process. It is certainly possible that AIM has two different regulatory activities in the initial period (harmful) and progressive phases (beneficial)(figure 5). On the one hand, the protein contributed to renal damage by preventing macrophage apoptosis, thereby at least partially prolongating local inflammation [66]. On the other hand, AIM contributed to renal tissue repair by enhancing phagocytosis and clearance of debris promoted by epithelial cells [29, 67]. During AKI, urine AIM concentration increased, and AIM accumulated on necrotic cell debris in proximal renal tubules and bound to KIM-1, which expressed on damaged renal tubular epithelial cells, enhancing phagocytosis and clearance of debris by epithelial cells, thus contributing to renal tissue repair [29]. When exposed to ischemia reperfusion-induced AKI, AIM-deficient mice showed loss of debris clearance and persistent renal inflammation, resulting in higher mortality than WT mice.

Similar role of AIM in cardiopulmonary diseases

The role of AIM in cardiovascular and pulmonary diseases seems to be related to inflammation, which plays a role by inhibiting macrophage apoptosis and enhancing the inflammatory response.

AIM may be detrimental to cardiovascular disease

AIM exacerbated metabolic disorders and atherosclerosis, including diabetes mellitus and cardiovascular events [2, 22]. Saturated fatty acids activated TLR4 and induced responses closely related to obesity-induced inflammation [68]. AIM was a key factor in the initiation of obesity-related chronic inflammation, leading to insulin resistance [21, 22], subsequently led to the progression of atherosclerosis and future cardiovascular events [22]. In fact, AIM was highly expressed in foam macrophages collected from atherosclerotic plaques and supported macrophage survival and its subsequent accumulation by inhibiting apoptosis, leading to inflammatory responses within the lesion and ultimately to disease progression [2].

The $AIM^{-/-}$ mice showed increased survival rate, reduced heart rupture rate, more M1 macrophages, lower levels of M1 markers (iNOS and IL-6) and MMP-2 and 9 in acute stage after myocardial infarction than WT mice [31]. The main functions of M1 macrophages include phagocytosis of cell fragments at the site of myocardial injury, secretion of inflammatory cytokines, and tissue reorganization by the production of MMPs in the acute phase [69, 70] (Fig. 6). M2 macrophages promoted the regression of inflammation and regeneration by promoting myofibroblast accumulation, collagen deposition and angiogenesis [71].

AIM loss also reduced infarct size and inflammatory response induced by neutrophil infiltration, leading to reduced interstitial fibrosis, heart weight, and cardiac remodeling. In addition, AIM consumption showed cardiac effects, such as reduced systolic dysfunction, reduced incidence of cardiac rupture, and reduced acute infarct size after MI, thus improving survival rate, suggesting that AIM played an important role in the progression of sustained inflammation and cardiac remodeling after MI [31, 72].

In the context of atherosclerosis, the loss of AIM in $LDLr^{-/-}$ mice led to a protective effect of atherosclerosis [2](figure 6). In the absence of MafB, lack of AIM induction in the LXR/RXR pathway after macrophage lipid loading was associated with accelerated macrophage apoptosis and attenuated early atherosclerosis formation [3]. Another study [73] suggested that the loss of plasma membrane SCARB1 in monocyte/macrophage lineage was responsible for the accelerated progression of atherosclerosis(figure 6).

AIM was secreted by epicardial adipose tissue in patients with heart failure after isoproterenol treatment, which may activate the TLR4/NF-κB pathway on adjacent cells to produce pro-inflammatory cytokines [32]. Further studies are needed to understand the paracrine role of catecholamines in myocardium. In experimental stroke models [33], AIM-deficient mice showed severe neurological damage and higher mortality compared with wild-type mice; but recombinant AIM administration can reduce aseptic inflammation in infarcted areas, thereby significantly reducing mice mortality (Fig. 6).

AIM was the only independent predictor of cardiac rejection, and the discovery of precise markers of cardiac rejection [34] may enable the establishment of improved groups and improved personalized regimens to improve patient survival while reducing the risks associated with immunosuppression. The role of AIM in cardiovascular disease has been demonstrated, especially in atherosclerosis [2] and myocardial infarction [31, 72], where the loss of AIM reduced inflammatory response and infarct size and improved survival. These data strongly suggest that AIM plays an important role in inflammatory response after myocardial injury.

Lung injury mediated by inflammatory signals

As a new biomarker, serum AIM had important value in differentiating bacterial infection from viral infection and predicting 30-day mortality in adult patients with pneumonia [35]. AIM was also an independent risk factor for

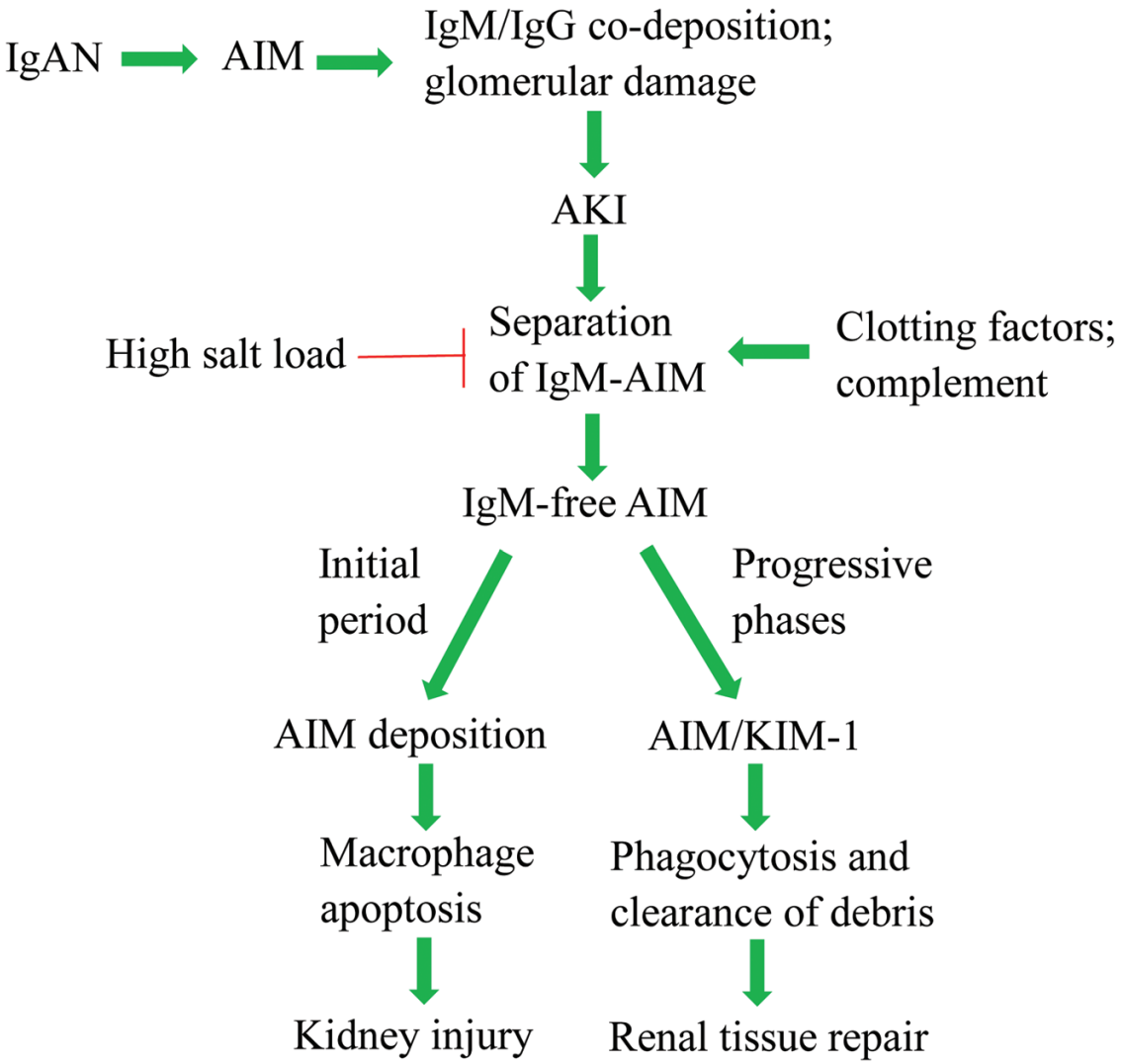

Figure 5: AIM removes debris deposited in the kidney and contributes to tissue repair. In the IgAN animal model [30], recombinant AIM can restore $AIM^{-/-}$ mouse glomerular IgM/IgG co-deposition and glomerular damage. AIM has two different regulatory activities in the initial period (harmful) and progressive phases (beneficial). A high salt load interferes with the dissociation of AIM from the IgM pentamer, resulting in a reduced removal efficiency of lumen debris and further exacerbating AKI [62]. In particular, clotting factors and complement may be involved in proteolytic cleavage of AIM in blood [63]. symbolize promotion; symbolize inhibtion.

trauma-related acute lung parenchyma injury (PLI) or acute respiratory distress syndrome (ARDS) within 24 h after trauma [36].

Methicillin-resistant Staphylococcus aureus (MRSA), a gram-positive bacterium, was the leading causative agent of hospital-acquired pneumonia and a rising cause of community acquired pneumonia [74]. MRSA was capable of producing a variety of toxins that can cause severe pneumonia with extensive tissue damage. The immunomodulatory proteins secreted by MRSA that helped evade the host immune system and can also cause more severe inflammation and tissue damage (Fig. 7) [75]. During MRSA pneumonia [37], pulmonary F4/80 macrophages were important cell source of AIM. AIM increased mice's lung TNF-α, IL-6, IL-10, and CXCL1 levels, and blocking AIM with anti-AIM antibodies improve bacterial clearance, which provided lower inflammatory stimulation, leading to a reduced inflammatory response during MRSA (Fig. 7). The authors believe that in mice, AIM did not directly affect the killing effect of macrophages and neutrophils on bacteria, but enhanced the uptake of macrophages and neutrophils on S. aureus [37].

The expression of AIM in extracellular vesicles (EV) was associated with the expression in cancer tissues and was a core regulatory factor in pathways related to cell dysfunction. Detection of EV-derived AIM by liquid biopsy may represent a potential biomarker for non-invasive diagnosis of lung cancer [38]. AIM overexpression in ATII epithelial cells of double transgenic mice blocked the apoptosis pathway, promoted epithelial cell proliferation and induced emphysema [76]. Activation of Stat3, Erk, Akt and p38 signal transduction in carcinogenic ATII epithelial cells were involved in the pathogenicity induced by AIM [76](figure 7). Therefore, overexpression of AIM induced carcinogenesis of ATII epithelial cells through at least two mechanisms, namely blocking apoptosis and activating carcinogenic pathways.

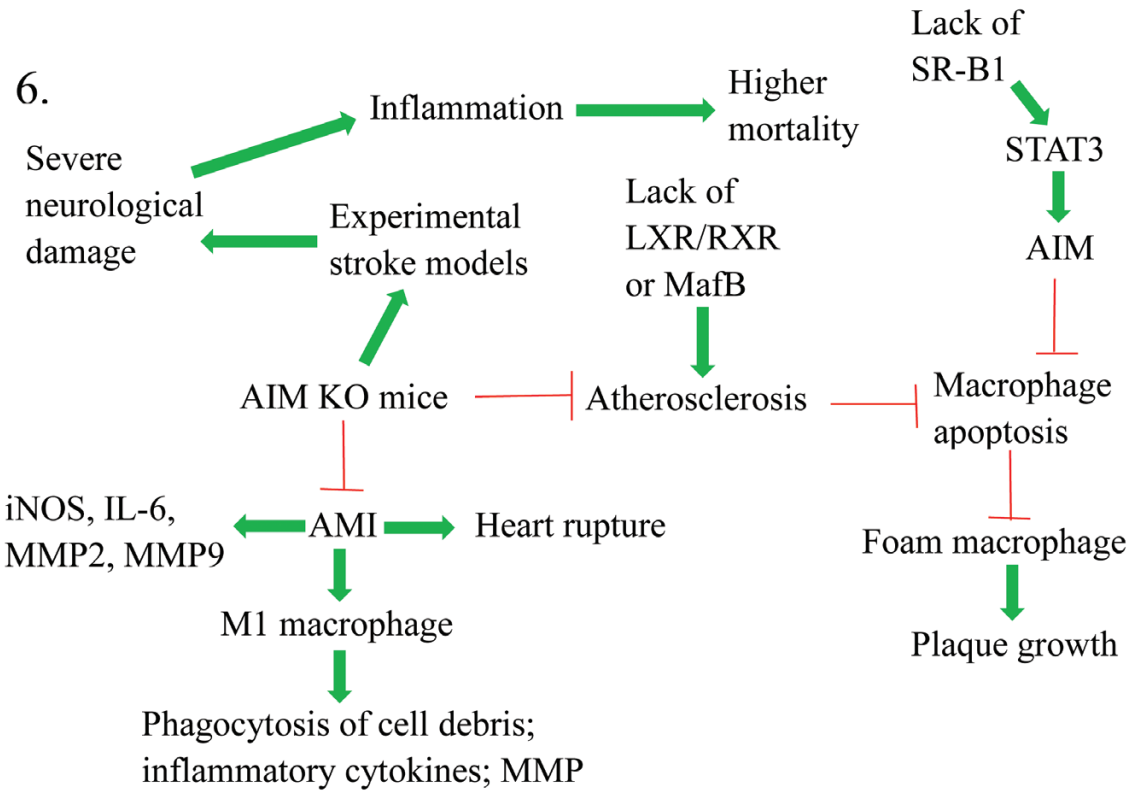

Figure 6: AIM may be detrimental to cardiovascular disease. The survival rate of AIM$^{-/-}$ mice increases after myocardial infarction, and the heart rupture rate, the number of M1 macrophages and expression levels of M1 markers are significantly reduced [31]. In the absence of LXR/RXR or MafB, AIM KO mice occurred to accelerate macrophage apoptosis and attenuate early atherosclerosis formation [3]. SR-B1 deficient macrophages may contribute to reducing apoptosis susceptibility and accelerating plaque growth by upregulating the expression of AIM in a STAT3-dependent manner [73]. In experimental stroke models, AIM-deficient mice showed severe neurological damage and higher mortality, higher levels of DAMP and associated inflammation in the brain [5]. symbolize promotion; symbolize inhibtion.

The increased expression of AIM in autoimmune diseases is a potential biomarker

Although studies on AIM in cardiovascular diseases and lipid metabolism have reached the peak and become the focus of current studies, studies on autoimmune diseases have just started. As a marker of elevated expression in autoimmune diseases, the possible role and mechanism of AIM have yet to be clarified. AIM levels were elevated in patients with ALS [39], secondary progressive multiple sclerosis [40], RA [41] and OA [42], and AIM can be used as a new sensitive biomarker to assist in the evaluation of disease activity. AIM was expressed in CD14^{+} macrophages in synovial membrane of obese knee-OA patients, rather than CD14^{-} fibroblast cells [77], suggesting that AIM may increase synovial macrophage survival and enhance pro-inflammatory phenotype mediated arthritis, but the mechanism is not fully understood. The increase of AIM concentration in SLE was significantly positively correlated with SLE disease activity index (SLEDAI) score, and AIM was also positively correlated with anti-dsDNA, ESR, and CRP levels, but negatively correlated with C3 and C4 levels. Serum AIM concentration can be significantly reduced after effective treatment of SLE [43].

Psoriasis is an immune-mediated systemic inflammatory disease characterized by well-defined erythema patches with silvery scales [78]. Macrophages may play a pathogenic role in psoriasis by releasing inflammatory products in the skin and synovium [44]. Although this has not been proven, AIM may play a role in maintaining the inflammatory environment present in psoriatic disease by inhibiting macrophage apoptosis.

AIM has been found to be actively secreted by active macrophages in the intestinal tract in patients with Crohn's disease (CD) and to cause intestinal inflammation. Since AIM levels were high only in patients with CD and not in patients with ulcerative colitis (UC) or intestinal Behcet's disease (BD), assessing AIM levels may help distinguish CD from other chronic intestinal diseases [45]. Although serum AIM level had no relationship with disease activity or clinical characteristics of CD, and there was no change in AIM level before and after treatment, the increment of AIM may be related to the pathogenesis of CD, that was, inhibiting macrophage apoptosis and causing the persistence of inflammation [45].

Extensive role of AIM in other diseases

AIM was a potential plasma biomarker for predicting pre-eclampsia [46], and was elevated in prostate cancer [47], atopic dermatitis (AD) [48], and age-related macular degeneration [49]. Increased AIM may play a role in AD patients by inducing eosinophilia. Furthermore, AIM levels in serum of mice infected with Mycobacterium tuberculosis significantly increased. However, AIM did not participate in bacterial uptake, but induced the increase of ROS production and antimicrobial peptide synthesis in infected mice, and accompanied by the increase of autophagy mechanism, enhanced the killing activity of macrophages [16](figure 7). AIM generally limited and enhanced the production of IL-17 in Th17

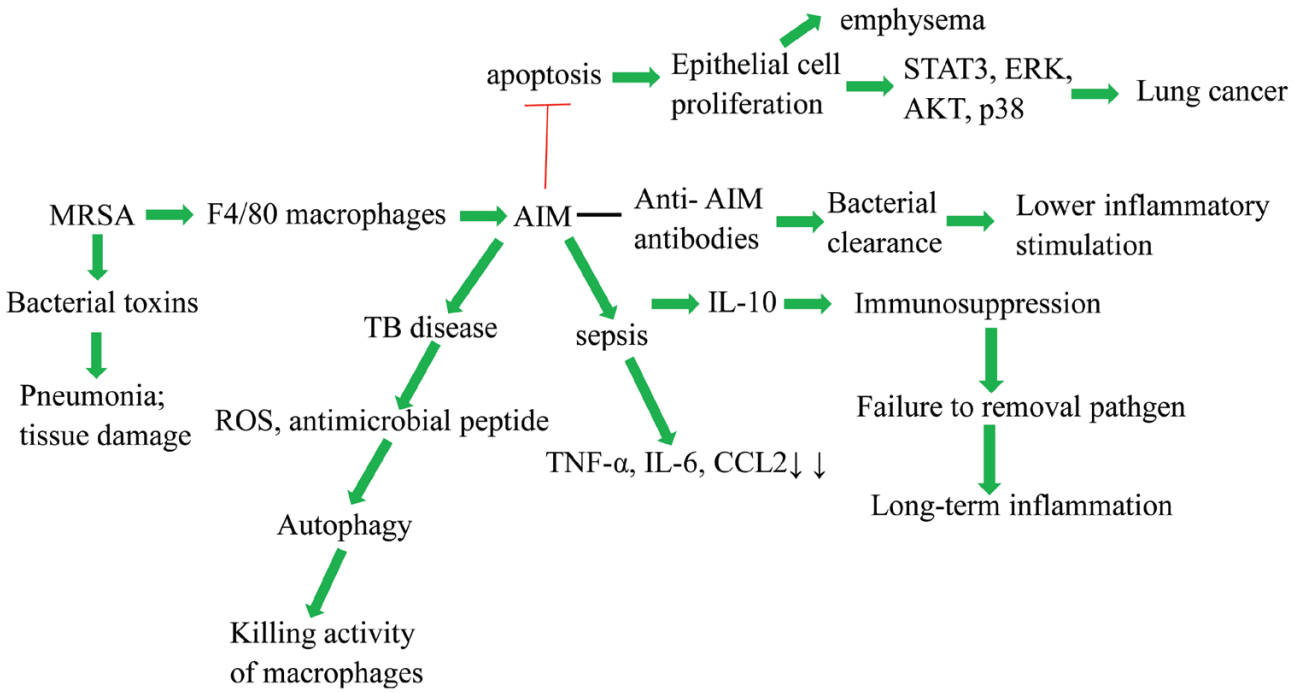

Figure 7: AIM-induced inflammatory signal-mediated lung disease. Blocking AIM with anti-AIM antibodies improve bacterial clearance, which provides lower inflammatory stimulation [37]. AIM overexpression promoted epithelial cell proliferation and induced emphysema [76]. AIM induced the increase of ROS production and antimicrobial peptide synthesis in infected mice, and accompanied by the increase of autophagy mechanism, enhanced the killing activity of macrophages [16]. AIM down-regulated production of inflammatory cytokines TNF-α, IL-6 and chemokine CCL2. Meanwhile, AIM disrupts immune homeostasis by inducing abnormal IL-10 production, leading to failure to eradicate invading pathogens in the immunosuppression stage, which may lead to long-term inflammation after sepsis [51]. symbolize promotion; symbolize inhibtion.

[11], and IL-10 has been proposed to play a role in controlling antimicrobial activity and subsequent caseation of lung tissues [79].

Lack or insufficiency of AIM may result in persistent inflammation of the peritoneum due to impaired clearance rather than necrosis. In the early stages [50], zymosan-induced peritonitis showed severe infiltration of macrophages and neutrophils, associated with cell fragmentation and nuclear fragmentation, resulting in the release of pro-inflammatory cytokines. In the late stage, mesenchymal cells were redistributed on the peritoneal surface of $AIM^{+/+}$ mice. Mesenchymal cells were non-professional phagocytes, and AIM enhanced the phagocytosis of mesenchymal cells to dead cell fragments [50].To date, the only known AIM/Spα mRNA expression inducer is LXR ligand. Martinez *et al.* [80] proposed a new mechanism to trigger AIM release. That is, AIM was mainly formed in cells and its release was triggered by PAMP. The pathogenic compounds can quickly be neutralized, thus protecting organization, the innate immune system through the mechanism to control infection and reduce inflammatory damage.

Sepsis is a pathological syndrome caused by an imbalance in the host's immune response to infection, usually characterized by long-term inflammatory immunosuppressive, tissue destruction, vascular damage, and multiple organ failure [81]. Patients with sepsis had significantly increased serum AIM admission levels, which were significantly associated with higher SOFA scores and significant increment in 28-day mortality [82]. In sepsis mouse models [51], AIM downregulated production of inflammatory cytokines TNF-α, IL-6, IL-10, and chemokine CCL2, as well as leukocyte infiltration in alveolar lavage fluid, including macrophages, neutrophils, and lymphocytes, were blocked. AIM disrupted immune homeostasis by inducing abnormal IL-10 production, leading to failure to eradicate invading pathogens in the immunosuppression stage, which may lead to long-term inflammation after sepsis [51] (Fig. 7). In summary, the role of AIM in sepsis can be summarized as follows: (1) amplification of inflammation mediators, partly by increasing the production of inflammatory mediators and leukocyte infiltration; (2) promotion of bacterial transmission at later time points in sepsis, in part by enhancing the release of anti-inflammatory IL-10. Thus, AIM disrupts host homeostasis in sepsis, including persistent inflammation and immunosuppression. These findings may also have broad implications for the AIM-mediated role in other inflammatory diseases.

Prospect

Past studies have provided a wealth of information about AIM, and overall, these studies have revealed new intersections between metabolic and inflammatory pathways where AIM plays a central role. In addition, during infection, AIM has a variety of functions, from recognition and aggregation of infectious agents to increased phagocytosis of macrophages, as well as other antibacterial properties. However, the unifying role of this protein in fighting infectious disease has not been established. The mechanism of AIM-induced apoptosis inhibition remains unsolved. Further evaluation of genetic variations associated with endogenous AIM expression and function. For example, through SNP analysis and/or genome-wide sequence studies, may be helpful in determining

the pathogenesis of autoimmune diseases. Given the variety of dietary patterns in humans, a large cohort study of humans may provide important information on the association between blood AIM and blood fatty acid levels and/or distribution.

Explanation for diseases in the form of annotations

The Liver X Receptors (LXRs)

encode highly homologous transcription factors that are members of the nuclear receptor superfamily of proteins. Both LXR alpha and LXR beta form heterodimers with the obligate partner 9-cis retinoic acid receptor alpha (RXR alpha; NR2B1). **LXR/RXR** heterodimers function as sensors for cellular oxysterols and, when activated by these agonists, increase the expression of genes that control sterol and fatty acid metabolism/homeostasis [83].

Primary hepatocellular carcinoma (HCC)

is the most common primary liver malignancy, and chronic hepatitis B or C virus infection seems to be the most important risk factor for HCC. Hepatocellular carcinoma may appear macroscopically as nodules, masses, or diffuse. Necrosis, hemorrhage, and fatty infiltration are often present [84].

Hepatocellular carcinoma associated with non-alcoholic steatohepatitis (NASH)

is one type of non-alcoholic fatty liver disease (NAFLD). NAFLD included the entire spectrum of fatty liver disease in patients who did not drink heavily, from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) to cirrhosis and ultimately hepatocellular carcinoma [85].

Acute chronic liver failure (ACLF)

is a syndrome that occurs in patients with acute decompensated liver cirrhosis (AD) and is characterized by a systemic hyperinflammatory state, leading to multiple organ failure [35].

Acute kidney injury (AKI)

is caused by renal ischemia reperfusion injury (IRI), sepsis or renal toxin, which causes cell death in renal tissue, physical obstruction of the tubule lumen, and impair renal filtration function. An important pathological feature of acute kidney injury is renal tubular obstruction caused by debris of dead tubule epithelial cells [37].

IgA nephropathy (IgAN)

is the deposition of abnormal IgA in the glomerulus and the formation of immune complexes with variable IgG and IgM and complement 3 (C3) in the mesangial of the glomerulus. It progresses to IgM/IgG/complement codeposition and leads to chronic inflammation and glomerular damage with a poor prognosis [43].

IgA vasculitis is an acute leukocyte fragmentation vasculitis of small blood vessels, mainly characterized by purpura, joint pain, abdominal pain and nephritis. **Henoch-Schonlein purpura nephritis (HSPN)** is one of the most important complications of IgA vasculitis with a good prognosis [86].

Acute respiratory distress syndrome (ARDS)

is a life-threatening syndrome consisting of respiratory failure and diffuse alveolar damage caused by local and systemic immune activation disorders, resulting in pulmonary vascular, parenchyma and alveolar damage [87].

Amyotrophic Lateral Sclerosis (ALS)

is a complex and common, frequently occurring neurodegenerative disease characterized by progressive loss of upper and lower motor neurons, progressive degeneration of limbs leading to muscle atrophy and paralysis, and finally death 3 to 5 years after onset [88].

Multiple sclerosis (MS) is a neurodegenerative inflammatory disease characterized by inflammation and demyelination, resulting in white matter plaque lesions and neuron damage/loss in the central nervous system (CNS). Relapsing remitting MS (RRMS) is the most common course of disease and may transition to **secondary progressive MS (SPMS)** characterized by progressive neurological dysfunction [89].

Rheumatoid arthritis (RA)

is a common systemic inflammatory autoimmune disease, characterized by joint pain and swelling that can seriously impair physical function and quality of life [90].

Osteoarthritis (OA)

is the most common type of arthritis and the leading cause of disability worldwide. It tends to occur in middle age or due to injury or obesity. OA occurs with the onset of symptoms, including swelling of the joints, fluid accumulation in the joints and limited movement in the later stages of the disease, leading to deformity and loss of joint function [91].

Systemic lupus erythematosus (SLE)

is a systemic autoimmune disease with vascular lesions. Its clinical manifestations vary from mild cutaneous and mucosal diseases to multiple organ involvement [92].

Crohn's disease(CD)

is a recurrent inflammatory disease that primarily affects the gastrointestinal tract and is often presented with clinical symptoms of abdominal pain, fever and intestinal obstruction or diarrhea with blood or mucus, or both [93].

Ulcerative colitis(UC)

is an idiopathic chronic inflammatory disease of the colonic mucosa, confined to the mucosal surface, beginning in the rectum and usually extending proximal in a continuous fashion through part or the entire colon. Bloody diarrhea is the characteristic symptom of the disease [94].

Behcet's disease (BD)

is a systemic inflammatory disease with recurrent oral ulcers, genital ulcers, eye lesions and skin lesions. Hyperactivity of neutrophils and excessive production of pro-inflammatory cytokines and reactive oxygen species (ROS) are believed to be the main mechanisms of the disease [95].

Atopic dermatitis (AD)

is a common pruritus and chronic recurrent inflammatory skin disease. The pathophysiology of AD includes dermal barrier dysfunction, frequent allergic reactions to allergens, antimicrobial immune defense deficiencies and genetic susceptibility [96].

Age-related macular degeneration (AMD)
is a complex, multifactorial, progressive degenerative disease that involves pathological changes in the macula and deeper retinal layer of the surrounding vascular system, leading to a loss of central vision. The accumulation of retinal deposits called vitreous verruca is the hallmark clinical finding of AMD [97].

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Conflict of interest

The authors declare no conflict of interest.

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Data availability

No new data were generated or analyzed in support of this review.

Author contributions

Huiqing Yang designed the framework and ideas of the manuscript, and finished writing the manuscript text. Yan Luo and Xiaofei Lai provided technical and academic guidance, and modified the manuscript. Xiaofei Lai provided financial support. All authors reviewed the manuscript.

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