Diabetes, Metabolic Syndrome and Obesity Dovepress

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The Role of the AIM2 Gene in Obesity-Related Glucose and Lipid Metabolic Disorders: A Recent Update

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Abstract: Absent in melanoma 2 (AIM2) is a protein encoded by the AIM2 gene located on human chromosomes, AIM2 can recognize and bind to double stranded DNA (dsDNA), leading to the assembly of the AIM2 inflammasome. The AIM2 inflammasome plays important proinflammation role in many diseases, and can induce pyroptotic cell death. It has also been closely linked to the development and progression of metabolic diseases and can be activated in obesity, diabetes, nonalcoholic fatty liver disease, and atherosclerosis. In this article, we mainly review the role of AIM2 in glucose metabolism, especially in obesity-related disorders of glucose and lipid metabolism, and provide insights to better understand the role of AIM2 in the pathogenesis, and clinical treatment of metabolic disease.

Keywords: AIM2, obesity, metabolic diseases, diabetes, glucose metabolism disorders

Introduction

Metabolic diseases are usually caused by abnormalities in the metabolism of certain substances or energy sources in the body, and the underlying mechanisms are multifaceted, and include genetic and nongenetic factors.[1] In the last few decades, with the continuous improvement in living conditions, the incidence of metabolic diseases, especially obesity-induced disorders of glucolipid metabolism, has increased. The World Health Organization defines obesity as an excessive accumulation of adipose tissue that is potentially damaging to health, diagnosed as a body mass index (BMI>30k/m^2).[2] Obesity is mainly caused by increased energy intake, excessive adipose tissue, and genetic factors and so on.[3] Obesity and its effects often lead to premature morbidity and mortality. With the growth of the aging population and the increasing prevalence of unhealthy dietary and lifestyle habits, glucose and lipid metabolic disorders have become major problems worldwide, and the pathological manifestations of glucolipid metabolic disorders include systemic dysfunction, inflammation, insulin resistance, and alteration in the intestinal flora.[4] Therefore, it commonly causes many clinical manifestations, such as diabetes, hyperuricemia, hyperlipidemia, hypertriglyceridemia and cardio-cerebrovascular disease. The increased occurrence of diabetes has posed a substantial economic burden on society. The International Diabetes Federation estimated that the number of people with diabetes will reach 783.2 million by 2045.[5] Moreover, diabetes usually causes macrovascular and microvascular complications, which are major causes of death in people with diabetes.

The AIM2 gene is located on chromosome 1q23.1-q23.3 and encodes the AIM2 protein. The main function of the AIM2 protein is to initiate the assembly of the AIM2 inflammasome after the recognition of double-stranded DNA (dsDNA).[6] The AIM2 protein acts as a cytosolic dsDNA sensor and can identify not only dsDNA released by pathogens into the cytoplasm, but also dsDNA released from damaged host cells. Recognition of dsDNA by AIM2 leads to the assembly of a large multiprotein oligomer complex called an inflammasome, which involves the activation of caspase-1, the cleavage of its downstream substrates, inflammatory signaling, and pyroptotic cell death.[7] In conclusion, the recognition of microbial dsDNA released into the cytoplasm by AIM2 plays a crucial role in protecting cells from invasion by pathogens such as bacteria,

Received: 28 July 2024
Accepted: 13 October 2024
Published: 21 October 2024

viruses, fungi and parasites.[8] However, the recognition of host cell dsDNA by AIM2 drives the development of aseptic inflammatory diseases,[9] such as skin diseases, neurological diseases, cardio-cerebrovascular diseases, diabetes.[10,11]

In addition, the newly study discovered that AIM2 plays an important role in different T-lymphocyte subtypes and B-lymphocyte, Analysis in regulatory T cells (Treg cell) demonstrated that AIM2 could promote Treg cell function and stabilize Treg cells by inhibiting the AKT-mTOR signaling pathway. Moreover, AIM2 was down-regulated the AKT-mTOR signaling pathway by promoting the interaction of AKT with the RACK1-PP2A axis thereby inhibiting AKT activation;[12] And AIM2 regulates the differentiation and proliferation of specific immune $CD4^+$ T cells, and is particularly important in regulating the activation and differentiation levels of the T follicular helper cell (TFH);[13] In TH17 cell, current research reveals that AIM2 deficiency decreases IL-17A production and downregulates key TH17 associated proteins(RORγt, IL-1R1, IL-23R), and AIM2 promotes TH17 cell differentiation. Analysis in B-lymphocyte demonstrated that AIM2 regulates B-cell differentiation via IL-10-DNA demethylation-AIM2-Blimp1/Bcl6 axis.[14] Given these T cells and B cells play crucial roles in regulating immune and inflammatory responses, So AIM2's involvement in these cells may contribute to obesity-related glucose and lipid metabolic disorders. This will provide a new dimension to understand the mechanism of AIM2's role in metabolic diseases.

This article outlines the biological function of AIM2 and discusses the latest research on the role of AIM2 in obesity-related glucose and lipid metabolism disorders, with the aim of providing new perspectives for the clinical treatment of this disease.

AIM2 Protein

The Structure of AIM2 and the AIM2 Inflammasome

The absent in melanoma 2(AIM2) protein encoded by the AIM2 gene comes is a member of the IFI20X/IFI16(PYHIN) protein family, and it is an innate immune DNA sensor. AIM2 can be found in the cytoplasm, and its structure consists of pyrin domain (PYD) at the N-terminus and one or two hematopoietic, interferon- inducible, and nuclear (HIN) domains at the C-terminus. The HIN domain is composed of two adjacent oligonucleotide/oligosaccharide binding structural domains (Figure 1A) and participates in the identification and binding of dsDNA.[15,16] The pyrin domain (PYD) is composed of six alpha spirals (Figure 1B), and it plays a key role in the recruitment of apoptosis associated speck-like protein containing a CARD (ASC).[17] It has recently been shown that AIM2 is localized in the liver near hepatic sinusoids and in innate immune cells, such as specific macrophages (ie, Kupffer cells) and dendritic cells.[18,19]

Infection with a DNA virus can trigger the activation and assembly of the AIM2 inflammasome. The HIN structural domain at the C-terminus binds to the viral dsDNA, causing the N-terminus to release PYD to bind to ASC.[20,21] ASC is

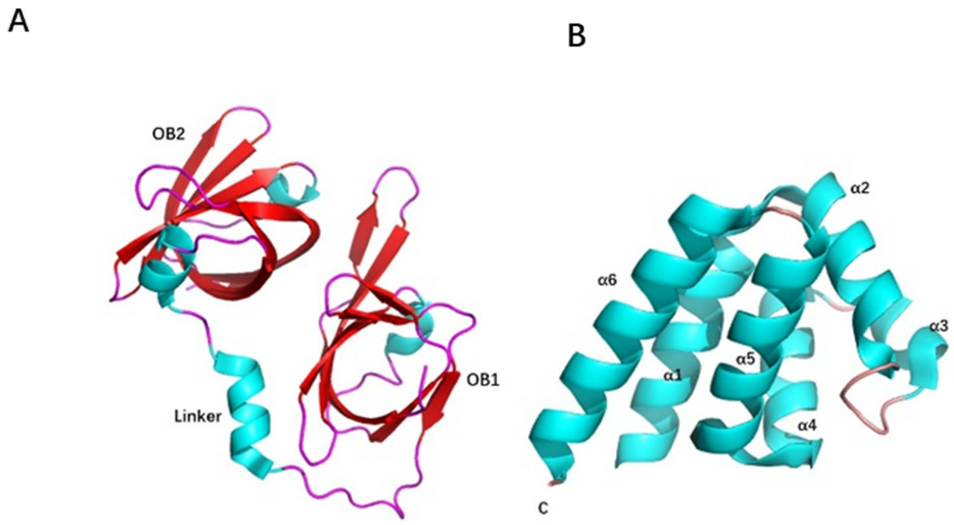

Figure 1 Structural basis of AIM2 inflammasome. (**A**) Cartoon representation of the human AIM2 hIN domain showing the tandem oligonucleotide/oligosaccharide-binding (OB) fold domain (https://doi.org/10.2210/pdb3RLN/pdb); (**B**) Cartoon representation of the human AIM2 PYD domain (https://doi.org/10.2210/pdb4O7Q/pdb).

an important adaptive molecule that possesses two structural domains: the PYD structural domain and the CARD structural domain. The CARD domain of ASC can interact with the CARD domain of caspase-1. After ASC recruit's pro-caspase-1, AIM2 assembles with ASC and pro-caspase-1 to form an inflammatory complex.[22] The inflammatory complex then activates Caspase-1, which leads to the cleavage of pro-IL-1β and pro-IL-18 into active IL-1β and IL-18.[23] Moreover, it cleaves gasdermin D (GSDMD). GSDMD is cleaved into a C-terminal fragment and an N-terminal fragment, and the N-terminus can anchor to the cell membrane, forming pore channels that disrupt cell membrane integrity and induce cell pyroptosis.[17] This process is defined as the canonical AIM2 activation pathway[24] (Figure 2).

The other pathway of AIM2 activation is mediated through the cGAS-STING axis. In most bacterial infections, bacteria first enter the cytoplasm and then bacterial DNA is released into the cytoplasm under the action of bacteriolysis. However, when *Francisella- novicida* DNA was accidentally released into the cytoplasm, its low concentration was not sufficient to induce the formation of AIM2 inflammatory complexes.[25] Therefore, low concentrations of bacterial DNA induce the production of type I interferon through other cytoplasmic DNA receptors, such as GAM-AMP synthase (cGAS). After, DNA binds to cGAS, cGAS synthesizes a cyclic dinucleotide second messenger (2',3'-cGAMP), and 2'3'-cGAMP can act as an affinity ligand for stimulator of interferon genes (STING).The binding of cGAMP to STING induces conformational changes, oligomerization and translocation of STING so that it can interact with two downstream molecules, TANK binding kinase 1 (TBK1) and Interferon regulatory factor 3 (IRF3), which then cause IRF3 to produce type I interferon (IFN-1). Finally, IFN-1 activates STAT1/STAT2. STAT1/STAT2 are phosphorylated and then activate the downstream transcription factors IRF9 and IRF1 to drive the transcription of interferon-stimulated genes (ISGs),

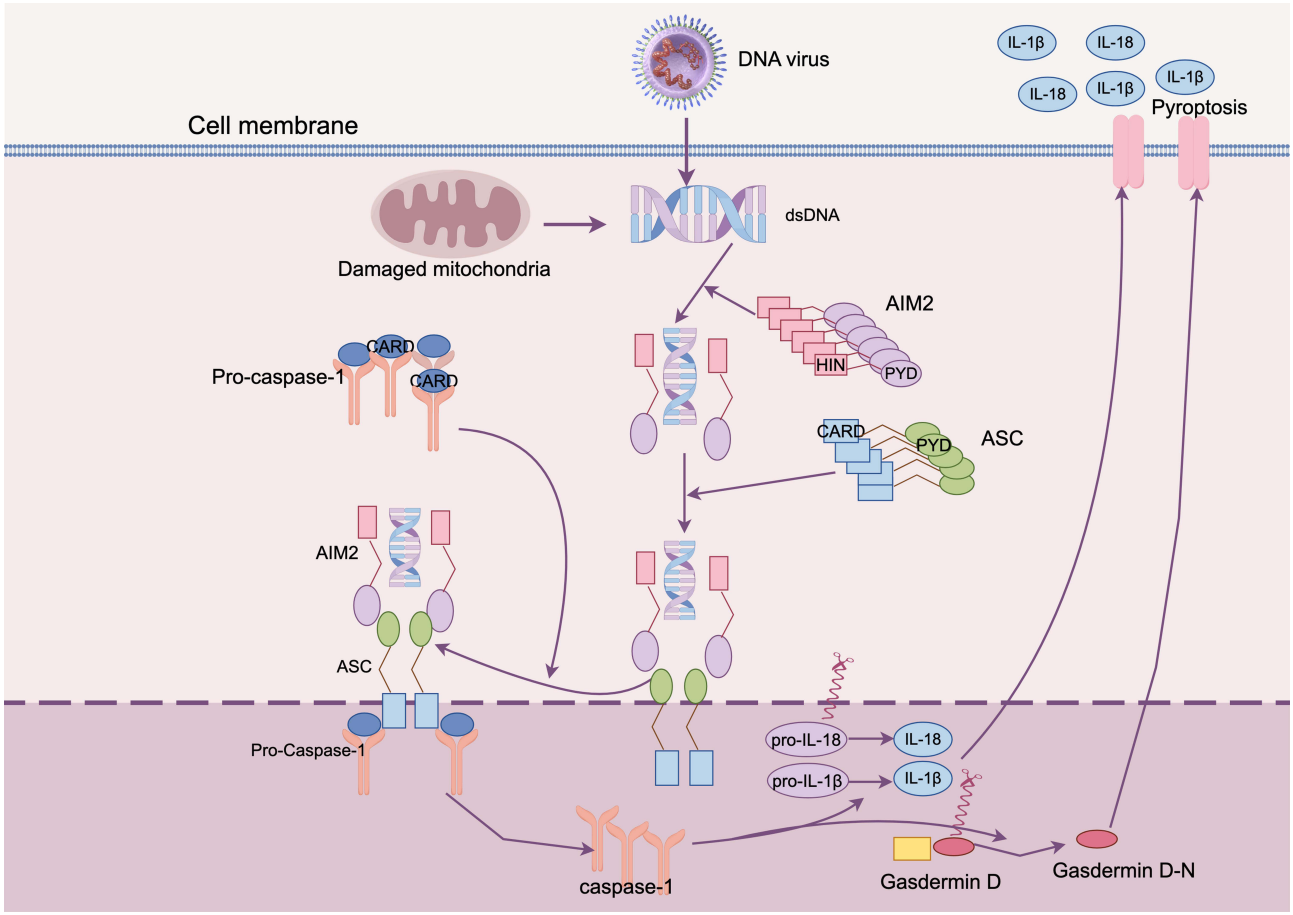

Figure 2 The canonical AIM2 activation pathway. In the case of infection with a DNA virus or transfection with a DNA analog, dsDNA released into the cytoplasm is directly recognized by AIM2. The HIN domain of AIM2 binds to dsDNA, and PYD binds to the junction protein ASC, which then recruits Pro-Caspase-1 to form an inflammatory complex. Activated Caspase-1 cleaves pro-IL-1β and pro-IL-18, leading to the maturation and secretion of the inflammatory factors IL-1β and IL18. Moreover, activated caspase-1 can cleave Gasdermin D, leading to the release of its N-terminal fragment and destruction of the integrity of the cell membrane, which ultimately leads to cell death.

particularly a series of interferon-inducible GTPases including guanylate-binding proteins (GBPs). Bacteria are lysed by these enzymes, which results in the release of large amounts of bacterial DNA into the cytoplasm. Bacterial DNA induces AIM2 expression after entering the classical pathway.[22] Surprisingly, the interferon-inducible protein IRGB10 is necessary to activate AIM2 in *Francisella novicida* infection.[26] Therefore, this process is also known as the noncanonical pathway of AIM2 activation[24] (Figure 3).

Regulators of the AIM2 Inflammasome

Positive Regulators of the AIM2 Inflammasome

The present study confirmed that AIM2 is predominantly present in the cytoplasm, dsDNA from various sources, such as bacteria, viruses or damaged nuclei and mitochondria, is a positive regulator of AIM2. Among the common bacteria that activate AIM2 inflammatory vesicles are *Streptococcus pneumoniae, Staphylococcus aureus, Mycobacterium avium, Listeria monocytogenes*, and *Francisella tularensis*.[27] These pathogens mainly activate the AIM2 inflammasome through bacterial lysis and the release of bacterial DNA, under normal conditions, nuclear dsDNA does not bind to AIM2 in the cytoplasm, mainly due to the spacing of the nuclear membrane and the protection of DNA-binding proteins; however, when the nuclear membrane loses its integrity, substances are released into the cytoplasm and AIM2 can bind to the released dsDNA, promoting the activation of AIM2 inflammatory vesicles.[28] The study of viral activation of AIM2, revealed that a variety of viruses' activation of AIM2, such as vaccinia virus and mouse cytomegalovirus, induce the

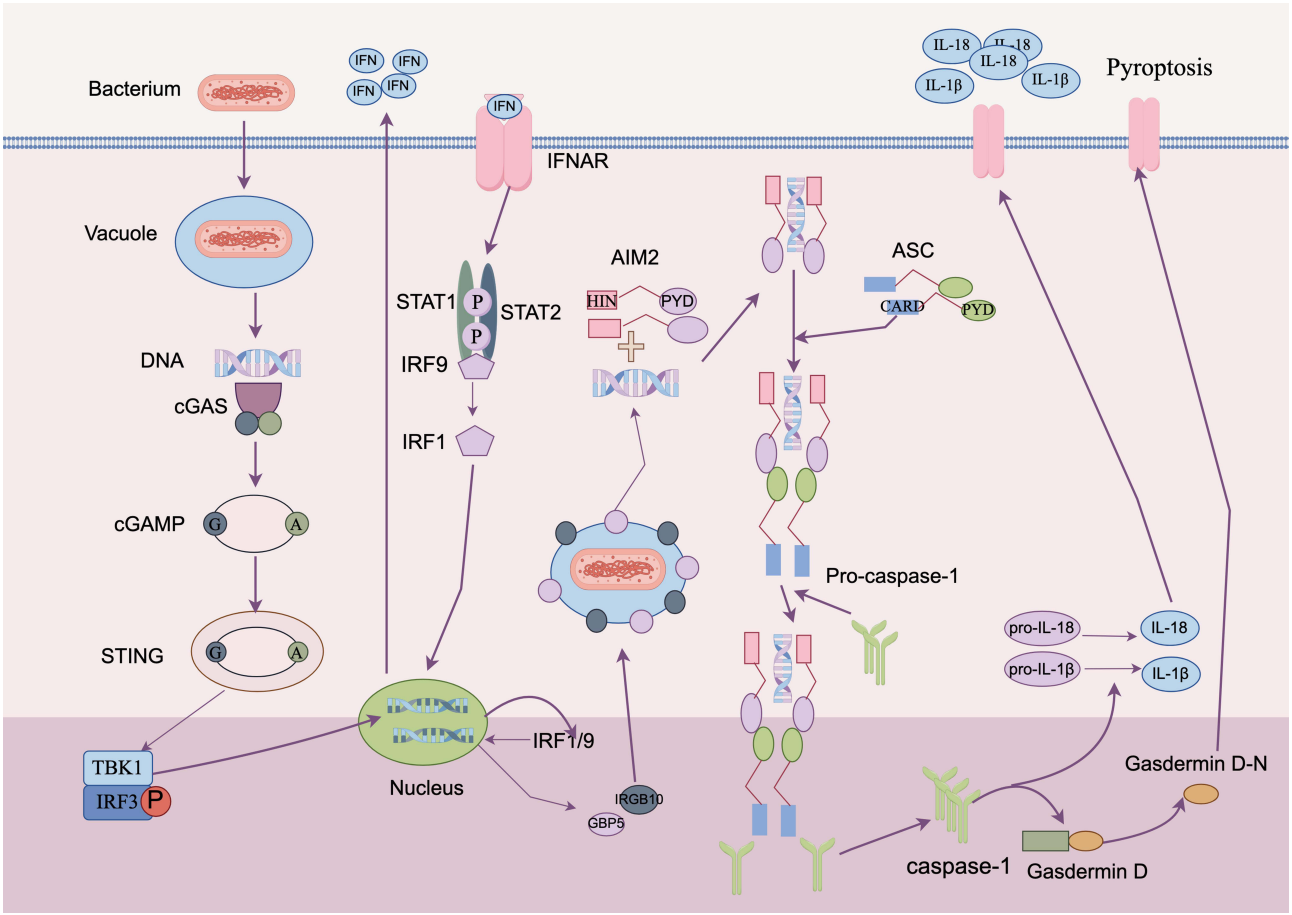

Figure 3 The noncanonical AIM2 activation pathway. IFN I production is first induced by cGAS at low concentrations in bacteria. dsDNA-activated cGAS produces a cGAMP, which serves as a high-affinity ligand for STING. cGAMP induces conformational changes, oligomerization, and translocation of STING and interacts with downstream TBK1 and IRF3, which phosphorylate IRF3 to produce IFN1. Moreover, IFN-β activates STAT1/STAT2 by binding to interferon receptors, which leads to the activation of the downstream transcription factors IRF9 and IRF1 after STAT1/STAT2 phosphorylation, which in turn drives ISG transcription and promotes cell lysis, resulting in the release of large amounts of bacterial DNA into the cytoplasm and thus sufficient concentrations of dsDNA for detection by AIM2 before entering the classical pathway.

activation of AIM2. A.K. Rathinam et al reported that cytomegalovirus induces the activation of AIM2, and the activation of AIM2 plays an important role in the activation of caspase-1 in macrophages or dendritic cells and the maturation of IL-1β and IL-18.[29]

Negative Regulators of the AIM2 Inflammasome

In mice, the negative regulation of the AIM2 inflammasome involves the P202 protein. P202 belongs to the PYHIN protein family, and it contains two HIN domains but is missing the PYD domain. However, there is a clear difference in the surface charge distribution between the HIN structural domains of P202 and AIM2. The crystal structure of the mouse P202-dsDNA complex indicates that the $P202^{H1N1}$ structural domain binds to DNA, whereas $P202^{HIN2}$ interacts with the AIM2 protein. P202 binds to dsDNA more strongly than AIM2 binds to dsDNA; thus, P202 competitively binds to the dsDNA that activates AIM2. Therefore, P202 inhibits the activation of AIM2.[30] Triterpenoid saponin (GL), which is the main bioactive product of licorice, inhibits AIM2 activation by inhibiting ASC aggregation.[31] Surprisingly, Jiang et al[32] studied the treatment of tendinopathy and reported that pristimerin (PM) promoted. The degradation of AIM2 through the autophagy-lysosome pathway and inhibited the activation of AIM2 inflammatory vesicles in macrophages, thus effectively inhibiting the progression of tendinopathy. An in vitro cellular experiment and in vivo study of the mechanism underlying the direct inhibition of AIM2 inflammasome activation revealed that the triple structural domain protein (TRIM11) binds to AIM2 via polyubiquitylation at the K458 locus, which results in the recruitment of the autophagy cargo receptor P62, thus mediating the degradation of AIM2.[33,34] In addition, studies on cultured primary microglia and experimental stroke mouse models revealed that histone deacetylase 3 (HDAC3) expression is increased. Moreover, RGFP966 is a selective inhibitor of HDAC3, and PGFP966 downregulates AIM2 by augmenting STAT1 acetylation and attenuating STAT1 phosphorylation, which was found to protect against ischemic brain injury in a previous study.[35] Wang et al[33] identified a new IFI16 transcriptional isoform, IFI16-β, which selectively inhibits the assembly and formation of AIM2 inflammatory vesicles. It colocalizes with AIM2 in the cytoplasm and blocks its detection by chelating cytoplasmic dsDNA to AIM2. It is structurally similar to P202, which interacts with AIM2 to block the activation of the AIM2-ASC functional complex. Competition binding assays showed that IFi16-β binds to dsDNA with a greater affinity than AIM2, thereby inhibiting the activation of the AIM2 inflammasome.[36]

The Role of AIM2 in Obesity-Associated Disorders of Glucose Metabolism

AIM2 and Obesity

Obesity is usually caused by genetic and environmental factors and is a low-grade chronic inflammatory disease, and persistent, unresolved inflammation in adipose tissue is a major contributor to obesity-associated metabolic complications.[37] Therefore, the connection between obesity and inflammatory vesicles has also received attention. Previous studies have shown that both the expression and activation of inflammatory vesicles are increased in obese mice fed a high-fat diet, and elevated mRNA levels of AIM2 have been detected in male mice fed a high-fat diet for 16 weeks.[38] However, the relationship between adipose tissue inflammation and obesity are currently less well studied because less attention has been given to endogenous inflammatory mediators. In addition, a study by Gong et al revealed that, in the absence of a significant change in food intake, compared to the control, AIM2 knockout promoted an increase in fat mass in mice by mediating the upregulation of P202, suggesting that the difference in body weight between the two groups of mice was not due to excessive energy intake but rather through energy expenditure. Moreover, AIM2 gene-deficient mice exhibit spontaneous obesity, suggesting that reduced or impaired brown adipose tissue function promote obesity.[39] In another study, it was shown that AIM2 deficiency leads to a decrease in bone mineral density by promoting bone marrow adipogenesis, and AIM2 deficiency was also shown to have an effect on bone morphology.[40] In conclusion, AIM2 may be a potential drug target for the treatment of obesity. Similarly, Liu et al[41] by performing high-fat modeling in AIM2 knockout mice, also showed that the level of weight gain in AIM2 knockout mice was greater than that in WT mice and that AIM2 mainly plays a regulatory role in adipose tissue macrophages. Previous studies have shown that deletion of the AIM2 gene in immune cells can stimulate the expression of the Ifi202b gene;[42] moreover, some studies have confirmed the relationship between Ifi202b and obesity, For example, Stadion et al showed that the Ifi202b gene promotes the development of obesity-associated insulin resistance by promoting the production and storage of white fat.[43] Thus, AIM2 plays a key role in obesity by upregulating the expression of Ifi202b.[39] In summary, obesity promotes

the activation of inflammatory vesicles such as AIM2 and causes inflammatory responses. Moreover, studies of AIM2 knockout mice, revealed that AIM2 deficiency causes spontaneous obesity and that a decrease in the expression of AIM2 tends to cause glucose intolerance and insulin resistance (Figure 4).

The Role of AIM2 in Diabetes

Diabetes mellitus is a chronic metabolic disease and one of the most common serious medical conditions in the world. The main types of diabetes are type 1 diabetes (T1D) and type 2 diabetes (T2D). T2D accounts for approximately 90% of all diabetes cases, with insulin resistance being one of the main pathophysiological features of T2D.[44] Currently, the link between AIM2 inflammatory vesicles and insulin resistance has been preliminarily studied. A previous study reported higher levels of AIM2 and mtDNA in the monocytes and serum cells, respectively, of people with T2D than in controls.[45] Higher levels of mtDNA increase the activation of AIM2 inflammasomes in macrophages and promote the development of insulin resistance and T2D. Moreover, elevated circulating no cellular mitochondrial DNA (CCF-mtDNA) levels can induce chronic inflammation by activating the AIM2 inflammasome.[44,46] However, less attention has been given to the role of AIM2 inflammatory vesicles in T1D. A previous study reported elevated levels of IL-18, IL-1β, and caspase-1 in the peritoneal interstitial fluid and plasma of mice with T1D, indicating an increase in inflammasome activation. Moreover, AIM2 can affect the size of lesions without causing a relative increase in necrosis in diabetes-induced Ldlr-KO mice.[47] This finding suggested that there is a link between AIM2 and TID. The triggers of T1D usually include viral infections, dietary habits, and alterations in the gut microbiota;[48] among these factors, the alteration of the intestinal microflora is considered an important part of the occurrence and development of T1D.[49] Through controlled experiments

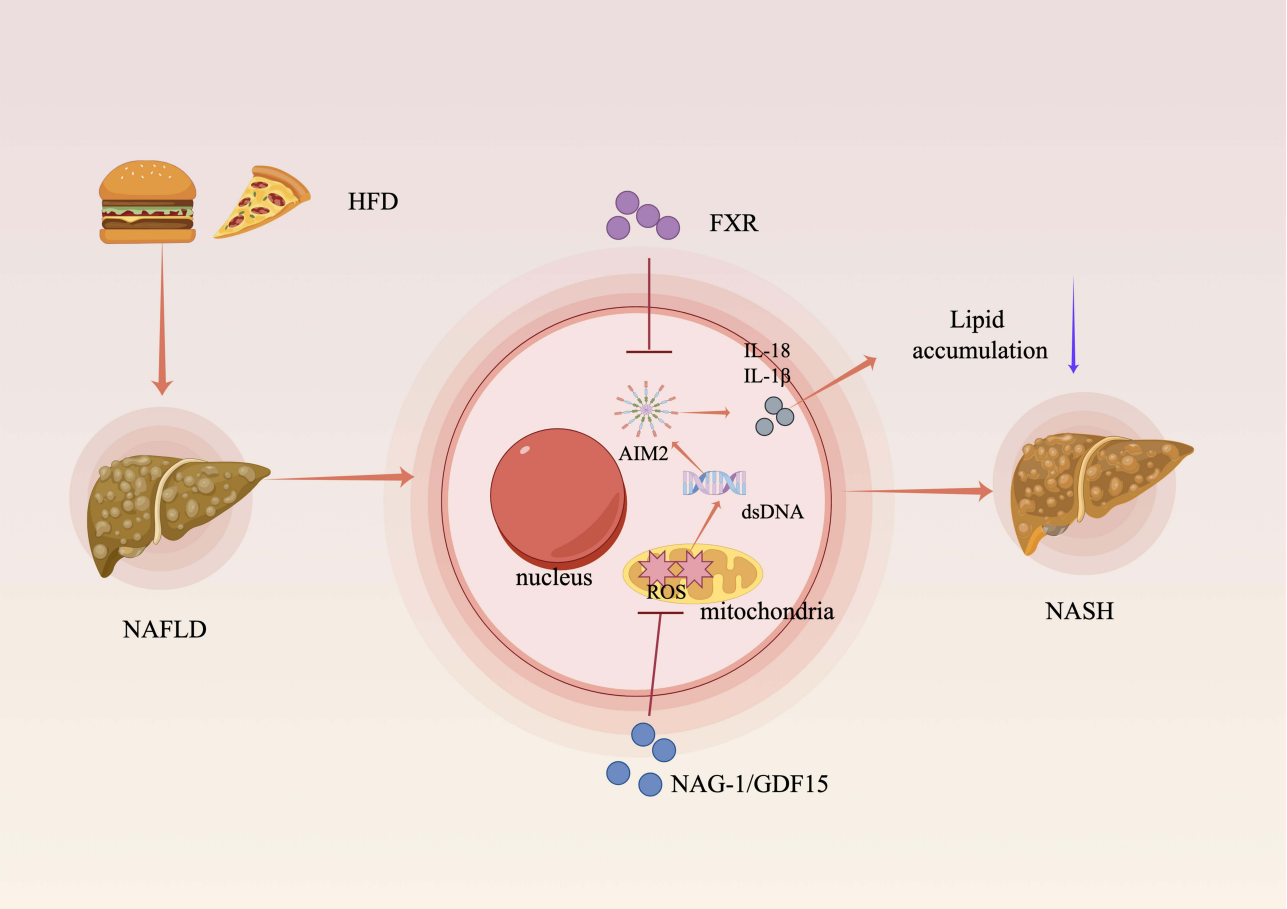

Figure 4 The relationship between AIM2, obesity, and diabetes. Exogenous entry of intracellular dsDNA or intracellular elevation of mtDNA binding to AIM2 can activate AIM2 inflammatory vesicles and promote the development of insulin resistance and T2D. AIM2 inhibits the upregulation of P202 and IFI202b to suppress the increase in adipose tissue mass.

with streptozotocin (STZ) in AIM2 knockout mice and wild-type mice, it was found that AIM2 knockout mice were more susceptible to STZ-induced T1D, due to the increased migration of microbial flora from the gut to the pancreatic lymph nodes (PLNs) and enhanced intestinal permeability after AIM2 knockout.[50] Notably, AIM2 may play an important role in regulating susceptibility to T1D.[51] Therefore assessing AIM2 activation in conjunction with other mechanisms of T1D may be particularly important in determining clinical interventions. In summary, in T1D, AIM2 provides a protective effect against disease progression by maintaining gut integrity. While in T2D, it exacerbates insulin resistance through its inflammasome-dependent cytokines. Therefore, AIM2 exhibits a dual role in T1D and T2D.

Furthermore, researchers have shown that there is a close correlation between the AIM2 gene and diabetic complications. For example, heart muscle structure and function are abnormal in people with diabetes. A study of diabetic rat models and HG-treated H9C2 myoblasts, revealed that the AIM2 protein is associated with the production of reactive oxygen species (ROS) and the death of cardiomyocytes in diabetic cardiomyopathy and that inhibition of AIM2 can alleviate cardiac remodeling and prevent diabetes-induced myocardial fibrosis in diabetic rats.[52,53] Diabetic foot ulcers are also common complications of diabetes. A study by Liu et al[54] showed that elevated neutrophil death in people with diabetes is secondary to foot ulcers and results in the formation of a neutrophil extracellular trap (NETs). NETs can induce AIM2 expression in macrophages via the P65 pathway, which eventually causes a persistent inflammatory response during trauma. Additionally, Nie et al[55] showed that metformin may alleviate diabetes-induced impairment through an AIM2-dependent pathway. In conclusion, AIM2 plays a nonnegligible role in T1D, T2D and their complications. Moreover, at present, diabetes is treated mainly through long-term drug treatment, and despite the large number of available antidiabetic drugs, most people with diabetes are unable to achieve optimal glycemic control and usually suffer from side effects such as drug dependence.[56] Overall, the study of AIM2-dependent pathways will likely reveal a new target for the treatment of diabetes and its complications (Figure 4).

Role of AIM2 in Lipid Metabolism Disorders

Studies have shown that most people with obesity and people with T1D and T2D have lipid metabolism disorders,[57,58] and common lipid metabolism disorders include hyperlipidemia, atherosclerosis, fatty liver and cardiovascular and cerebrovascular diseases. Inflammation is a risk factor for lipid metabolism disorders, and a strong association between AIM2 inflammatory vesicles and lipid metabolism disorders, especially fatty liver and atherosclerosis, has been widely reported in the literature.

Research Advances in the Role of AIM2 in Fatty Liver Disease

Fatty liver disease mainly refers to the accumulation of fat in the liver. Nonalcoholic fatty liver disease (NAFLD) is a type of fatty liver disease that is not related to alcohol abuse and is usually not accompanied by inflammation; however, its occurrence is closely associated with metabolic disorders. When NAFLD is accompanied by inflammation and hepatic fibrosis, it is called nonalcoholic steatohepatitis (NASH). AIM2 inflammatory vesicles may play an important role in the progression of NAFLD to NASH. Related studies have reported the upregulation of AIM2 inflammatory vesicle expression in steatohepatitis, for example, in a mouse model of methionine-choline deficiency (MCD) diet-induced steatohepatitis, where AIM2 was found to increase its expression in a manner that could be dependent on the activation of TLR signaling by the innate immunity signal transduction junction (myeloid differentiation primary response gene 88 (MyD88) activates TLR signaling to increase its expression.[59] In a high-fat diet-induced nonalcoholic fatty liver disease (NAFLD) mouse model, AIM2 expression was also found to be activated in the liver and to promote the development of NASH in male mice.[60] However, A recent study found that overexpression of AIM2 enhanced the expression of LC3B and decreased the expression levels of p62, beclin1, and p-mTOR after acetaminophen (APAP) stimulation, indicating that AIM2 can directly regulate the autophagy pathway and play a promoting role.[61] In conclusion, AIM2 plays a complex role in fatty liver disease. However, the mechanism of action of AIM2 in NAFLD and NASH is currently poorly understood and lacks human studies.

AIM2 may be a therapeutic target for the treatment of fatty liver disease. Farnesoid X receptor (NR1H4, FXR) is a ligand-activated transcription factor, and FXR has been found to ameliorate hepatic steatosis by inhibiting the activation of the AIM2 inflammasome in mouse models overexpressing FXR and in palmitic acid-treated AMI-12

cells.[62] In addition, nonsteroidal anti-inflammatory drug-activated gene (NAG-1) and growth differentiation factor 15 (GDF15) can play therapeutic roles in obesity-induced NAFLD by decreasing mitochondrial damage, reducing dsDNA release, and directly inhibiting the activation of AIM2 inflammatory vesicles.[63] In summary, inflammation is one of the most important disease processes in the development of fatty liver, and the expression of AIM2 inflammasome components is upregulated in steatohepatitis. Molecules such as FXR, NAG-1 and GDF15 can inhibit the activation of AIM2 inflammatory vesicles to treat steatohepatitis, so targeting AIM2 may be a new therapeutic strategy for the treatment of steatohepatitis in the future (Figure 5).

Research Advances in the Role of AIM2 Inflammasome in Atherosclerosis

Atherosclerosis is a complex and multistage pathological process that can be roughly divided into three stages, from early endothelial cell damage and monocyte migration to midterm plate formation and inflammatory cell infiltration to late plaque rupture and thrombosis. The AIM2 Inflammasome plays an important role in this process. In the early stage, activation of AIM2 has been found to lead to reduced endothelialization and increased production of proinflammatory factors in a mouse model of acute vascular injury,[64] but the specific role and of AIM2 in the early stage of atherosclerosis is currently unclear and deserves further exploration. More studies are reporting the important role of AIM2 in the middle and late stages of atherosclerosis, where Gasdermin D, a target protein of AIM2, may affect plaque progression through several different mechanisms. Gasdermin D is involved in the release of inflammatory factors such as IL-1β and IL-18 and cellular pyroptosis and can exacerbate the release of foam cells in an IL-1β-dependent manner. Moreover, the knockdown of Gasdermin D in a LDLR ASO-induced hyperlipidemia mouse model led to reduced expression of vascular

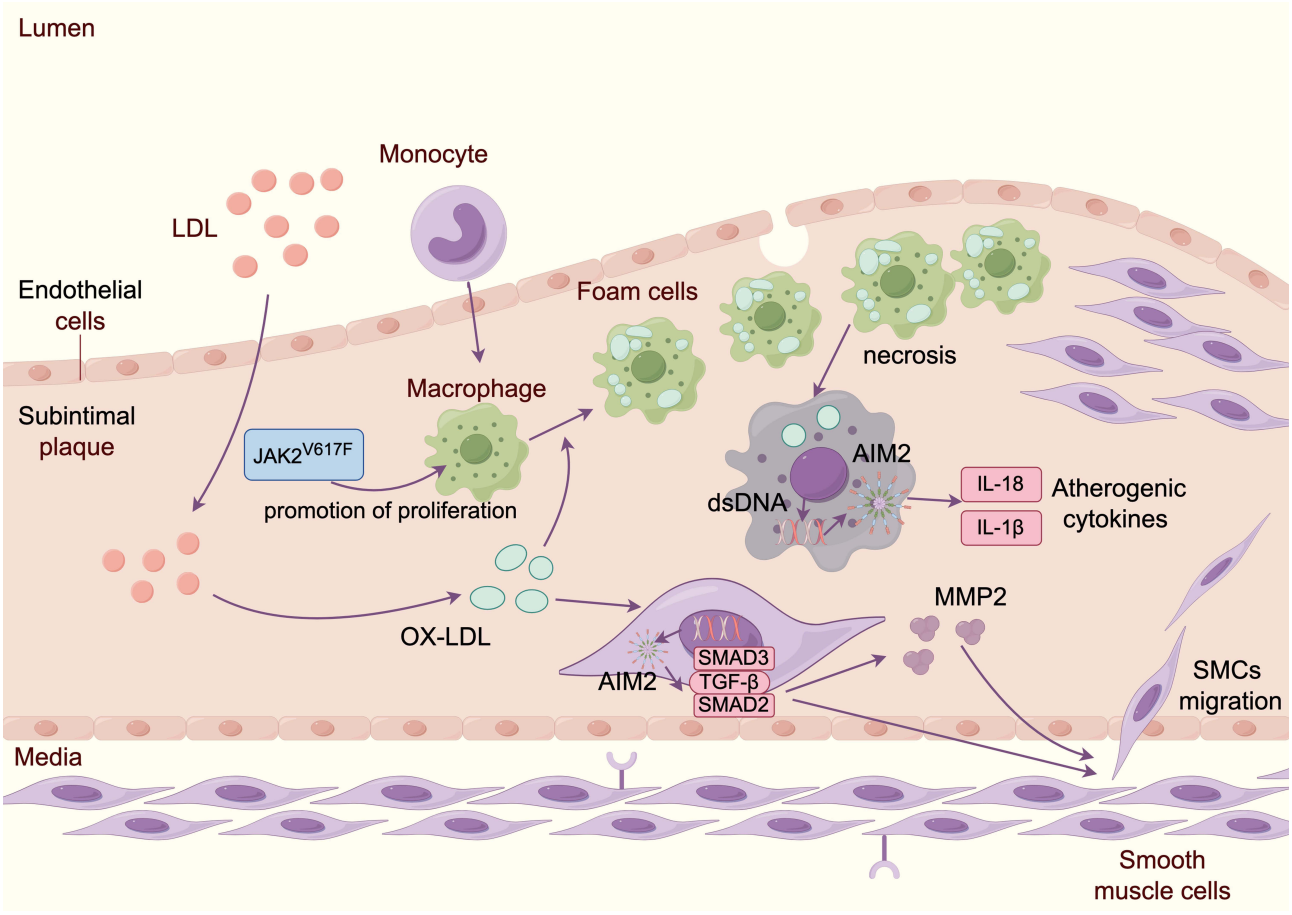

Figure 5 The role of AIM2 in fatty liver disease. A high-fat diet promotes the development of NAFLD, and AIM2 activation promotes the progression of NAFLD to NASH. FXR can inhibit the activation of AIM2. In addition, NAG-1 and GDF15 can play therapeutic roles in NAFLD by decreasing mitochondrial damage, reducing the release of dsDNA, and inhibiting the activation of AIM2.

cell adhesion molecule 1 (VCAM1) and fewer atherosclerotic lesions.[65] Plaque formation can be triggered by the migration of vascular smooth muscle cells (VSMCs) in the vessel wall, which requires the interaction of cellular and extracellular molecules. Matrix metalloproteinase (MMP2) is considered a clinical marker of atherosclerotic plaques, and activation of AIM2 increases the activities of TGF-β, SMAD2, and SMAD3 in VSMCS, which promotes the upregulation of MMP2 expression and the migration of VSMCs in the vessel wall, contributing to the progression of atherosclerosis.[66] In the later stages of atherosclerosis, AIM2 has been reported to be localized close to the core of atherosclerotic necrosis,[21] and it is associated with atherosclerotic plaque instability.[47] Knockdown or inhibition of AIM2 can reduce IL-1β and IL-18 level in atherosclerotic lesions and enhance the stability of atherosclerosis.[47] In a study using ApoE-/- model mice, it was also found that aortic plaque lesions were significantly larger when AIM2 was overexpressed. When AIM2 was knocked out, aortic plaque lesions were smaller, the number of intimal smooth muscle cells was significantly increased, the number of TUNEL-positive cells was reduced, the collagen content of the lesion increased, the fibrous membrane was thickened, and AIM2 was abundantly expressed in the later stages of atherosclerosis compared with earlier stages.[47,67] Furthermore, it has been shown that $JAK2^{VF}$, a mutant of JAK2, that is associated with clonal hematopoiesis and atherosclerosis, has a greater prevalence in elder people.[68] Intrinsic JAK2-V617F drives macrophage proliferation, leading to the accumulation of mitochondrial oxidized DNA, which promotes DNA damage and dsDNA breaks, leading to the activation of AIM2 and ultimately to increased levels of inflammatory macrophages and necrotic core formation in atherosclerosis.[69] To understand the role of the NLRP3 and AIM2 inflammasomes in atherosclerosis caused by $Jak2^{vf}$ mutation. $Jak2^{VF}$Nlpr3-/- and $Jak2^{VF}$AIM2-/- mouse models of atherosclerosis were constructed, and it was found that NLRP3 deficiency had no significant effect on the core range of lesions or necrosis, but AIM2 deficiency significantly reduced the extent of the core lesions.[68] In summary, AIM2 is involved in the entire process of atherosclerosis in a complex manner, and much evidence indicates that activation of AIM2 promotes the development of atherosclerosis, whereas inhibition of AIM2 results in of the reduction of atherosclerotic lesions. Therefore, AIM2 may be an important target for precision medicine.[70] However, the role of AIM2 in atherosclerosis still needs to be further explored (Figure 6).

The Potential Research Value of AIM2 as a Therapeutic Target for Metabolic Diseases

Research on targeting AIM2 for the treatment of metabolic disease has received much attention. J114 is reported to be a novel series of aryl acetamide derivatives as pyroptosis inhibitors that contains an antpyroptotic lead scaffold, it can indirectly block the AIM2-ASC interaction and showed discrepant inhibitory activity against both NLRP3 and AIM2 inflammasome activation in human and mice macrophages.[71] So, J114 is potential for therapeutic purposes in various human diseases, such as multiple sclerosis, type 2 diabetes, and gout. Furthermore, biochemistry and molecular modeling have uncovered 4-sulfonic calixarenes as formidable inhibitors of AIM2, likely functioning by competitively binding to the DNA-binding HIN domain. For instance, 4-sulfonic calixarenes could prove effective in countering post-stroke immunosuppression and be swiftly repurposed to address a growing clinical demand.[72] Likewise, A151 functions as an inhibitor of AIM2, which directly obstructs AIM2 by disrupting the AIM2-dsDNA interaction. Mice administered A151 exhibited a subdued immune response to stroke, characterized by diminished counts of neutrophils, microglia, and microglial production of IL-6 and TNF-α following MCAO. Furthermore, A151 treatment markedly decreased infarct volume, alleviated neurodeficits, and curtailed cell death.[73] In addition to this, there are studies that have demonstrated that both Probenecid and Quercetin can act as inhibitors of AIM2. Probenecid successfully diminished mortality induced by pressure overload and reinstated measures of disease severity in a rat model of chronic heart failure (HF) in vivo.[74,75] Quercetin suppressed both the NLRP3 and AIM2 inflammasomes by obstructing ASC oligomerization and may serve as a promising therapeutic candidate for Kawasaki disease vasculitis and other IL-1 mediated inflammatory disorders.[74] So targeting AIM2 may be a new therapeutic strategy in the future.

Other Inflammasomes and Metabolic Diseases

The NLRP3 inflammasome has attracted much attention in recent years for its broad biology in signaling, inflammation, and cell death. It mediated inflammatory cytokines in both autocrine and paracrine manners in various metabolic tissues

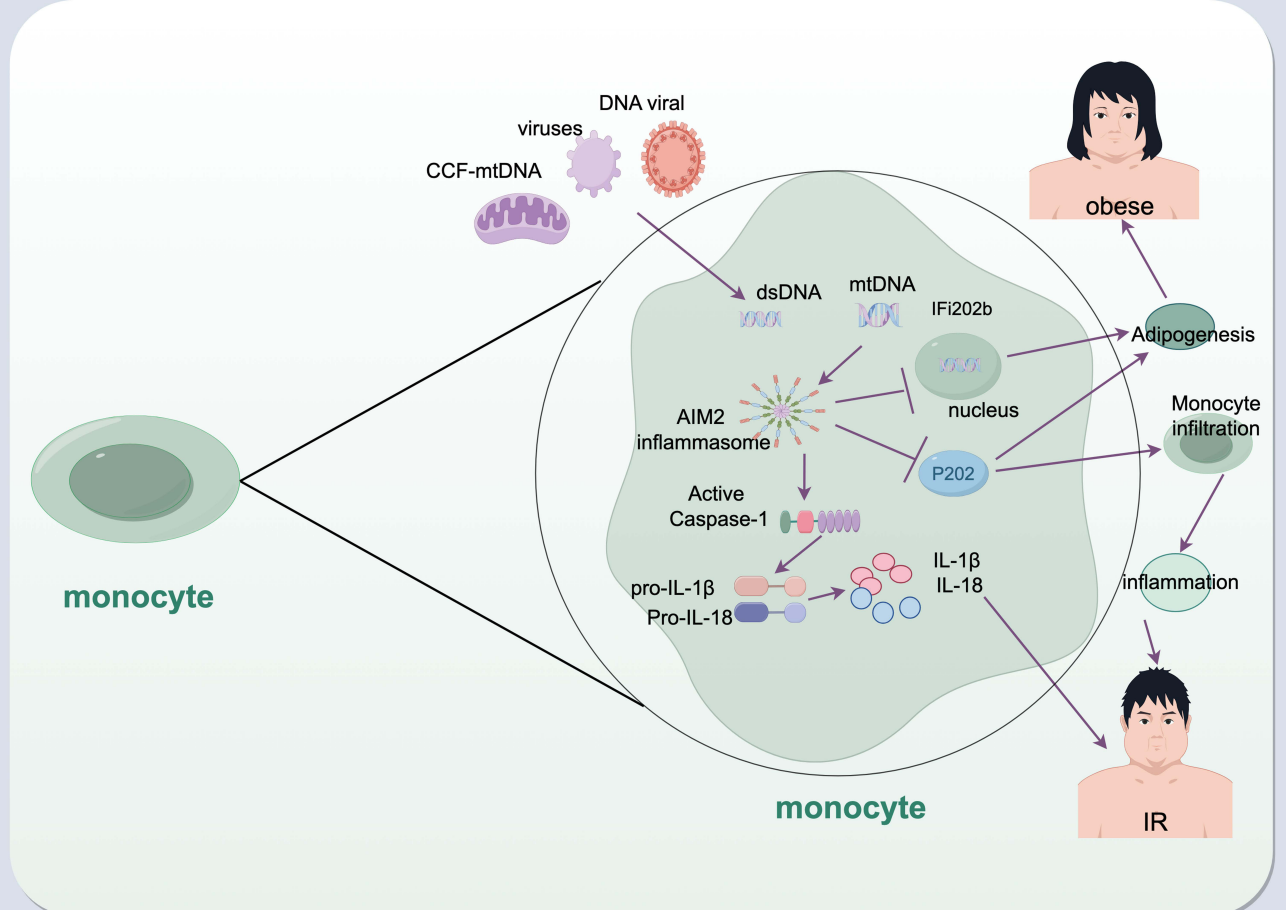

Figure 6 The role of AIM2 in atherosclerosis. When low-density lipoprotein (LDL) enters endothelial cells and becomes oxidized, it damages vascular endothelial cells, and macrophages are activated to phagocytose oxidized LDL and form foam cells. Oxidized LDL increases the expression of the Aim2 gene in VSMCs, activates MMP-2, SMAD-2 and SMAD-3, and increases smooth muscle cell proliferation. The dsDNA released from necrotic cells during advanced atherosclerosis activates AIM2 inflammatory vesicles in macrophages and releases IL-1β and IL-18, which are cytokines that promote atherosclerotic plaque formation. In addition, JAK2-V617F drives macrophage proliferation, leading to the accumulation of mitochondrial oxidized DNA, which promotes DNA damage and dsDNA breaks, thereby activating AIM2.

and contribute to metabolic disorders.[76] In diabetes and obesity, obesity-related danger signals such as palmitate, lipids, and ceramides promote the activation of the NLRP3 inflammasomes and the release of IL-1β downstream of NLRP3 activation causes insulin resistance and reduces glucose uptake in insulin target tissues such as muscle, liver, and adipose tissues, leading to the pathogenesis of diabetes and obesity.[77] In atherosclerosis, NLRP3 inflammasome can be activated by a variety of danger signals, such as oxidized low-density lipoprotein (ox-LDL) and cholesterol crystallization. Upon activation, NLRP3 inflammasome assemble and contribute to cysteine asparaginase-1 (caspase-1) activation. Caspase-1 further cleaves pro-IL-1β and pro-IL-18 signals to neighboring monocytes/macrophages, endothelial cells, and smooth muscle cells to promote the pathogenesis of atherosclerosis.[78] In conclusion, AIM2 plays overlapping role in the progression of metabolic disorders. Both AIM2 and NLRP3 inflammasomes have significant effects in metabolic diseases, but they differ significantly in their mechanisms.

Noninflammatory Effects of AIM2

The inflammatory role of AIM2 has been the focus of recent research, but with the in-depth study of the molecular structure and biological function of AIM2, AIM2 was found to be involved not only in inflammation but also in other important biological processes. Previous studies, have shown that the inflammatory vesicle-independent function of AIM2 is mainly related to the development of cancer, such as breast cancer, colorectal cancer, and kidney cell carcinoma.[79,80] A 15-year study, revealed that AIM2 inhibited the proliferation of tumor-inducing intestinal stem cells in the lining of the base of the crypts after dysregulation of Wnt signal transduction, and that the production of factors that mediate inflammation was essentially intact in AIM2-deficient

mice, However, in these mice, intestinal stem cells were prone to uncontrolled growth, exacerbating tumorigenesis and suggesting that AIM2 suppresses tumorigenesis by inhibiting the proliferation of intestinal cells in the intestine rather than promote inflammation.[81] In the same year, Wilson et al, who evaluated the role of AIM2 in colon cancer, reported that AIM2 can physically interact with and limit the activation of DNA-dependent protein kinase (DNA-PK), a member of the P13K-related family that the promotes phosphorylation of protein kinase B (AKT), a regulator of cell survival; therefore, when AIM2 is absent, DNA-PK-mediated AKT overactivation still occurs, which promotes cell proliferation and reduces apoptosis, leading to the development of cancer.[82] In recent years, AIM2 has been found to promote the progression of renal cell carcinoma by regulating ferroptosis through the FOXO3a-ACSL4 axis.[79] In addition, in immune cells, AIM2 acts as an immunomodulatory factor in B-cells that inhibits CXCL16 production and reduces CD8+ T-cell aggregation in inflamed gastric mucosa.[83] Moreover, AIM2 also has an inflammatory vesicle-independent role in obesity and insulin resistance, where it prevents p202-induced monocyte infiltration and adipogenesis, mainly by inhibiting the encoded protein 202, which in turn ameliorates obesity and insulin resistance.[39] In conclusion, the noninflammatory role of AIM2 is important for maintaining homeostasis and preventing disease development. These findings may provide new perspectives for understanding the pathogenesis of diseases and potential therapeutic targets for intervention.

Conclusion

In metabolic diseases, AIM2 regulates disease progression through complex processes, and it participates in a variety of signaling pathways, therefore, it is crucial to thoroughly study the roles of AIM2 in different metabolic processes. The structural features and physicochemical properties of AIM2 have been thoroughly investigated in recent years. Moreover, AIM2 plays a role in obesity, T1D, T2D, fatty liver disease, and atherosclerosis. Understanding the specific roles of AIM2 in different metabolic diseases can lead to the development of activators and inhibitors targeting AIM2 for the prevention, control and treatment of these diseases. In conclusion, the search for drugs targeting AIM2 is a worthy direction for research on the diagnosis and treatment of obesity-related disorders of glucose and lipid metabolism, which will provide new perspectives for the diagnosis and treatment of these diseases.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Shandong First Medical University (Shandong Academy of Medical Sciences) Youth Science Foundation Funding Program (Grant No. 202201-083), the Natural Science Foundation of Shandong Province, China (Grant No. ZR2023MH031; No. ZR2023QH232).

Disclosure

The authors declare no conflicts of interest in this work.

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