Mincle as a potential intervention target for the prevention of inflammation and fibrosis (Review)

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Abstract. Macrophage-inducible C-type lectin receptor (Mincle) is predominantly found on antigen-presenting cells. It can recognize specific ligands when stimulated by certain pathogens such as fungi and *Mycobacterium tuberculosis*. This recognition triggers the activation of the nuclear factor-κB pathway, leading to the production of inflammatory factors and contributing to the innate immune response of the host. Moreover, Mincle identifies lipid damage-related molecules discharged by injured cells, such as Sin3-associated protein 130, which triggers aseptic inflammation and ultimately hastens the advancement of renal damage, autoimmune disorders and malignancies by fostering tissue inflammation. Presently, research on the functioning of the Mincle receptor in different inflammatory and fibrosis-associated conditions has emerged as a popular topic. Nevertheless, there remains a lack of research on the impact of Mincle in promoting long-lasting inflammatory reactions and fibrosis. Additional investigation is required into the function of Mincle receptors in chronological inflammatory reactions and fibrosis of organ systems, including the progression from inflammation to fibrosis. Hence, the present study showed an overview of the primary roles and potential mechanism of Mincle in inflammation, fibrosis, as well as the progression of inflammation to fibrosis. The aim of the present study was to clarify the potential mechanism of Mincle in inflammation and fibrosis and to offer perspectives for the development of drugs that target Mincle.

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Abbreviations: Mincle, macrophage-inducible C-type lectin; PRR, pattern recognition receptor; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; CRD, carbohydrate recognition domain; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; CARD9, caspase-recruitment domain 9; Syk, splenic tyrosine kinase; APCs, antigen-presenting cells; ECM, extracellular matrix; UUO, unilateral ureteral obstruction; CIAKI, cisplatin-induced acute kidney injury; IRI, ischemia reperfusion injury; CKD, chronic kidney disease; TBI, traumatic brain injury; A&P, *Astragalus mongholicus* Bunge and *Panax notoginseng* formula; IronQ, iron(III)-quercetin complexes; MS, multiple sclerosis; KCs, Kupffer cells; ROS, reactive oxygen species; ACLF, acute-on-chronic liver failure; CLS, crown-like structures; NASH, non-alcoholic steatohepatitis; BMDMs, bone marrow-derived macrophages; mTECs, macrophages and renal tubular epithelial cells; MF, myofibroblast; RA, rheumatoid arthritis; MMT, macrophage to MF transition; SAP130, spliceosome-associated protein 130

Key words: Mincle, PAMPs, DAMPs, inflammation, fibrosis, MMT

Contents

1. Introduction

Inflammation is a physiological response to tissue damage or infection, characterized by the recruitment of immune cells,

release of proinflammatory cytokines and increased blood flow and vascular permeability (1). While acute inflammation is beneficial for tissue repair and pathogen clearance, chronic inflammation can lead to tissue damage and fibrosis (2).

Macrophage-inducible C-type lectin (Mincle) recognizes pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) and triggers immune responses (3), primarily expressed in macrophages (4). Once activated by various ligands, including pathogen-derived components and endogenous molecules released from damaged cells, Mincle triggers a series of signaling pathways, leading to the production of proinflammatory cytokines, which are crucial for the initiation and progression of inflammation (5). Studies have shown that Mincle is involved in the initiation of inflammation and also in the progression to fibrosis. For example, Mincle activation has been found to promote liver injury by inducing the production of pro-fibrotic cytokines (6). The expression of Mincle is upregulated in various fibrotic diseases, including liver, lung, and kidney fibrosis, suggesting a potential role of Mincle in the progression of inflammation to fibrosis (7). Moreover, Mincle has been shown to interact with other receptors and signaling pathways involved in inflammation and fibrosis. For instance, Mincle can synergize with Toll-like receptors (TLRs) to amplify inflammatory responses and activate the nuclear factor-κB (NF-κB) pathway, which plays a vital role in inflammation and fibrosis. Additionally, the progression of inflammation to fibrosis is a complex process that involves various cellular and molecular mechanisms. The involvement of Mincle in fibrosis is not merely a consequence of inflammation. Instead, it appears to directly contribute to the fibrotic process. Mincle activation has been shown to promote the differentiation of fibroblasts into myofibroblasts (8). Therefore, Mincle may play a significant role in the inflammatory-fibrotic axis and targeting Mincle could be a promising strategy to alleviate inflammatory and fibrotic diseases. The present review summarized the role of Mincle in inflammation and fibrosis and discussed its potential as a therapeutic target.

2. Mincle

The innate immune response and the adaptive immune response make up the immunological response of the body. The innate immune response purges the body of foreign substances and serves as the initial line of defense against infections brought on by the environment. The pattern recognition receptors (PRRs) of innate immune cells interact with PAMPs derived from pathogenic bacteria, triggering an innate immune response. The lineage encoded PRRs have the ability to recognize various ligands, such as proteins, nucleic acids and carbohydrates. Notably, four classes of PRRs have been identified: TLR, RIG-I-like receptor, NOD-like receptor and C-type lectin receptor (CLR) (9). Mincle is a type II transmembrane CLR belonging to the same gene cluster as dectin-2 and dectin-3 and encoded by C-type lectin domain family 4 member E (Clec4e) (10), mainly expressed on the surface of immune cells such as macrophages, dendritic cells and NK cells (11,12). The structure of Mincle is characterized by the presence of an extracellular carbohydrate recognition domain (CRD), a stalk region and a transmembrane region with positively charged residues (13) (Fig. 1). This allows it to recognize and bind a wide range of pathogens and viral particles.

In the transmembrane area of Mincle, there is a positively charged arginine residue. Following recognition of PAMP or DAMP by the extracellular CRD of Mincle, the positively charged arginine residue binds to the negatively charged residue of the Fc receptor γ (FcRγ) chain and transmits the activation signal through the immunoreceptor tyrosine-based activation motif (ITAM). ITAM then activates splenic tyrosine kinase (Syk) via phosphorylation (1). According to previous studies, caspase-recruitment domain 9 (CARD9) is considered a crucial downstream of ITAM signaling, forming a complex with B-cell lymphoma 10 (Bcl10) and mucosa-associated lymphoid tissue lymphoma translocation protein 1 (Malt1). Phosphorylated Syk activates the NF-κB signaling pathway through this complex, resulting in the release of chemokines from antigen-presenting cells (APCs) (Fig. 2) (3,13-16).

Glycolipids make up the majority of the ligands of Mincle. In 2008, spliceosome-associated protein 130 (SAP130), an endogenous ligand derived from injured and necrotic cells, was reported to be recognized by Mincle (3). The groundbreaking observation of Wells *et al* (17) in the same year established the identification of *Candida albicans* by Mincle and its pivotal role in orchestrating host protective immune responses against fungal pathogens, marking the first documentation of the involvement of Mincle in the immune system. In the subsequent year, Mincle was firmly recognized as a PRR for trehalose-6,6'-dimycolate (TDM), a glycolipid predominantly located on the cellular membranes of *Mycobacterium*, unravelling further insights into its functional significance (4). Notably, an increasing number of ligands have been discovered, such as sterols (18,19), β-gentiobiosyl diacylglycerides (20), glucosyl-diacylglycerol (21), α-glucosyl diglyceride (22), brartemicin (23), *Agrocybe aegerita lectin* (24), β-glucosylceramides (25), α-mannose (12), glyceroglycolipid (26,27) and peroxiredoxin 1 (Prdx1) (28). The ligands are summarized in Table I. The binding of Mincle with the ligands is associated with inflammatory related diseases such as acute nephritis, hepatitis (29,30), Crohn's disease (31), stroke (32,33), cancer (34,35), immune diseases (36,37) as well as numerous other diseases (Fig. 3) The relationship between these diseases, Mincle and its ligands is still under continuous investigation and exploration and the specific mechanisms and regulatory processes require further in-depth research.

3. Mincle and inflammation

Inflammation is essential for the healing process of tissue injury and wounds. Inflammation facilitates the prompt arrival of cellular and humoral defenses to the damaged spot, thereby impeding the process of injury and aiding in the elimination of debris produced during the injury while promoting repair (38). If the culpable agent is not eliminated or controlled, it leads to the emergence of persistent inflammation, which can have adverse effects on the host. Tissue damage, excessive collagen buildup and fibrosis occur due to the presence of growth factors released by neutrophils and macrophages, proteolytic enzymes and reactive oxygen species (ROS) (39).

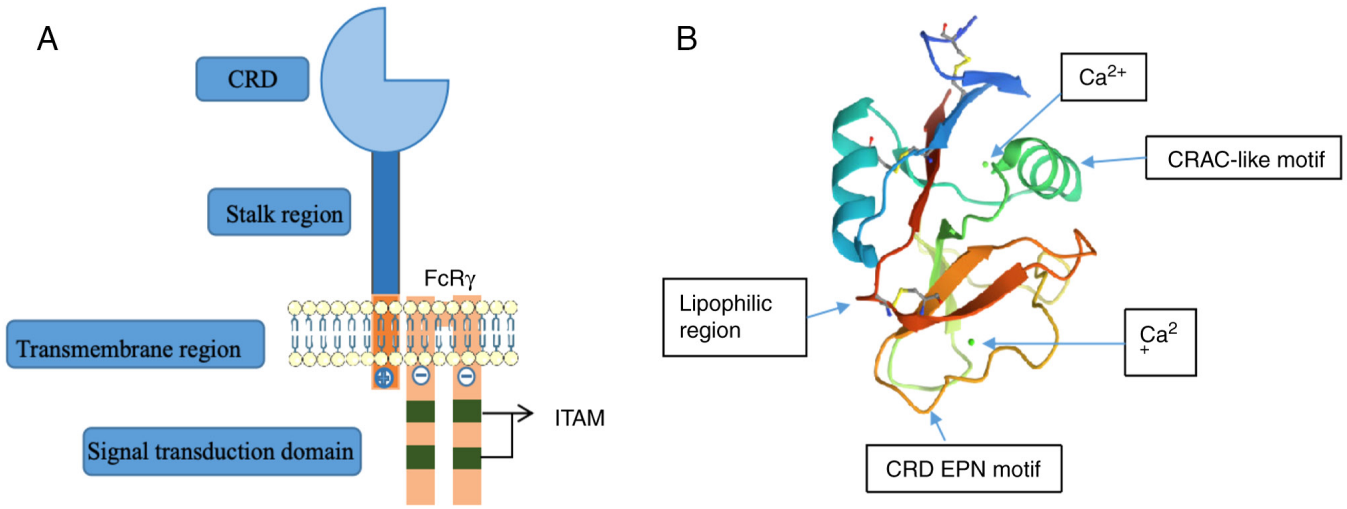

Figure 1. (A) Structure diagram of Mincle. Mincle is encoded by six exons, including a single extracellular CRD, a variable length stalk region, a transmembrane region and a short cytoplasmic domain free of tyrosine residues. Among them, CRD contains conserved residues that coordinate two Ca^{2+}, responsible for binding to carbohydrates. Moreover, a positively charged arginine residue exists in the transmembrane region, which drives Mincle to couple with FcRγ and transmits the activation signal through ITAM in FcRγ. (B) Three dimensional structures of human Mincle (ligand-free form) from the Protein Data Bank (https://www.rcsb.org/structure/3WH3) are illustrated, with the CRD EPN motif indicated in yellow, the lipophilic region in dark orange and the CRAC-like motif in green. Mincle, macrophage-inducible C-type lectin receptor; CRD, carbohydrate recognition domain; FcRγ, Fc receptor γ; ITAM, immune receptor tyrosine activation motif; EPN, glutamic acid-proline-asparagine; CRAC, cholesterol recognition/interaction amino acid.

Mincle and sterile inflammation. In the absence of microorganisms, inflammation typically arises from trauma or chemical injury, which is commonly referred to as sterile inflammation. The main features of sterile inflammation include the recruitment of chemokines, macrophages, neutrophils and inflammatory cytokines, with a particular emphasis on tumor necrosis factor (TNF) and interleukin (IL)-1 (40).

The development of inflammatory diseases, such as brain damage, liver injury and autoimmune disorders is significantly influenced by Mincle. This is explained by the capacity of Mincle to trigger sterile inflammation by identifying and attaching to DAMPs. Necrotic cells which emit DAMPs such as SAP130, are just a few of the proinflammatory cytokines that are upregulated as a result of the interaction between Mincle and these DAMPs. These elements contribute to neutrophil infiltration and M1-type macrophage polarization, which exacerbate tissue injury (41).

Mincle and renal inflammation. Mincle contributes to the promotion of M1 macrophage-mediated acute kidney injury (AKI). The TLR4/NF-κB signaling pathway tightly controls the expression of Mincle on M1 macrophage and Mincle plays an important role in sustaining the M1 macrophage phenotype (42). Lv *et al* (43) found that Mincle contributes to the development of unilateral ureteral obstruction (UUO) and cisplatin-induced acute kidney injury (CIAKI) by regulating inflammatory responses mediated by macrophages, thereby enhancing renal tubule injury. Subsequently, it was discovered that damaged renal tubule cells release SAP130, which controls the activation of macrophages and the occurrence of renal inflammation by miRNA-219c-3p-dependent mechanisms in UUO and CIAKI animal models, as well as in individuals with acute tubular necrosis (44). miR-219c binds to Mincle and inhibits Mincle translation, resulting in the negative regulation of Mincle expression in macrophages. The activation of Mincle was revealed to occur when dead cells released β-glucosylceramide and free cholesterol. The activation of Mincle was found to elicit a robust response in macrophages, leading to the secretion of proinflammatory cytokines and impairing the efficient clearance of apoptotic cells. As a consequence, this cellular process played a pivotal role in orchestrating the persistent inflammatory milieu following AKI, ultimately leading to the development of renal atrophy (45). Li *et al* (28) identified that kidney-derived serum Prdx1 plays a role in AKI by activating Mincle and downstream pathways. The experimental results of these researchers revealed an increase in serum Prdx1 levels and a decrease in Prdx1 expression in renal tubular epithelial cells associated with AKI induced by lipopolysaccharide and renal ischemia reperfusion injury (IRI) in animal models. Furthermore, it was revealed that gene knockout of Prdx1 or using Prdx1 neutralizing antibodies protected mice from AKI, while exogenous recombinant Prdx1 (rPrdx1) introduction weakened this protective effect. Further study of peritoneal macrophages revealed that rPrdx1 induced M1 polarization, activated the Mincle signaling and enhanced the production of inflammatory cytokines. Additionally, Prdx1 interacted with Mincle, leading to acute kidney inflammation. These findings suggested that serum Prdx1 derived from kidneys promotes AKI by activating the Mincle signaling and downstream pathways. Collectively, Mincle triggers and sustains M1 macrophages via the Mincle-associated pathway and controls macrophage-driven inflammation, which ultimately contributes to the promotion of renal inflammation and exacerbation of renal injury. Targeting Mincle and its associated pathways could be a potential approach for addressing renal damage.

Mincle and liver damage. Mincle exerts a proinflammatory role in liver damage and contributes adversely to the progression of chronic alcoholic hepatitis. A previous study revealed

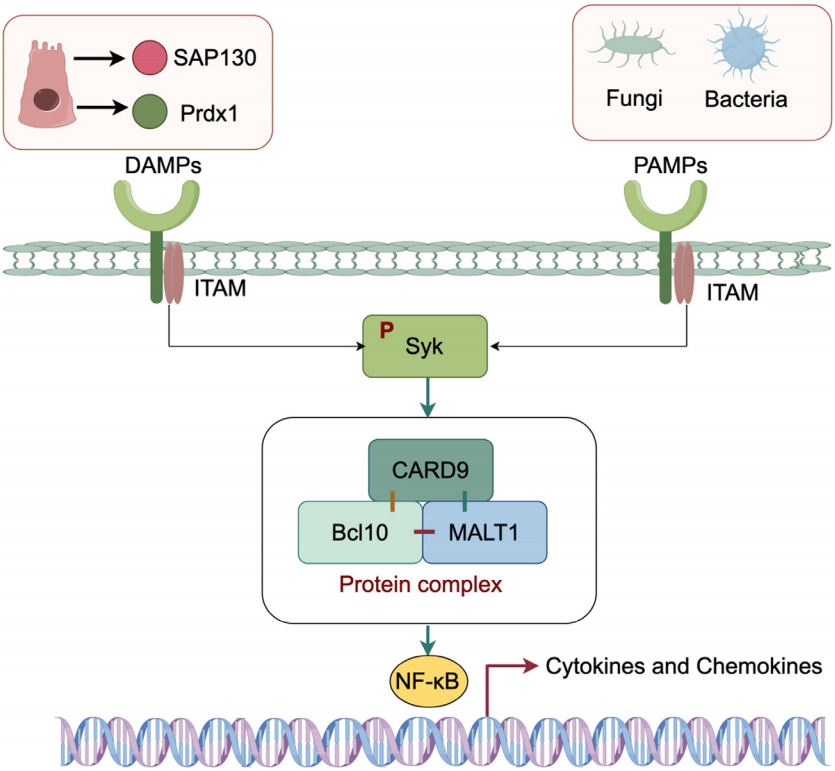

Figure 2. Functions of Mincle. After recognition of PAMP or DAMP by the extracellular carbohydrate recognition domain of Mincle, the positively charged arginine residue binds to the negatively charged residue of the FcRγ chain and transmits the activation signal through ITAM. Then, ITAM activates Syk via phosphorylation. According to reports, CARD9 is considered a crucial adaptor molecule downstream of ITAM signaling, forming a complex with Bcl10 and Malt1. Phosphorylated Syk activates the NF-κB signaling pathway through this complex, resulting in the release of chemokines from APCs. This figure was created by Figdraw 2.0 (https://www.figdraw.com; Hangzhou Huikeyan Technology Co. Ltd, China). Mincle, macrophage-inducible C-type lectin receptor; PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; FcRγ, Fc receptor γ; ITAM, immune receptor tyrosine activation motif; Syk, splenic tyrosine kinase; CARD9, caspase-recruitment domain 9; Bcl10, B-cell lymphoma 10; Malt1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; APCs, antigen-presenting cells; SAP130, spliceosome-associated protein 130; Prdx1, peroxiredoxin 1.

that the interaction between Mincle and its endogenous ligand SAP130 could regulate proinflammatory reaction to enhance concanavalin A (ConA) hepatitis. In addition, the protection against ConA hepatitis was observed when Mincle was deleted or blocked, which resulted in reduced expression of CAAT/enhancer-binding protein beta and hypoxia-inducible factor 1α (29). According to a different study, Kupffer cells (KCs) are activated to generate and secrete proinflammatory cytokines, which in turn promote neutrophil infiltration and liver damage in acetaminophen (APAP)-induced liver injury (30). The liver experienced damage when there was an overabundance of APAP, leading to the activation of the Mincle/Syk pathway and the subsequent release of a significant amount of proinflammatory mediators. However, it is possible to reverse these effects and decrease APAP-induced liver damage in case of Mincle deficiency or KC deletion.

Mincle exacerbates chronic alcoholic liver injury caused by alcohol abuse through the activation of the innate immune system. The IL-1 receptor-associated kinase 3 (IRAKM)-Mincle axis was first reported to be activated by low concentrations of lipopolysaccharides (LPS) and SAP130 when they worked together to cause IL-1 receptor-associated kinase injury, which was a major factor in the emergence and progression of chronic alcohol-induced liver injury (30). Ethanol-induced hepatocellular damage required the activation of the Mincle/Syk signaling pathway by SAP130 released from ethanol-exposed hepatocytes, while low dose LPS activated IRAKM Myddosome, significantly increasing the expression of Mincle. Subsequently, a previous study found that Mincle interacting with SAP130 enhanced the infiltration of inflammatory immune cells by promoting the secretion of IL-1β in KCs. The deficiency of Mincle or the inhibition of its downstream pathways reduces the production of inflammatory factors and alleviates alcohol-induced liver injury. On the contrary, the activation of Mincle signaling produces the opposite effect (46).

In patients with cirrhosis and rat models of acute-on-chronic liver failure (ACLF), there was a notable elevation in Mincle protein levels across multiple organs, including the heart, liver, kidney and spleen, with particularly higher expression observed in liver failure models. Surprisingly, this upregulation did not uniformly result in improved downstream signaling in all organs. While significant enhancement of Mincle downstream signaling was observed in the heart, liver and kidney, it was disrupted in the peripheral blood mononuclear cells, spleen and small intestine. These findings suggested that Mincle may have a significant impact on the immune paralysis observed in ACLF (47).

Mincle plays a pivotal role in the progression of chronic liver injury at various stages. The metabolic syndrome in the liver is manifested as non-alcoholic steatohepatitis (NASH), which is defined by increased hepatic lipid buildup without a history

Table I. Ligands of Mincle.

Category	Description	Examples
Exogenous ligands	Molecules derived from microbes, fungi, plants and other external sources	Trehalose-6,6'-dimycolate, trehalose-6,6-dibehenate, α-mannose, gyceroglycolipid, β-gentiobiosyl diacylglycerides, glucosyl-diacylglycerol, α-glucosyl diglyceride, brartemicin, unique mannosyl fatty acids-linked to mannitol.
Endogenous ligands	Molecules produced within the body, including metabolites and cellular components	Sin3-associated protein 130, cholesterol crystal, cholesterol sulfate, peroxiredoxin 1, β-glucosylceramides, etc.
Oxidized ligands	Ligands that have undergone oxidation modifications and can be recognized and activate the Mincle signaling.	Oxidized LDL (malondialdehyde-modified LDL).

Mincle, macrophage-inducible C-type lectin receptor; LDL, low-density lipoprotein.

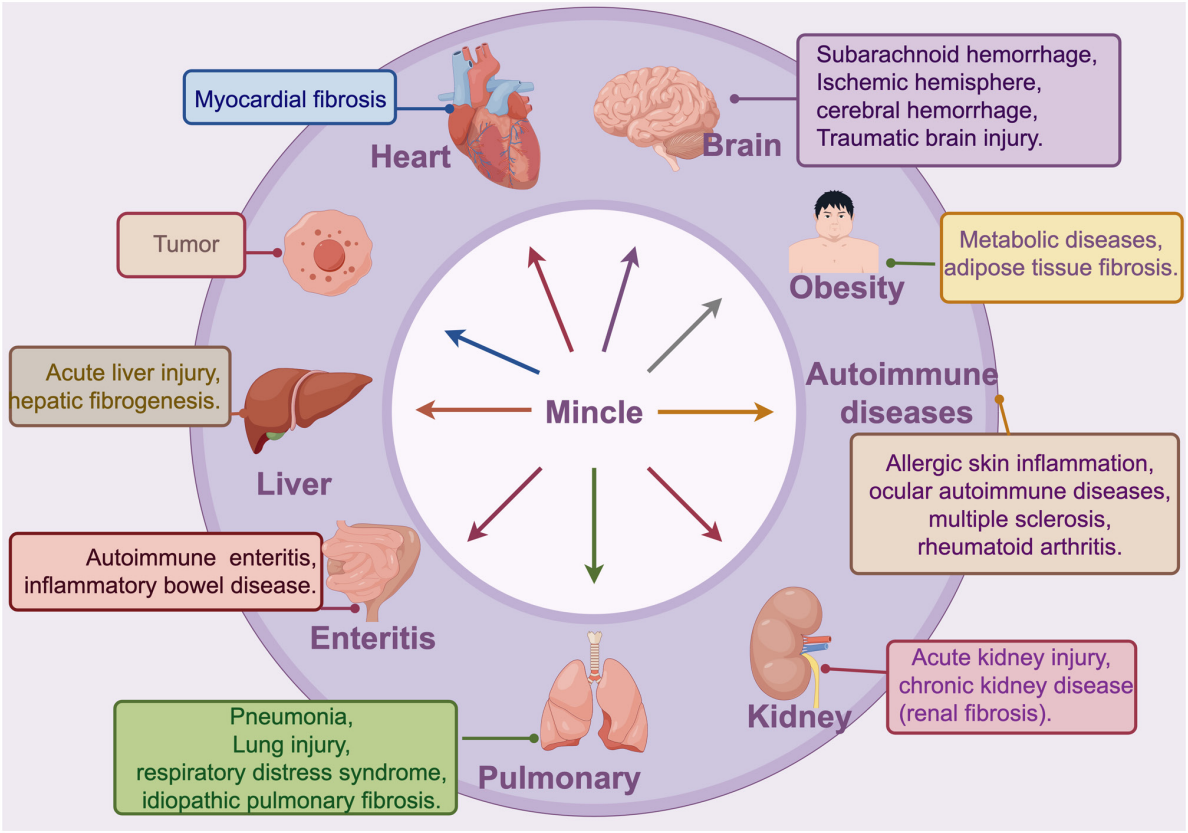

Figure 3. Mincle in the treatment of various diseases. The Mincle signaling pathway is associated with diseases such as traumatic brain injury, acute kidney injury, nephritis, hepatitis, obesity, and skin allergies. This figure was created by Figdraw 2.0 (https://www.figdraw.com; Hangzhou Huikeyan Technology Co. Ltd, China).

of alcohol use. It is mostly brought on by obesity-induced inflammation and fibrosis of adipose tissue, which causes an inflow of free fatty acids into the liver through the portal vein. Initially, this causes the onset of simple steatosis, which then develops into NASH. Hepatocytes undergo death due to lipid overload, resulting in their encapsulation by macrophages and subsequent infiltration of inflammatory cells, ultimately culminating in NASH (48).

In a recognized model for NASH, scientists have observed hepatocellular crown-like structures (hCLS), reminiscent of CLS observed in tissue under microscopic examination. hCLS consist of CD11-positive macrophages clustering around lipid droplets within hepatocytes (43). The interaction between macrophages in hCLS and dying hepatocytes leads to their phagocytosis, activating fibroblasts, promoting fibrosis, and resulting in cirrhosis and hepatocellular carcinoma.

Upregulation of Mincle was observed in liver tissue obtained from animal models and patients with NASH. Additionally, the expression levels of collagen 1, a fibrosis and a Kupffer cell marker, were found to be elevated (47). These findings strongly indicated that the upregulation and activation of Mincle contributes to the aggravation of hepatic fibrogenesis in NASH.

Mincle-mediated inflammation and immune response promote lung injury

Pneumonia. The role of Mincle in pneumonia primarily lies in its ability to identify pathogens and control the immune response. Mincle has the capability to recognize and bind to a variety of pathogens, including bacteria, fungi and viruses, to initiate an immune response that clears the pathogen. Sharma *et al* (49) investigated the role of Mincle in pneumonic sepsis induced by *Klebsiella pneumoniae* (*K. pneumoniae*), which demonstrated that Mincle played a protective role by coordinating bacterial clearance mechanisms of neutrophils. A different study revealed that the Mincle-Glc-DAG axis is a lung protective immune factor in focal pneumonia induced by *Streptococcus pneumoniae* (*S. pneumoniae*) (50). In addition, it was revealed that leukocytes, especially neutrophils expressing Mincle, play a critical role in contributing to the regulation of protective immunity against focal pneumonia-causing *S. pneumoniae* (21).

Notably, Rabes *et al* (51) indicated that Mincle can recognize *S. pneumoniae*. However, experiments with Mincle-deficient mice revealed that this receptor does not have a significant beneficial role in antibacterial immune response during pneumonia. In other words, the protective effect of Mincle in focal pneumonia may be indispensable, but it is not protective in the model of invasive pneumococcal disease (IPD). Ishikawa *et al* (4) revealed the ability of Mincle to detect apoptotic cells and recruit inflammatory cells and that TDM-induced pulmonary granuloma formation is entirely dependent on Mincle. Therefore, it is possible that TDM and necrotic cells potentially collaborate to promote the formation of pulmonary granulomas in tuberculosis through the secretion of inflammatory cytokines/chemokines mediated by Mincle. Thus, the role of mincle-mediated immune responses in lung inflammatory diseases appears to be bidirectional. The relevant published studies according to research grouping, modeling and detection methods are included in supplementary file Table SI.

Lung injury. Mincle recognises and binds to DAMPs released by deceased cells, which initiates an inflammatory response and promotes the repair of damaged tissues. However, excessive inflammation may lead to further aggravation of lung injury. Yamasaki *et al* (3) showed that Mincle recognises and binds to SAP130 released by dead alveolar epithelial cells, which activates macrophages to enhance lung injury. Fisher *et al* (52) established a lethal mouse model of *Orientia tsutsugamushi* (*O. tsutsugamushi*) and cultured macrophages and neutrophils to investigate the involvement of immune sensors and inflammatory responses in the infection process. In addition, a selective stimulation of Mincle expression was observed in the lungs of infected mice by *O. tsutsugamushi*, accompanied by an increase in proinflammatory markers and markers associated with type 1 responses. Moreover, it was found that both live and inactivated bacteria treatment of macrophages resulted in enhanced Mincle expression, along with elevated levels of proinflammatory markers related to type 1 and M1 responses. However, some of these markers were significantly reduced in Mincle cells. The activation of Mincle and its associated inflammatory profile induced by live and inactivated *O. tsutsugamushi* may lead to an excessive immune response, ultimately causing lung injury and acute respiratory distress syndrome. Therefore, Mincle may become a new target for the treatment of pneumonia and lung injury. Further studies are needed on the specific mechanism of action and regulatory strategies of Mincle in pneumonia and lung injury.

In metabolic disorders, Mincle increases adipose tissue inflammation. Obesity is the key contributing factor to metabolic syndrome, a common metabolic condition affecting several organs. A distinct CLS found in obese adipose tissue is made up of decomposing adipocytes encircled by macrophages (53). Within the CLS, adipocytes and macrophages collaborate to create a paracrine pathway that causes adipose tissue to be chronically inflamed. Increased adipose tissue inflammation can promote tissue fibrosis, which in turn causes ectopic adipose tissue buildup and insulin resistance.

As a result of the involvement of Mincle in CLS creation, fibroblast activation and transformation, adipose tissue inflammation and fibrosis are promoted. The expression of Mincle in macrophages is induced partly by palmitate esters through the TLR4/NF-κB pathway, showing significant enhancement in adipose tissue of obese mice and humans (54). Furthermore, Mincle expression is observed in proinflammatory M1 macrophages derived from bone marrow cells *in vitro*, distinguishing them from the anti-inflammatory M2 macrophages. Thus, Mincle could promote the initiation and progression of inflammation of adipose tissue brought on by obesity. Collectively, Mincle is linked with the onset of obesity-associated metabolic disease, indicating its potential as an intervention target for obesity-related diseases, thus, offering promising possibilities.

Mincle promotes the initial stages and progression of neurological inflammation in patients with brain damage

Traumatic brain injury (TBI). TBI refers to the brain damage caused by an external mechanical force, leading to neuronal injury, microglial activation and subsequent neuroinflammatory processes. This can result in temporary or permanent impairment of brain functions (55,56). Additionally, innate immune response and inflammatory activity following TBI are intimately linked (57,58). Therefore, identifying interventions to target neuroinflammatory processes is crucial in the treatment of TBI.

According to the study published by de Rivero Vaccari *et al* (59), it was found that SAP130 can activate Mincle in cortical neurons, leading to the synthesis of the inflammatory cytokine, TNF. Additionally, elevated levels of Mincle and SAP130 were observed in both brain tissue and cerebrospinal fluid samples obtained from patients and animal models of brain injury. Subsequently, the researchers discovered that the application of SAP130 and a Mincle neutralizing antibody on cultured cortical neurons effectively suppressed Mincle signaling, resulting in decreased TNF

production. These findings suggested a potential mechanism where SAP130 activates Mincle in cortical neurons, leading to an upregulation of phosphorylated (p)-Syk expression, thereby triggering TNF production and initiating an inflammatory response.

He *et al* (60) found that BAY61-3606 inhibited the Mincle/Syk signaling pathway and promoted the transition of proinflammatory microglia to an anti-inflammatory phenotype. This effectively suppressed microglial migration, contributing to attenuation of microglia-mediated neuroinflammation and improvement of neurological deficits after TBI. Therefore, Mincle signaling is involved in the development of neuroinflammation following TBI and targeting the Mincle signaling pathway could be a promising therapeutic approach for TBI.

Non-TBI. Mincle has a detrimental effect on brain injuries and may be a target for reducing damage to neurovascular units and enhancing neurological function after brain injury. It was discovered that the Mincle signaling pathway contributed to the development of early brain damage following cerebral hemorrhage. Rats with subarachnoid haemorrhage (SAH) showed elevated ipsilateral cerebral hemispheres with higher IL-1β levels and increased expression of CARD9, Mincle, Syk phosphorylation and SAP130 (61). Altogether, upregulation and activation of Mincle expression on microglia and neurons during brain injury results in increased release of inflammatory mediators, exacerbating the initiation of inflammatory responses and promoting the progression of brain damage. Conversely, the blocking of the Mincle pathway can suppress inflammation, attenuate brain injury and enhance neuronal function.

Although there is no direct evidence to suggest a direct association between Mincle and neurodegeneration, Mincle could serve as a promising molecular target in neurodegenerative diseases. Neurodegeneration encompasses a group of disorders involving the loss of neurological function, such as Parkinson's disease, Senile dementia, Huntington's disease, and Alzheimer's disease. In these diseases, neuronal damage and death lead to neuroinflammation which in turn exacerbates neuronal damage, forming a vicious cycle. Neuroinflammation is a crucial feature of neurodegenerative diseases (62-65). As aforementioned, inhibition of Mincle could attenuate neuroinflammation and neurofunctional damage (60). It was hypothesized that neuronal apoptosis may occur due to increasing age (42), drugs (66) and brain injury (67) and that Mincle recognises and binds to neuronal death signals, triggering neuroinflammation. A previous study identified TH17 cells as mediators of central nervous system inflammation and suggested that they can sense danger signals through Mincle (68). Perhaps this inflammatory response is beneficial in the short term for the removal of dead cells and tissue repair, but persistent and excessive inflammation can have toxic effects on healthy neurons. Secondly, activation of Mincle signaling may promote the production of inflammatory factors. These inflammatory factors would further exacerbate neuroinflammation and neuronal damage (55,56). In addition, Mincle appears to play a role in the development of neurodegenerative diseases by affecting neuronal autophagy and apoptosis processes. A different study demonstrated that neuroinflammation in demented rats can be effectively alleviated by reducing glial cell proliferation and inhibiting neuronal apoptosis/autophagy (69). Therefore, Mincle may be an important molecule in mediating neurodegenerative diseases through its involvement in neuroinflammation. Further studies are required to confirm these hypotheses.

Mincle and autoimmune diseases. Autoimmune diseases manifest as a breakdown of immune tolerance towards self-antigens, resulting in persistent inflammation and irreparable harm to multiple organ systems (70). Numerous complex disorders, such as uveitis, atopic dermatitis and multiple sclerosis (MS) (71,72), are classified as autoimmune diseases. In various autoimmune diseases, Mincle exerts a proinflammatory effect, thereby modulating the progression of these diseases.

Mincle is involved with skin inflammation. As a PRR expressed on the surface of skin, Mincle is upregulated in skin trauma and directly recognizes cholesterol sulfate, leading to Mincle-dependent proinflammatory responses. Activation of Mincle by cholesterol sulfate triggers the secretion of various proinflammatory mediators, which contribute to the development of atopic dermatitis. In an experimental model of allergic contact dermatitis, skin inflammatory responses were significantly less severe when Mincle was absent, indicating that Mincle promotes skin inflammation (19). These findings highlighted the crucial role of Mincle in driving the onset and progression of allergic skin inflammation and suggested its potential as a target for therapeutic interventions in related skin disorders. Psoriasis is an immune and inflammatory disorder, while Mincle serves as a key factor in maintaining the M1 macrophage phenotype during the proinflammatory process. A previous study confirmed that Mincle exhibits a marked upregulation in macrophages derived from individuals and mouse models afflicted with psoriasis. Furthermore, it revealed the significant role of the Mincle pathway in macrophage-mediated psoriasis and demonstrated that inhibiting Mincle in macrophages can suppress skin lesions and damage. Subsequently, the study discovered that targeted treatment of Mincle can improve symptoms in psoriasis mouse models (73). Therefore, this research suggested that therapeutic interventions targeting Mincle may offer a novel approach for the treatment of psoriasis.

Mincle has a fatal role in MS and promotes the growth of neuroinflammation resembling MS. MS is a chronic autoimmune disease affecting the central nervous system, which is characterized by inflammation and axonal degeneration leading to various symptoms such as muscle weakness, spasticity, fatigue, visual and sensory disturbances, cognitive impairment and bladder/bowel dysfunction (74-76). N'Diaye *et al* (77) demonstrated the involvement of Mincle in the development of MS-associated inflammation. Inhibiting the MCL/Mincle signaling pathway weakened the ability to recruit T cells in the central nervous system (78). Furthermore, in patients with MS, the Mincle pathway was upregulated in peripheral blood monocytes (77).

Mincle plays a pathogenic role in intestinal mucosal inflammation. Several studies have shown that the Mincle pathway is obviously upregulated in human inflammatory bowel disease and animal models. Deficiency of Mincle

alleviates colonic inflammation. Conversely, activation of Mincle with agonists exacerbates intestinal inflammation (79). Another study has shown that the Mincle pathway can induce the release of proinflammatory factors through macrophage pyroptosis (2).

Mincle may be associated with the progression of rheumatoid arthritis (RA) and considered as a biomarker for RA. There may be a sex-specific correlation between Mincle rs10841845 G allele and susceptibility to RA (80). Additionally, it was found that the expression level of Mincle in the synovial tissue was significantly higher in patients with RA compared to patients with osteoarthritis (OA) and Mincle expression levels were higher in the macrophage component compared to the non-macrophage component (81). Mincle could serve as a significant biomarker and therapeutic target for these conditions.

4. Mincle and fibrosis

Mincle may induce the macrophage to myofibroblast (MF) transition (MMT), promoting fibrosis occurrence. Fibrosis, an immune-mediated disease (82), is a pathological condition marked by excessive extracellular matrix (ECM) protein deposition that causes organ failure. It is a common pathological outcome of chronic inflammatory diseases, such as liver cirrhosis, pulmonary fibrosis, and kidney fibrosis.

As aforementioned, Mincle is a crucial initiator and maintainer of macrophage inflammation and essential factors. Although current research on the proinflammatory role of Mincle primarily focuses on acute diseases such as AKI, an increasing body of evidence has suggested its critical involvement in chronic inflammation and fibrosis. Pulmonary fibrosis is a process characterized by abnormal remodeling of the ECM. It has been found that the role of Mincle in pulmonary fibrosis is mediated by activation of inflammatory and fibrosis-related signaling pathways. Specifically, Mincle activates pathways such as NF-κB, which promote inflammatory and fibrotic responses. In addition, Mincle activates immune cells such as alveolar macrophages and dendritic cells, thereby enhancing the extent of inflammatory and fibrotic responses (83). Furthermore, it was also found that by blocking the expression or function of Mincle, the pathological process of pulmonary fibrosis could be effectively attenuated (84). In human non-alcoholic fatty liver disease, Mincle is upregulated concomitant with increased collagen production. Similarly, in animal models of alcoholic fatty liver, cirrhosis, and chronic liver failure, Mincle activation significantly enhances hepatic collagen synthesis, highlighting its significant role in chronic liver fibrosis (47). Tanaka (53) discovered that Mincle promoted the formation of CLS and adipose tissue fibrosis in adipose tissue macrophages, which could lead to reduced adipose tissue storage capacity, insulin resistance and ectopic lipid accumulation (85). Mincle activation induces the fibrosis-related genes, thereby promoting the formation of MFs. According to Watanabe *et al* (86), isoliquiritigenin (ISL) can reduce the fibrosis-related genes in the interstitial blood vessels between TLR4 and Mincle-stimulated adipose tissue and macrophages, relieving itching. In addition, studies have reported elevated expression of Mincle in kidneys with UUO-induced fibrosis, predominantly expressed in macrophages and specific monomers of traditional Chinese medicine targeting Mincle effectively suppress its expression, thereby ameliorating kidney fibrosis (87).

Notably, a previous study suggested that MMT has a role in the development of interstitial fibrosis in cases of chronic renal allograft damage (88). Infiltrating macrophages exhibit a remarkable ability to transdifferentiate into MFs, which are pivotal cellular drivers of pathogenic fibrosis by promoting excessive synthesis of ECM proteins. Renal tissue biopsies were performed on patients with various forms of kidney diseases, revealing the presence of MMT cells. It was observed that MMT cells were virtually absent in cases of acute inflammation or sclerotic lesions, but significantly present in cases of active fibrotic lesions, indicating the potential role of MMT cells in progressive renal fibrosis (89). The process known as MMT is implicated in the pathogenesis of macular fibrosis associated with neovascular age-related macular degeneration, ultimately leading to the onset of retinal fibrosis (90). Therefore, it was hypothesized that macrophage Mincle may induce MMT, thereby promoting fibrosis occurrence.

5. Inhibition of Mincle with drugs alleviates inflammation-related diseases

Numerous drugs that protect against AKI, hinder the occurrence of inflammation by suppressing the activation of Mincle signaling. Tan *et al* (91) discovered that curcumin diminishes renal inflammation and enhances CIAKI by blocking the Mincle pathway. Curcumin effectively inhibits the expression of Mincle in CIAKI, thereby suppressing the signaling pathway of Syk/NF-κB, activated and maintained by Mincle, as well as the M1 macrophage phenotype. This leads to a reduction in the release of proinflammatory factors and promotes the polarization of macrophages towards the M2 phenotype, ultimately relieving CIAKI inflammation. Consequently, they exhibited renal protection in cisplatin-induced nephrotoxicity. Similar effects were found in quercetin treatment of AKI. Quercetin significantly inhibited LPS-induced expression and secretion of inflamination including IL-6, IL-1β, and TNF-α in bone marrow-derived macrophages (BMDMs) and reduced the activity of the Mincle/Syk/NF-κB signalling, thereby alleviating cisplatin-induced AKI (92). Moreover, Diao *et al* *Astragalus mongholicus* Bunge and *Panax notoginseng* (A&P) formula intervened in a LPS-induced macrophage inflammatory cell model and a cisplatin-induced mouse AKI model. The results revealed that A&P significantly inhibited the expression level of Mincle *in vitro* and *in vivo*, and decreased the expression and secretion of IL-1β, IL-6, and TNFα in LPS-stimulated BMDM cells (93). Lei *et al* (94) established a CIAKI mouse model and a co-culture system of bone marrow-derived macrophages (BMDMs) and macrophage renal tubular epithelial cells (mTECs), demonstrating that Mincle in macrophages exacerbates LPS-induced inflammation and necrotic apoptosis in mTECs. The study also revealed that artemether inhibits the expression of Mincle in macrophages of AKI mice. However, the overexpression of Mincle in BMDMs restored the damage and necrotic apoptosis in mTECs suppressed by artemether. This suggested that artemether may improve renal function in AKI by inhibiting Mincle-mediated macrophage inflammation, reducing injury

and necrotic apoptosis in renal tubular cells. Additionally, BAY61-3606 can inhibit Mincle and decrease the production of ROS and the release of inflammatory factors, ultimately reducing renal inflammation (95). Oridonin also exerts its anti-inflammatory function in renal IRI through the same mechanism (96).

Certain drugs exert protective effects on chronic kidney disease (CKD) by mitigating kidney inflammation through blocking the activation of Mincle signaling in macrophages. Tan *et al* (96) established a 5/6 nephrectomy-induced CKD animal model as well as *in vitro* and *in vivo* macrophage inflammatory cell models using LPS and uremic toxins. In this study, the activation of Mincle was observed in the kidneys and intestines of CKD mice, as well as in toxin-stimulated macrophages, which was effectively suppressed by the combination therapy of A&P formula with bifidobacterium. Subsequent findings demonstrated that the inhibitory effect of A&P combined with bifidobacterium on uremic toxin-stimulated inflammation in RAW264.7 cells could be eliminated by Mincle gene overexpression. These results suggested that the combination of A&P with bifidobacterium can protect the kidneys from CKD-induced damage by downregulating macrophage-mediated inflammation in the kidneys and intestines through the inhibition of Mincle signaling (97). Moreover, A&P can suppress Mincle, resulting in a decrease in renal inflammatory response, ultimately leading to an enhancement in renal function in individuals with diabetic nephropathy (98). CKD-protective drugs have also been found to reduce the renal inflammation by targeting Mincle, leading to a reduction in renal fibrosis and an improvement in renal function. Liao *et al* (87) discovered that ISL exhibited robust inhibition of mRNA and protein expression of Mincle in both BMDM and UUO models, concurrently suppressing the phosphorylation of Syk and NF-κB, which is the downstream of Mincle. Consequently, expression of fibrotic markers was reduced. Notably, the opposite results were observed when stimulating Mincle using its agonist. This suggested that ISL exerts its protective effects on UUO-induced CKD by inhibiting Mincle and its downstream inflammatory pathways, thus suppressing renal fibrosis. In summary, a multitude of renal protective medications achieve their renoprotective effects by inhibiting Mincle.

A recently published study by Yang *et al* (99) revealed that co-treatment of bone marrow mesenchymal stem cells (BMSCs) with Iron(III)-quercetin complexes (IronQ), which has excellent dual functions with the use of an imaging probe for MRI and act as a stimulating agent by favoring circulating proangiogenic cell differentiation (100-102), alleviates intracerebral hemorrhage (ICH) by ameliorating inflammation-induced neurological deficits through inhibition of the Mincle/Syk signaling pathway. The conditioned medium generated from BMSC combined with IronQ reduced the LPS-induced inflammation, Mincle expression and its downstream target activity in the BV2 cell line. Liu *et al* (103) established a model of ICH using autologous blood injection into the caudate nucleus. They found that acupuncture at Baihui (DU20) and Qubin (GB7), with each session lasting 30 min, every 12 h for a total of three sessions, significantly improved neurological function and reduced brain edema. This was achieved by inhibiting the immune reactivity and expression of Mincle, Syk, CARD9 and IL-1β. These findings demonstrated that acupuncture at Baihui and Qubin may be an effective treatment for improving neurological deficits associated with intracerebral hemorrhage. A different study (104) demonstrated that 3D spheroid-cultured mesenchymal stem cells (MSCs) reduced the level of microglial Mincle, thereby enhancing the anti-inflammatory effect of MSCs on microglia and improving their homing ability. These effects were associated with improved therapeutic outcomes in the ischemic hemisphere of rats. Xie *et al* (33) found that human albumin attenuates SAP130-induced Mincle upregulation and subsequent microglial inflammatory response after SAH by inhibiting Mincle/Syk/IL-1β signaling. Collectively, several neuroprotective therapeutic approaches alleviate brain damage by inhibiting the Mincle signaling pathway.

In Table II, studies on treatment through Mincle-related pathways are summarized, including Chinese herbal extracts (curcumin, artesunate, oridonin, ISL), natural monomers (quercetin), Chinese herbal compounds (A&P), a pair of acupuncture points (Baihui and Qubin), Mincle inhibitors (BAY61-3606), MSCs and Mincle-neutralizing antibodies. These treatments act mainly through the Mincle/Syk pathway to relieve inflammation and thus serve a therapeutic role. However, more studies are needed to confirm the role of Mincle in these diseases.

6. Inflammatory and fibrotic axis

Inflammation is a normal physiological response, which is a protective response of the body to external stimuli (39). The inflammatory response usually includes processes such as the release of inflammatory mediators, infiltration of leukocytes and tissue repair. However, when the inflammatory response lasts too long or occurs frequently, it leads to tissue damage and persistence of the inflammatory response, which promotes the transition from inflammation to fibrosis (105).

Fibrosis is a pathological process, a common stage in the progression of inflammatory lesions in a variety of organs, which usually occurs after prolonged or repetitive tissue injury and is typically characterized by the deposition of collagen and ECM (106). The pathological process of fibrosis is the activation of macrophages and the release of numerous cytokines such as transforming growth factor-β and IL-1β after endogenous/exogenous factors damage the organ (107). These cytokines converge the intrinsic cells in the organ to fibroblasts through receptors on the surface of the cell membrane, leading to activation of the intrinsic cells, production of large amounts of collagen and ECM and formation of fibrosis in the organ (39) (Fig. 4). This process usually leads to changes in tissue structure and loss of function, which affects the normal physiological functions of the organism.

The inflammatory-to-fibrotic transition plays an important role in numerous diseases such as liver fibrosis, lung fibrosis and cardiac fibrosis, which are all closely related to each other (108-110). Therefore, it is important to study the mechanism of inflammation-to-fibrosis transition to prevent the occurrence of fibrosis.

It is well known that molecules on the immune pathway such as programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) (111) or NY-ESO-1/MAGEA (112) play an important role in disease development and intervention. Similar to Mincle, PD-1/PD-L1 mediates inflammation and fibrosis-related diseases to a certain extent. A previous

Table II. Summary of research on disease treatment through Mincle-related pathways.

	Intervention drug	Intervened pathway	Alleviated disease model	(Refs.)
Kidney	Curcumin	Mincle/Syk/NF-κB signaling	Cisplatin-induced AKI	(91)
	Quercetin	Mincle/Syk/NF-κB signaling	Cisplatin-induced AKI	(92)
	A&P	Mincle/Syk/NF-κB signaling	Cisplatin-induced AKI	(93)
	Artesunate	Mincle/RIPK1/RIPK3/MLKL signaling	Cisplatin-induced AKI	(94)
	BAY61-3606	Mincle/Syk/NF-κB signaling	IRI-induced AKI	(95)
	Oridonin	Mincle signaling pathway	Renal IRI	(96)
	A&P combined with Bifidobacterium	Mincle/NF-κB signaling	Chronic renal failure	(97)
	A&P	Mincle/CARD9/NFκB signaling	Diabetic nephropathy	(98)
	Isoliquiritigenin	Mincle/Syk/NF-kappa B signaling	UUO-induced CKD with renal fibrosis	(87)
Brain	BMSCs pretreated with IronQ	Mincle/Syk signaling pathway	Inflammation and neurological deficits after ICH	(99)
	Acupuncture (Baihui and Qubin points)	Mincle/Syk/CARD9/IL-1β signaling	Neurological deficits and brain edema after ICH	(103)
	3D spheroid cultured MSCs	Mincle signaling pathway	Ischemia injury in the brain	(104)
	Human albumin	Mincle/Syk/IL-1β signaling pathway	Inflammatory response after SAH	(33)
	BAY61-3606 (BAY)	Mincle/Syk signaling	Neuroinflammation after TBI	(60)
Autoimmune diseases	Mincle-neutralizing antibody	Mincle-Syk pathway	Psoriasis	(73)

Mincle, macrophage-inducible C-type lectin; Syk, splenic tyrosine kinase; A&P, *Astragalus mongholicus* Bunge and *Panax notoginseng* formula; RIPK, receptor-interacting serine/threonine-protein kinase; MLKL, mixed lineage kinase domain like pseudokinase; IRI, ischemia reperfusion injury; AKI, acute kidney injury; IronQ, Iron(III)-quercetin complexes; CKD, chronic kidney disease; UUO, unilateral ureteral obstruction; BMSCs, bone marrow mesenchymal stem cells; ICH, intracerebral hemorrhage; SAH, Subarachnoid hemorrhage; CARD9, caspase-recruitment domain 9; MSCs, mesenchymal stem cells; TBI, traumatic brain injury.

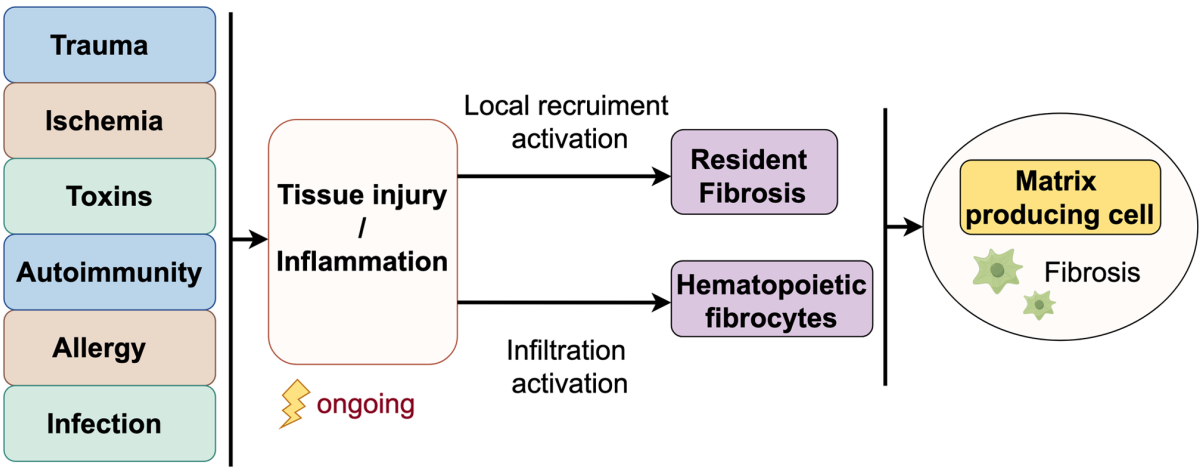

Figure 4. From inflammation to fibrosis. Immune cells get activated, polarized and recruited in response to different forms of tissue injury. Inflammation may result in more tissue damage or initiate fibrosis and tissue healing. Production of collagen by invading collagen-producing hematopoietic cells (fibrocytes) and indigenous mesenchymal fibroblasts. Local recruitment and activation of mesenchymal fibroblasts results in myofibroblast formation. By means of transendothelial migration, hematopoietic fibrocytes are attracted and then stimulated locally to generate matrix proteins. In addition to causing fibrosis, inflammatory cells also control the turnover of the matrix. This figure was created using Figdraw 2.0 (https://www.figdraw.com; Hangzhou Huikeyan Technology Co. Ltd.).

study demonstrated that the activation of the PD-1/PD-L1 signaling pathway by MSCs effectively attenuated the inflammatory response in lung tissue, leading to a reduction in fibrosis (113). The PD-1 signaling pathway holds significant value as a biomarker for assessing immune status in patients diagnosed with sepsis or septic shock, playing a pivotal role in risk stratification and prognostic prediction of patients with sepsis (114). This observation also implies the potential feasibility of activating the PD-1/PD-L1 signaling pathway as a means of attenuating the inflammatory response for the

therapeutic management of pulmonary fibrosis. Mincle senses dead cells through its primary endogenous ligand SAP130, the expression of which is involved in the presentation of cancer cell antigens to cells of the immune system (115). SAP130 is a histone deacetylase protein involved in the regulation of gene transcription and chromatin structure and is closely related to biological processes such as cell proliferation, differentiation and apoptosis. There are no clear conclusions about the role and value of SAP130 in fibroma therapy and it may be a potential topic to be investigated. NY-ESO-1/MAGEA belongs to a group of cancer-testis antigens, primarily expressed in germ cells and placental cells and aberrantly expressed in malignant tumor cells. Moreover, these antigens have been explored as potential targets for tumor immunotherapy (111,116). However, it is unclear whether the immune system of NY-ESO-1 and MAGEA-4 is effective during inflammation and fibrogenesis. There is no clear evidence for their role in the fibrotic process.

Altogether, Mincle is closely associated with inflammation and fibrosis, including the progression of inflammation to fibrosis. It promotes inflammatory responses and fibrosis by activating inflammatory signaling pathways and inducing the production of inflammatory cytokines. In addition, Mincle can interact with other molecules involved in the regulation of inflammation and fibrosis. These findings provide an important theoretical basis for further exploration of the mechanisms underlying the excessive progression of inflammation to fibrosis and for the development of related therapies. In the future, Mincle may offer new insights into halting the progression of inflammation to fibrosis.

7. Conclusion

Mincle is known as a multifunctional receptor. It plays a crucial role in eliminating pathogens and preserving immune balance by recognizing various pathogens such as bacteria, fungi, parasites, and even endogenous ligands. As research has advanced, the importance and adaptability of Mincle in immune response have become more apparent, sparking greater interest in its potential use in treating different diseases. Mincle ligands are being increasingly recognized as natural lipids produced by pathogens. Mincle agonists have been deliberately designed to attain comparable or enhanced levels of immune activation compared to natural core factors, considering the arrangement of these ligands. Additionally, the process of simplifying structures has already begun. Researchers have shown significant interest in trehalose dibehenate (TDB), due to its minimal toxicity and aim to utilize TDB as an adjuvant in subunit vaccines for tumors and some infectious diseases (27). CAF01, a mixture of TDB and liposome, has shown promise in stimulating both humoral and cellular immunity, rendering it suitable as an adjuvant in vaccines for infectious diseases and potentially for cancer immunotherapy, including adjuvant vaccines targeting tumor-associated carbohydrate antigens (71).

Nevertheless, the investigation and revelation of inhibitors for Mincle signaling in sterile inflammatory circumstances have not been extensively explored. Due to its ability to cause inflammation in sterile inflammatory conditions, Mincle signaling is associated with various diseases, promoting the progression of inflammation to fibrosis, ultimately resulting in organ failure. The discovery of small compound antagonists for Mincle signal transmission could hold immense importance in reducing inflammation, prolonging the advancement of inflammation into fibrosis and halting the progression of organ fibrosis. Moreover, Mincle has been shown to interact with other receptors and signaling pathways involved in inflammation and fibrosis. These findings suggest that Mincle is a central player in the inflammatory-fibrotic axis and targeting Mincle could be a promising strategy to treat inflammatory and fibrotic diseases. However, the exact mechanisms by which Mincle promotes inflammation and fibrosis are still not fully understood. Further in-depth research is necessary to elucidate the downstream signaling pathways of Mincle and to identify the cell types and contexts in which Mincle exerts its proinflammatory and fibrotic effects. Additionally, the development of Mincle inhibitors or antagonists requires careful consideration of potential side effects.

In conclusion, Mincle is an important mediator of inflammation and fibrosis and represents a potential therapeutic target. Understanding the molecular and cellular mechanisms of Mincle will not only shed light on the pathogenesis of inflammatory and fibrotic diseases, but also pave the way for the development of novel anti-inflammatory and anti-fibrotic therapies.

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Authors' contributions

ND and LW conceived the review. YZ and JCL wrote the original draft preparation. YZ and HS wrote, reviewed and edited the manuscript. JL and HS helped to draw

figures/generate tables included in the article and revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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