Stabilin-1: An immunoregulatory scavenger receptor in inflammation and tissue homeostasis (Review)

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Abstract. Inflammatory dysregulation and tissue homeostatic imbalance are the fundamental pathological mechanisms underlying the progression of various types of chronic disease, and identifying key regulatory molecules is important for achieving effective anti-inflammatory therapeutic goals. Stabilin-1, an immunoregulatory scavenger receptor, regulates inflammation and tissue homeostasis in multiple ways. In the field of innate immunity, Stabilin-1 acts as a monocyte-recruiting factor through the interaction of fibronectin with its extracellular fasciclin domain and mediates the polarization of macrophages to M2-type cells. In addition, its extracellular epidermal growth factor-like domain can recognize and interact with phosphatidylserine on the surface of apoptotic cells, and bind to its corresponding Gulp1 adapter molecules, activating downstream signalling pathways and making the clearance of these apoptotic cells possible. It can also specifically recognize and take up oxidative stress products, such as oxidized low-density lipoprotein and lipopolysaccharide, inhibiting the activation of any proinflammatory signal transduction pathway. In adaptive immune regulation, Stabilin-1 can inhibit the T-helper cell (Th)1 type immune response and regulate the Th2 type immune response. The inflammatory microenvironment induces the synthesis of Stabilin-1 and its surface localization on blood and lymphatic endothelial cells, mediating the transendothelial migration of immune cells such as regulatory T cells and B cells to regulate the intensity of immune responses. Stabilin-1 has regulatory functions in different diseases, such as atherosclerosis, chronic liver disease, viral myocarditis, infection, sepsis and tumours. The present review discusses the role of Stabilin-1 as an immunomodulatory scavenger receptor in inflammatory microenvironments and tissue homeostasis, providing novel theoretical support and potential therapeutic targets for the targeted treatment of inflammation-related diseases.

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1. Introduction

Inflammation is a broad systemic physiological response of the human body to various entities, including pathogens, dust particles and viruses (1). There are essentially two main types of inflammation: Acute and chronic. Acute inflammation is a temporary process that lasts from minutes to days, and is an important component of the immune response (2). Its main role is to deliver leukocytes and plasma mediators to the site of injury to eliminate inflammatory stimuli (2). However, because these leukocytes and associated plasma mediators fail

to discriminate between microbial and host targets, it inevitably results in collateral host tissue damage (3,4). Chronic inflammation results from long-term stimulation by inflammatory agents, represented by a protracted course, usually measured from months to years. Chronic inflammation generally occurs when acute responses fail to eliminate pathogenic agents or repair tissue damage at the site of inflammation, or in response to stimuli that provoke low-intensity, asymptomatic reactions (2). In contrast to acute inflammation, chronic inflammation promotes angiogenesis, fibrosis and tissue destruction at the affected site (5). Evidence is growing that inflammation serves a key role in promoting the development of a set of chronic diseases (1).

With a better understanding of the aetiologies of various diseases, inflammation has become increasingly recognized as having a critical role in the development and continuation of a number of diseases, such as atherosclerosis, chronic liver disease and sepsis. No method has been developed to date that can delay or stop the progression of inflammation effectively (6). Anti-inflammatory therapies have been widely applied to treat various diseases; although they are effective when used to treat primary inflammatory dysregulation and autoimmune diseases, they have notable limitations, including osteoporosis caused by long-term glucocorticoids and gastrointestinal injury induced by non-steroidal anti-inflammatory drugs (7). Thus, research has been dedicated to identifying more effective therapeutic targets for anti-inflammatory interventions.

Stabilin-1, also referred to as Feel-1=, belongs to the scavenger receptor class H family. As a large multidomain molecule, Stabilin-1 contains multiple atypical epidermal growth factor (EGF)-like repeats; tandem fasciclin-like domains; and a membrane-proximal link module, a conserved C-type lectin-like domain that binds to matrix glycosaminoglycans, hyaluronic acid (HA) and chondroitin sulphate (8). Stabilin-1 expression occurs in a highly tissue-specific manner; under homeostatic conditions, Stabilin-1 is highly expressed by discontinuous sinusoidal endothelial cells (SECs) of the spleen, lymph nodes and liver, whereas expression in conventional vascular endothelial cells is induced only under angiogenic and proinflammatory stimuli (9,10). Stabilin-1 is also expressed by certain tissue-resident macrophages and M2-like monocyte subsets (11,12).

Stabilin-1 serves a notable role in various diseases related to inflammation, such as *Listeria monocytogenes* (Lm) infection and chronic liver disease. For example, in the case of Lm infection, Stabilin-1 protects the host by facilitating macrophage phagocytosis of Lm, and modulating the production of cytokines such as TNF-α, IL-6 and IL-10, as well as chemokines including CCL7 and CXCL10 (13). In a study on atherosclerosis, mice with upregulated Stabilin-1 exhibited markedly reduced aortic plaque formation with no readily apparent side effects, such as liver fibrosis or renal injury (14). Moreover, in studies on diseases including sepsis and chronic liver disease, the level of Stabilin-1 has been shown to strongly affect disease progression and prognosis (15,16). Thus, Stabilin-1 may be considered a novel therapeutic target for inflammation-related diseases.

The present study collected and organized relevant literature up to December 2025 by searching databases such as Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Cochrane (https://www.cochranelibrary.com/), CINAHL (https://search.ebscohost.com/) and Web of Science (https://www.webofscience.com/), using core keywords and snowball method The search strategy employed a combination of medical subject headings and free-text terms: 'Stabilin-1' or 'Clever-1' or 'Feel-1', alongside 'inflammation', 'inflammatory response', 'cytokines', 'tissue homeostasis', 'receptor', 'scavenger', 'macrophage', 'specific immunity', 'cancer', 'tumour', 'atherosclerosis', 'viral myocarditis', 'hepatitis', 'sepsis' and '*Listeria* infection'. The inclusion criteria were as follows: i) The type of literature included basic experimental research, preclinical research, literature reviews, meta-analyses and case reports (based on clinical cases of Stabilin-1 with irregular expression and inflammation-related diseases) and was not limited by language restrictions; ii) The research clearly elaborated on the molecular structure, distribution of expression and signal transduction pathways of Stabilin-1, or directly investigated the regulatory role of Stabilin-1 in the generation, development and reduction of inflammation or certain diseases, or the mechanisms by which Stabilin-1 participates in the maintenance of tissue homeostasis (such as tissue repair, immune cells and metabolic homeostasis); iii) The research contained complete data, with clear conclusions, providing direct evidence to support the relationships between Stabilin-1 and inflammation or tissue homeostasis. The exclusion criteria were as follows: i) Research literature that did not involve Stabilin-1, studies that only described the gene names or protein expression, and did not explore the mechanism of action; ii) duplicate publications (in this case, the latest, most complete version was selected); and iii) abstract literature published for conferences, dissertations without complete research data and literature that had direct discrepancies in conclusions that were not supported by any valid literature, or non-research literature.

At present, research mainly focuses on the function of Stabilin-1 as a scavenger receptor. Park *et al* (17) reported that, in acidic environments, Ets-2/JNK signalling can promote Stabilin-1 expression to improve macrophage phagocytic ability. With the advancement of research, Park and Kim (18) further indicated that Stabilin-1, as a receptor for phosphatidylserine (PS), is involved in the phagocytosis of apoptotic cells. Research on the pathological importance of Stabilin-1 has mainly focussed on cancer. Gurung *et al* (19) elucidated the immunosuppressive effect of Stabilin-1 on tumour-associated macrophages (TAMs) and its potential as a cancer immunotherapy target. Existing research has been limited to a single mechanism or disease of Stabilin-1. Therefore, the present review aims to systematically expand the research perspective and scope. To the best of our knowledge, based on the existing research, the present review is the first to construct a biological mechanism framework of 'Stabilin-1 > innate immunity + adaptive immunity > multi-disease regulation'. In terms of research scope, aside from not being limited to the scavenger activity of Stabilin-1, the present study also comprehensively analyses the multi-link regulatory functions of Stabilin-1 in non-specific and specific immunity. Moreover, in terms of pathological importance, aside from atherosclerosis, viral myocarditis, chronic hepatitis, sepsis, *Listeria* infection and

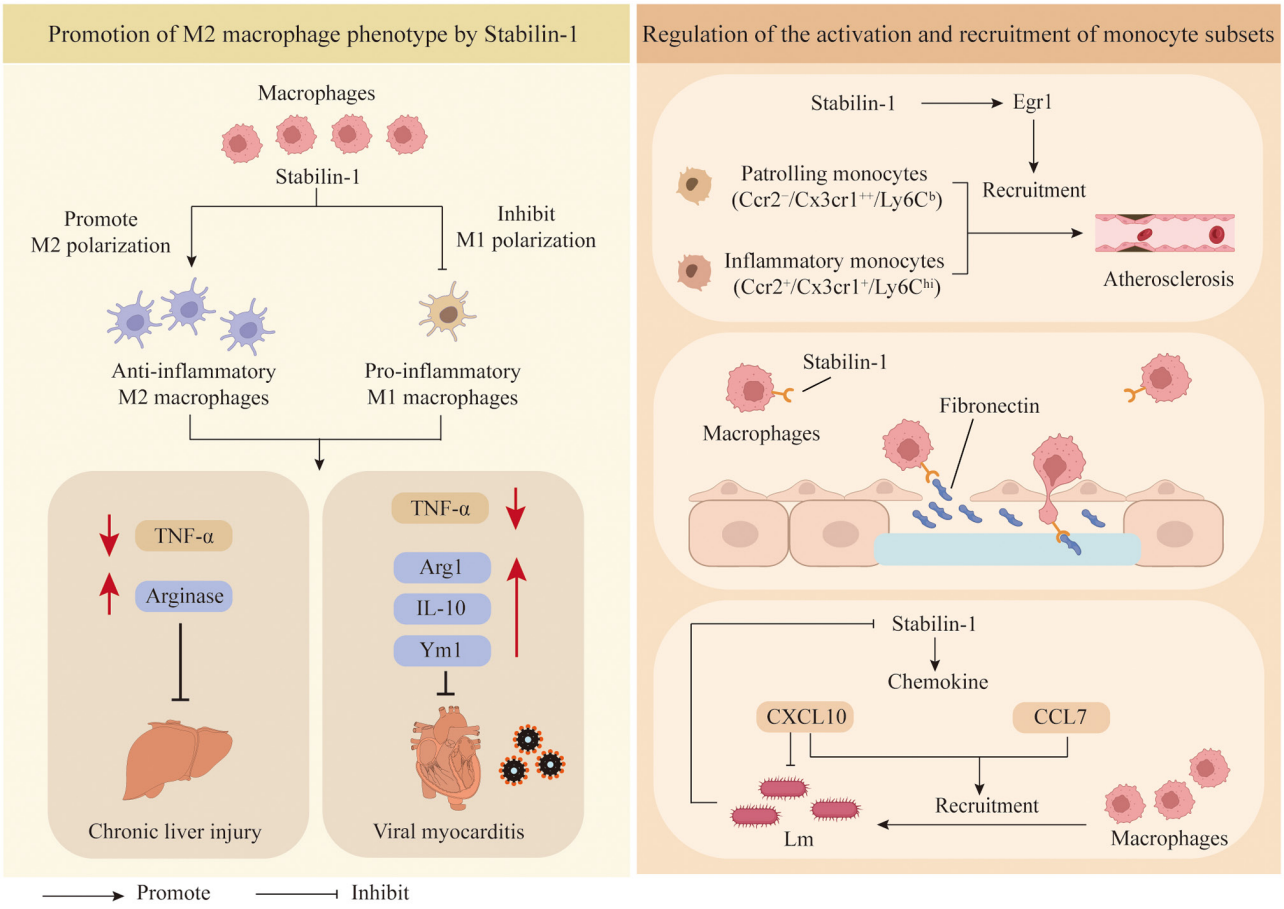

Figure 1. Regulation of monocyte/macrophage activation and recruitment by Stabilin-1. Macrophages expressing Stabilin-1 are more inclined towards the M2 phenotype. This reduces the expression of TNF-α, increases the level of arginase and slows down chronic liver injury. In addition, this upregulates the expression of Ym1, Arg1 and IL-10, thereby improving viral myocarditis. Stabilin-1 can also regulate the activation and recruitment of monocyte subpopulations. Stabilin-1 deficiency can markedly alter the transcriptome characteristics of circulating monocytes. The interaction between Stabilin-1 and the extra-domain A of fibronectin is a key mechanism for monocytes to recruit to the site of inflammation. At the level of chemokine expression, Stabilin-1 upregulates the expression of chemokines such as CXCL10 and CCL7. Lm, *Listeria monocytogenes*.

cancer, the review systematically summarizes the diversity of the functional roles of Stabilin-1, as well as their common regulatory mechanism in different diseases. Finally, aside from proposing verifiable research hypotheses for important scientific questions that have not yet been answered in this research area, the present review may fill a gap in the research that exists between basic mechanistic studies and clinical translation applications, providing a more systematic and comprehensive theoretical basis for in-depth studies on Stabilin-1, as well as for developing targeted therapeutic strategies for related diseases.

2. Innate immunity

Regulation of monocyte/macrophage activation and recruitment by Stabilin-1

Promotion of the M2 macrophage phenotype by Stabilin-1. The recruitment and activation of macrophages are closely associated with the initiation and progression of inflammation. Macrophages can be divided into M1 (classically activated) and M2 (alternatively activated) types (20). M1 macrophages exhibit high expression of IL-12 and IL-23, low expression of IL-10, and generate reactive oxygen compounds, nitrogen compounds and inflammatory cytokines, such as TNF-α and IL-6 (21). M1 macrophages are key contributors to the T-helper cell (Th)1 immune response, and they also exhibit strong microbicidal and tumoricidal activity (22). On the other hand, M2 macrophages exhibit low expression of IL-12 and IL-23, and high expression of IL-10 (21). M2 macrophages are key components in the processes of tissue repair and regeneration, inflammation resolution, apoptotic cell clearance and elimination of extracellular parasites (22,23). Macrophages expressing Stabilin-1 display a phenotypic bias towards the M2 subset (24). When polarization occurs towards the M2 phenotype occurs, human monocytes maintain surface expression of Stabilin-1, whereas they lose Stabilin-1 expression upon M1 induction, a finding consistent with the functional immunosuppressive role of Stabilin-1 (25) (Fig. 1).

Stabilin-1 regulates the activation and recruitment of monocyte subsets. Single-cell RNA sequencing has revealed that Stabilin-1 deficiency can markedly alter the transcriptomic characteristics of circulating monocytes (14) (Fig. 1). Stabilin-1 knockout (KO) in mice has been reported to result in the dysregulated expression of 231 proteins in the plasma, among which 41 proteins were shown to differ across ApoE-KO, ApoE-Stabilin-1-KO and ApoE-Stabilin-2-KO mice (14). The

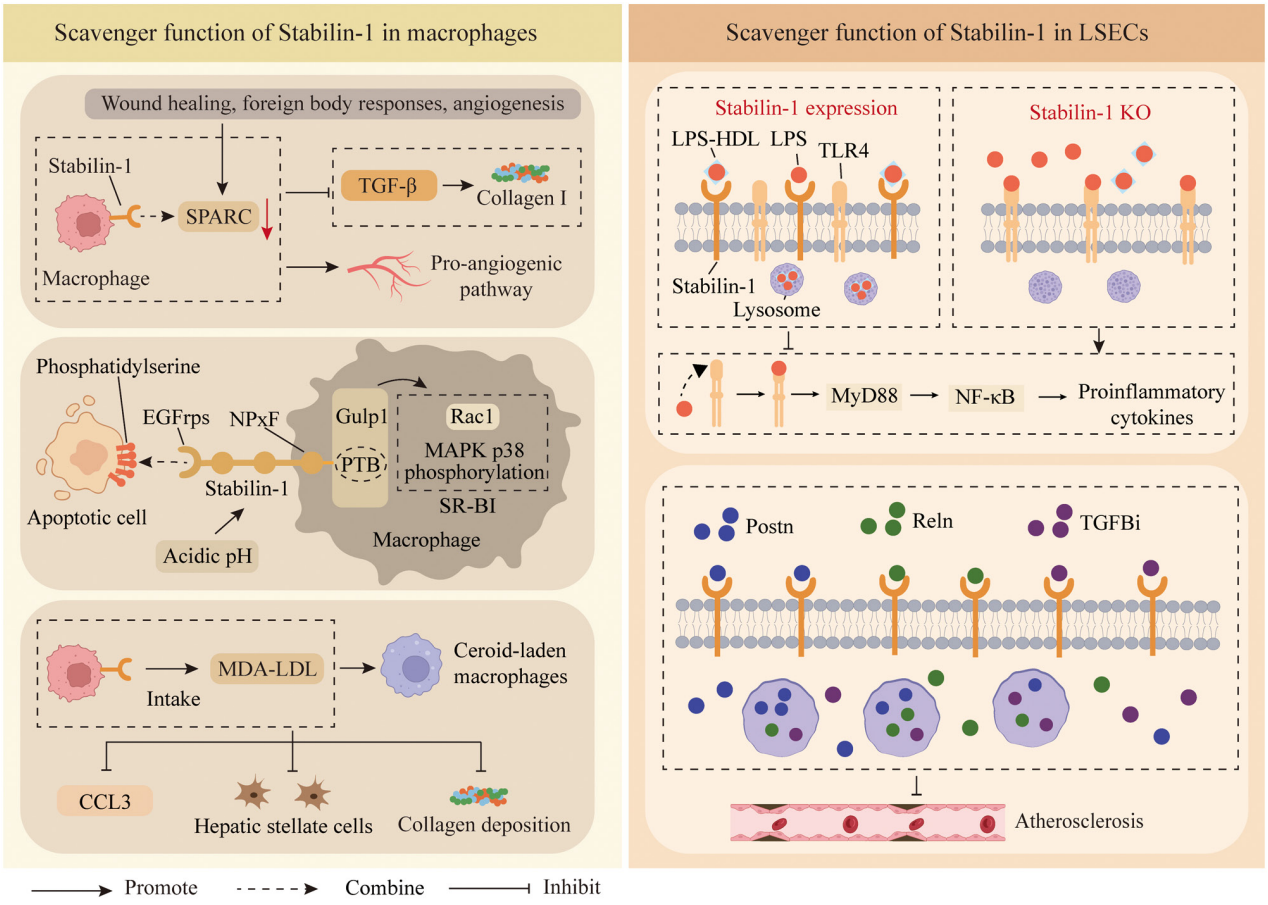

Figure 2. Scavenger function of Stabilin-1 in macrophages and LSECs. Stabilin-1 mediates the effective uptake and intracellular delivery of SPARC by M2 macrophages. Stabilin-1 directly binds to phosphatidylserine through its EGFRps, thereby mediating macrophage clearance of apoptotic cells. Acidic pH values can also upregulate the expression of Stabilin-1. Stabilin-1 can specifically recognize oxidative stress products, such as MDA-LDL, form waxy loaded macrophages and thereby inhibit the release of the proinflammatory chemokine CCL3. Normal expression of Stabilin-1 inhibits the TLR4 signalling pathway by mediating LPS clearance. Stabilin-1 reduces the risk of atherosclerosis by mediating the endocytosis of circulating ligands such as Postn, Reln and TGFBi. The 'combine' arrow refers to the relationship in which two substances at both ends of the arrow are combined together. EGFRp, EGF-like repeat domain; HDL, high-density lipoprotein; KO, knockout; LPS, lipopolysaccharide; LSEC, liver sinusoidal endothelial cell; MDA-LDL, malondialdehyde-modified low-density lipoprotein; MyD88, myeloid differentiation factor 88; NPxF, asparagine-proline-x-phenylalanine; Postn, Periostin; PTB, phosphotyrosine-binding; Reln, Reelin; SPARC, secreted protein acidic and rich in cysteine; SR-BI, scavenger receptor class B member 1; TGFBi, TGF-β-induced protein; TLR4, Toll-like receptor 4.

interaction between Stabilin-1 and the extra-domain A (EDA) of fibronectin is a key mechanism through which monocytes are recruited to the site of inflammation (26) (Fig. 1). Stabilin-1 directly binds to fibronectin through its extracellular fascicular domain (P9 fragment). In addition, chemokines are key signalling molecules that regulate immune cell migration. At the level of chemokine expression, Stabilin-1 upregulates the expression of chemokines such as CCL2, CXCL10 and CCL7 (13). CXCL10 not only mediates immune cell migration but also directly reduces Lm activity, and its upregulation may further increase the anti-infective capacity of the host (27). As a ligand for the CCR2 receptor, CCL7 is indispensable for monocyte recruitment during inflammation (28). Thus, Stabilin-1 may mediate myeloid cell recruitment by regulating the expression of CCL7 and CXCL10 (Fig. 1).

Scavenger function of Stabilin-1 in macrophages

Stabilin-1 mediates the internalization of extracellular secreted protein acidic and rich in cysteine (SPARC) and its transport to lysosomes. SPARC is an evolutionarily highly conserved protein with a molecular weight of 43 kDa (29), which is produced by endothelial cells, fibroblasts and macrophages during wound healing, foreign body responses and angiogenesis (30-32). SPARC is involved in collagen mineralization, wound healing and organ fibrosis (33), and it interacts with various extracellular matrix (ECM) proteins, regulating their functions and affecting the composition of the ECM (34,35). Specifically, it stimulates TGF-β, leading to increased synthesis of type I collagen (36). Furthermore, SPARC inhibits the pro-angiogenic pathway (37). The ablation of SPARC expression has been shown to diminish apoptosis and inflammation (38).

Stabilin-1 mediates the effective uptake and intracellular delivery of SPARC by M2 macrophages, and acetylated low-density lipoprotein (acLDL) competes with SPARC for efficient internalization mediated by Stabilin-1 (38) (Fig. 2). In addition, both acLDL and SPARC follow the endocytic pathway into lysosomes (38).

Stabilin-1 mediates the clearance of apoptotic cells by macrophages. Macrophage clearance of apoptotic cells is

important for peripheral tolerance during homeostasis in healthy tissues and serves a crucial role in reducing inflammation (39). Dying cells release 'find-me' signals to activate phagocytes. Then, phagocytes distinguish apoptotic cells from healthy viable cells via specific phagocytic receptors that recognize 'eat-me' signals on dying cells. Phagocytes undergo extensive cytoskeletal rearrangement to internalize apoptotic cells. The ingested cargo is processed and elicits specific phagocyte responses, predominantly the release of anti-inflammatory mediators.

To date, PS is the best-studied 'eat-me' signal and has been well characterized (40); during apoptosis, PS is present on the outer surface of the cell membrane and acts as an 'eat-me' signal (41). PS receptors can directly bind to PS on apoptotic cells, including TIM, Bai1, Stabilin-1 receptors and CD300 receptors. In addition, other receptors can indirectly bind to apoptotic cells through soluble PS binding proteins (such as Mfge8 and Gas6), including Tyro3/Axl/Mer receptors (Tyro3, Axl, and Mer) and integrin receptors (αvβ3 and αvβ5) (42,43). Under physiological conditions, macrophages bind to apoptotic cells, PS is recognized by specific receptors, and apoptotic cells are cleared by macrophages. This process induces macrophages to secrete anti-inflammatory mediators and downregulates the production of proinflammatory factors (44).

The EGF-like domains of Stabilin-1 function as recognition receptors for PS (45). It has been shown that the ectopic expression of Stabilin-1 endows mouse fibroblast L cells with the ability to phagocytose damaged red blood cells in a PS-dependent manner (46). In macrophages cocultured with apoptotic cells, Stabilin-1 is recruited to the sites of apoptotic cell recognition and phagocytosis, and colocalizes with ingested apoptotic bodies in early phagosomes (46). Blocking Stabilin-1 with anti-Stabilin-1 antibodies has been shown to markedly inhibit macrophage phagocytosis of apoptotic cells (46). Researchers have prepared microspheres coated with PS to simulate apoptotic cells; most of these PS-coated beads are bound and phagocytosed by Stabilin-1-expressing cells, with the EGF-like repeat domain (EGFrp) of Stabilin-1 directly binding to PS-coated beads (46). Collectively, these findings indicate that Stabilin-1 may act as a receptor that directly binds to PS via the EGFrp, thereby mediating the clearance of apoptotic cells by macrophages (46) (Fig. 2).

The Gulp1-dependent signalling pathway for apoptotic cell clearance is essential for Stabilin-1-mediated phagocytosis (47,48). Gulp1 consists of a phosphotyrosine-binding (PTB) domain, a leucine zipper domain and a proline-rich domain. Acting as an adaptor protein, it transduces cytoskeletal rearrangement signals among several phagocytic receptors, including MEGF10, LDL receptor-related protein 1, platelet endothelial aggregation receptor 1 and scavenger receptor class B member 1 (SR-BI) (49-52). The asparagine-proline-x-phenylalanine (NPxF) motif of Stabilin-1, where x is any amino acid, binds to the PTB domain of Gulp1 (18). Gulp1 functions downstream of the receptor Stabilin-1, and its knockdown has been reported to markedly cripple the phagocytic functions mediated by Stabilin-1 in PS-exposed red blood cells (46). Taken together, these findings suggest that Stabilin-1 promotes apoptotic cell phagocytosis by engaging Gulp1 as an interacting partner, which facilitates anti-inflammatory processes. Gulp1 acts as a signalling hub to recruit and activate more downstream molecules. On the one hand, Gulp1 activates MAPK p38 via phosphorylation, which is involved in the regulation of endothelial cell proliferation, migration and the inflammatory response (49). On the other hand, Gulp1 activates the Rac family small GTPase 1 (Rac1) protein via intermediate signalling molecules (which are not currently fully understood). The Rac1 protein acts as a central regulatory component in cytoskeleton reorganization, and promotes the polymerization and reorganization of actin, providing the driving force for the decisive phases of angiogenesis, such as endothelial migration and vascular luminal formation (47,48). It has been shown that a reduction in the phagocytic ability of PS-exposed erythrocytes is mediated by the Stabilin-1 protein after endogenous Gulp1 protein is knocked down, whereas overexpressing the Gulp1 protein may result in an exaggerated response, where the phagocytic ability of PS-exposed erythrocytes mediated by Stabilin-1 is increased (47). An important cause of vascular fibrosis and instability is endothelial-to-mesenchymal transition (EndMT), in which the inflammatory microenvironment serves a pivotal role. The signalling pathway involving Stabilin-1/Gulp can inhibit the activation of transcription factors related to the EndMT (such as Snail and Twist) by removing apoptotic bodies, thus preventing the conversion of endothelial cells into mesenchymal cells, preserving the phenotype of the vascular wall, and preventing vascular fibrosis and stenosis (53).

In addition to Gulp1, the cytoplasmic domain of Stabilin-1 contains a DXXLL motif that binds to the Golgi-localizing, γ-adaptin ear domain homology, ARF-binding proteins (GGA) family of adaptor proteins (GGA1-3) and takes part in the transport of Stabilin-1 from the trans-Golgi network to endosomes (54). Moreover, sorting nexin 17 can bind to the NPxF motif of Stabilin-1, thereby regulating the expression of the latter on vascular endothelial cell surfaces (55). These interactions collectively constitute the regulatory network of the Stabilin-1 signalling cascade, wherein Gulp is primarily responsible for phagocytosis-related signal transmission, and GGA and SNX17 are involved in intracellular transport and the regulation of surface homeostasis of receptors (47).

Stabilin-1 mediates macrophage clearance of oxidative stress products. Oxidative stress is a state of imbalance between oxidants and antioxidants, in which either a lack of antioxidant defence or overproduction of free radicals can turn into toxic compounds, which are associated with cellular and biomolecular damage (56). Notably, inflammation is a typical example of the pathogenesis of oxidative stress, and a combination of oxidative stress and inflammation has been reported in several chronic diseases (57). In the context of chronic liver injury, the oxidative stress produced by injured hepatocytes results in the generation of toxic products, including oxidized LDL (oxLDL), of which malondialdehyde-modified LDL (MDA-LDL) is a key proinflammatory mediator (16). Stabilin-1 is able to specifically recognize and internalize these oxidative stress products, giving rise to ceroid-laden macrophages and leading to a subsequent reduction in the release of the proinflammatory chemokine CCL3 (16). This can be an effective way to reduce the activation of hepatic stellate cells and collagen deposition, thereby ameliorating the development of liver fibrosis (58) (Fig. 2).

Scavenger function of Stabilin-1 in liver SECs (LSECs). The main source of circulating lipopolysaccharide (LPS) molecules is the intestinal microbiome (59). When intestinal permeability changes, a small amount of LPS crosses the mucosal barrier into the portal vein and is then transported to the liver (60). The liver can clear 80% of the LPS injected into the systemic circulation within several minutes (61), among which ~75% of LPS clearance is mediated by LSECs (62).

In this process, circulating high-density lipoprotein (HDL) serves as the carrier of LPS (61). HDL promotes the endocytosis of LPS and prevents LSECs from producing inflammatory cytokines (62). LSECs express a limited number of surface receptors that can bind the LPS-HDL complex (62). Therefore, the clearance of LPS-HDL by LSECs is a receptor-mediated process. All LPS-HDL bound to LSECs is internalized through endocytosis (62), and once internalized, the LPS-HDL complex is degraded in the lysosomes of LSECs (62). By contrast, LPS that escapes hepatic elimination acts as a major pathogen triggering systemic inflammation (63-65), and this process is involved in cellular and humoral immune responses mediated by Toll-like receptor 4 (TLR4) (66,67).

The TLR4 signalling pathway is tightly linked to the occurrence and progression of inflammation (68). The TLR family consists of type I transmembrane receptors involved in innate immunity that can recognize pathogen-associated molecular patterns and damage-associated molecular patterns, serving as crucial links between adaptive immunity and innate immunity (69,70). When signals from LPS act on TLR4, it undergoes oligomerization to intracellularly transmit signals, activating the myeloid differentiation factor 88 (MyD88)-dependent signalling pathway (71). MyD88, together with IL receptor-associated kinase 1 and 4, and TNF receptor-associated factor 6, serves a decisive role in the activation state of several transcription factors, such as NF-κB and activator protein 1. Additionally, several transcription factors have the potential to induce the secretion of proinflammatory mediators via the MAPK pathway (72).

It has been shown that scavenger receptors are involved in the clearance of plasma endotoxins (73). Deficiency of the Stabilin-1 receptor leads to reduced systemic clearance and endocytosis of LPS by LSECs, but increased production of systemic inflammatory cytokines (62). Research has indicated that Stabilin-1-deficient mice are highly sensitive to LPS, suggesting that TLR4 and Stabilin-1 act as functionally antagonistic receptors in the immune response to LPS: TLR4 senses LPS to activate inflammatory signalling, leading to increased cytokine secretion, whereas Stabilin-1 clears LPS and thus indirectly regulates the production of inflammatory cytokines (62) (Fig. 2). Stabilin-1 and Stabilin-2 exhibit similar functions during LPS clearance. Although the two Stabilin receptors share structural similarity (55% homology), Stabilin-1 serves a more protective role against endotoxin-mediated injury compared with Stabilin-2, and Stabilin-1 is the major contributor to long-term LPS clearance (62).

3. Adaptive immunity

Regulation of adaptive immune cell expression by Stabilin-1. In monocytes, Stabilin-1 functions as an immunosuppressive factor, thereby inhibiting lymphocyte activation (25). Stabilin-1 downregulation is associated with the upregulation of proinflammatory genes and Stabilin-1 in human monocytes controls the activation of several proinflammatory genes (25). Under normal conditions, Stabilin-1 is expressed in $CD14^+CD16^+$ and $CD14^+CD16^-$ cell populations, and $CD14^+$ monocytes with high Stabilin-1 expression exhibit reduced proinflammatory potential (25). Furthermore, Stabilin-1 expression promotes the induction of Th2 immunosuppressive responses and inhibits the formation of Th1 proinflammatory immune responses (25). It has been demonstrated that, in the early stage of sepsis, Stabilin-1 may downregulate excessive inflammatory activation by inhibiting Th1-type immune responses, whereas in the late stage, it serves a protective role by maintaining vascular barrier function (25) (Fig. 3). Knockdown of Stabilin-1 in monocytes leads to increased production of inflammatory cytokines (such as TNF-α), inhibits the production of interferon (IFN)-γ by T lymphocytes, and promotes their secretion of IL-4 and IL-5 (25).

Stabilin-1 regulates the activity of B cells through the production of inflammatory cytokines, such as TNF-α (74). In the absence of Stabilin-1, plasma IgM and IgG levels are elevated, accompanied by reduced B lymphocyte generation and a decrease in peritoneal B1 cells (74) (Fig. 3).

Stabilin-1 regulates the migration of adaptive immune cells. Stabilin-1 expression demonstrates unique tissue-specific and inflammation-dependent regulatory features. Under normal conditions, Stabilin-1 is constitutively expressed in lymphatic endothelial cells but not in vascular endothelial cells in skin tissue. In chronic inflammatory skin diseases, such as psoriasis and lichen planus, vascular endothelial cells induce the expression of Stabilin-1, and the expression level is positively associated with the degree of lymphocyte infiltration (75). This makes Stabilin-1 a key molecule that links the vascular and lymphatic systems in immune trafficking (75).

In vascular endothelial cells, Stabilin-1 regulates transendothelial migration under shear stress. The extravasation of lymphocytes from the bloodstream follows a multistep adhesion cascade, including rolling, firm adhesion and transendothelial migration. Under physiologically relevant laminar shear stress conditions, Stabilin-1 on the surface of vascular endothelial cells is involved primarily in the transendothelial migration step, and has only a minor regulatory effect on the rolling process without influencing firm adhesion (75). Stabilin-1-mediated transendothelial migration is independent of binding to HA (75).

In lymphatic endothelial cells, Stabilin-1 mediates transendothelial migration under static conditions. The mechanism underlying lymphocyte trafficking in the lymphatic system has long remained elusive, and Stabilin-1 is the first adhesion molecule demonstrated to be involved in the lymphatic endothelial cell-mediated transendothelial migration of peripheral blood mononuclear cells (PBMCs) (75). Blood flow velocity within lymphatic vessels is slow, and *in vitro* simulation experiments have shown that Stabilin-1 on the surface of lymphatic endothelial cells has no notable effect on the firm adhesion of PBMCs but can mediate the transendothelial migration process (75). Furthermore, Stabilin-1 mediates the binding of

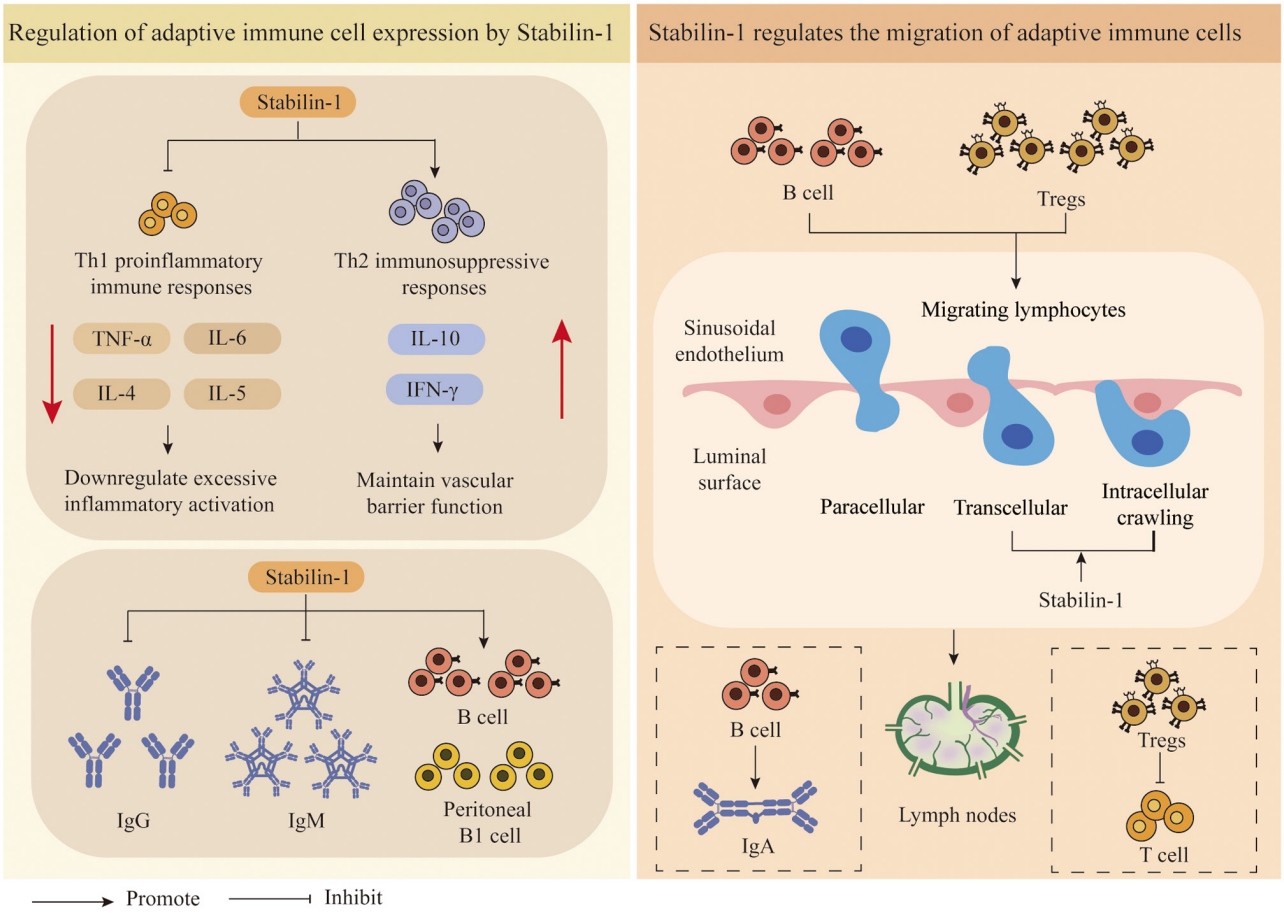

Figure 3. Role of Stabilin-1 in adaptive immunity. Stabilin-1 promotes Th2 immunosuppressive responses and inhibits Th1 proinflammatory immune responses. Stabilin-1 downregulates plasma IgM and IgG levels, and promotes the generation of B lymphocytes and peritoneal B1 cells. Stabilin-1 facilitates the migration of T cells and B cells across the endothelium towards draining lymph nodes. Among T cells and B cells, Stabilin-1 preferentially mediates the migration of Tregs and B cells. IFN-γ, interferon-γ; Th, T-helper; Treg, regulatory T cell.

lymphocytes to the efferent lymphatic vessels of lymph nodes, suggesting that it regulates lymphocyte trafficking at multiple nodes of the lymphatic circulation (75).

In a proinflammatory microenvironment that simulates liver injury, Stabilin-1 facilitates the transendothelial migration of T cells and B cells to draining lymph nodes (76). Stabilin-1 preferentially mediates the migration of regulatory T cells (Tregs) and B cells (77-79) (Fig. 3). This selective recruitment mechanism has notable pathological implications: Tregs can promote tumour immune escape by inhibiting effector T-cell responses, whereas IgA secreted by B cells impairs anti-hepatocellular carcinoma immune responses, both collectively driving the initiation and progression of liver tumours (80,81).

4. Pathological implications

Atherosclerosis. Novel ligands for Stabilin-1 include Periostin (Postn), Reelin (Reln) and TGF-β-induced protein (TGFBi) (14). All of these proteins are markedly increased in the absence of Stabilin-1 and are similarly targeted to lysosomes for degradation through their binding to the fasciclin domain of Stabilin-1 (14,82). Among these, Postn has been demonstrated to be involved in the pathological process of atherosclerosis because of its role as a macrophage migration-regulating factor, and genetic deficiency (knockout of Postn) could mitigate atherosclerosis (83). Furthermore, TGFBi is highly expressed in smooth muscle cells and macrophages in human atherosclerotic plaques (84), and Reln deficiency can reduce atherosclerotic risk by decreasing leukocyte-endothelial cell adhesion (85). Although Stabilin-1 is expressed in aortic endothelial cells and plaque stromal cells, which likely contain macrophages, haematopoietic system-specific Stabilin-1 deficiency has been reported to have no effect on the degree of atherosclerosis in LDL receptor-KO mice (86). These findings suggest that Stabilin-1 controls the progression of atherosclerosis primarily through its ability to clear circulating ligands mediated by LSECs, rather than through local cell-autonomous effects (14). Moreover, Stabilin-1 deficiency did not markedly influence plasma lipid levels, further confirming that traditional lipid metabolism pathways are not involved in its mode of action (14) (Fig. 2).

Chronic liver injury. Stabilin-1 acts via its antifibrotic effect on macrophages through scavenging, clearing oxidative stress products and blocking proinflammatory mediators. In relation to chronic hepatocellular injury, oxidative stress products from injured hepatocytes, such as oxLDL, particularly MDA-LDL, which acts as a proinflammatory mediator, have toxic effects. Stabilin-1 specifically targets and removes products of

oxidative stress, resulting in macrophages containing waxy materials, thereby blocking the proinflammatory chemokine CCL3, hepatic stellate cell activation and collagen deposition, thereby reducing liver fibrosis (62,87). This regulatory pathway has been validated by studies using Stabilin-1 KO mice, which exhibited changes from anti-inflammatory to proinflammatory programming of macrophages, with increased levels of the proinflammatory cytokine TNF-α and decreased arginase levels, and a lower representation of repair macrophages with low Ly6C expression, resulting in increased liver fibrosis with delayed repair (16,88,89). In addition, Stabilin-1 takes part in the intracellular routing function of macrophages through taking up and processing other proteins, such as SPARC, into lysosomes, thereby controlling tissue repair (38,90).

Viral myocarditis. Stabilin-1 neither inhibits viral replication nor has anti-inflammatory effects, but relieves myocardial injury by modulating immune responses, resulting in an anti-inflammatory effect in pathological viral myocarditis. The recruitment of monocytes and macrophage polarization serve crucial roles in immune responses in viral myocarditis (26). On the one hand, Stabilin-1 may preserve the balance of myocardial immunity by promoting anti-inflammatory macrophage polarization and suppressing hypertrophy of adaptive immune responses; this will also upregulate the expression of Ym1, Arg1 and IL-10, thereby improving viral myocarditis (26) (Fig. 1). On the other hand, Stabilin-1 directly interacts with fibronectin via the extracellular fasciclin domain (P9 fragment). Binding between Stabilin-1 and the EDA of fibronectin is the most important mechanism through which monocytes are recruited to the inflammatory area (26). To date, for viral myocarditis, there is no specific treatment strategy, and broad-spectrum immunosuppressive agents induce viral rebound (91). Broad-spectrum immunosuppressants indiscriminately suppress the function of all immune cells, and cannot distinguish between 'overactivated damaging immune cells' and 'normal antiviral immune cells'. When using such drugs, although they can to some extent suppress excessive inflammatory reactions and reduce myocardial immune damage, they can also weaken the body's antiviral immune ability. When the ability to clear viruses decreases due to broad-spectrum immune suppression, the virus that was originally suppressed by the immune system will replicate in large quantities again in myocardial cells, resulting in viral rebound.

Listeria infection. Stabilin-1 can facilitate the phagocytosis and uptake of Lm by macrophages, mainly by regulating the internalization of Lm by phagocytic cells rather than reducing bacterial adhesion ability (13). Stabilin-1 may regulate the strength of the immune response through the balance between inflammatory and anti-inflammatory mediators, not merely through the promotion of inflammatory cytokine production (13). The effective recruitment of immune cells to the site of infection is a core aspect of controlling the spread of Lm, and chemokines are key signalling molecules that regulate the migration of immune cells. At the level of chemokine expression, Stabilin-1 upregulates the expression of chemokines such as CCL2, CXCL10 and CCL7. CXCL10 not only mediates the migration of immune cells but also has direct anti-Lm activity, and upregulating its expression may further increase the ability of the host to resist infection (27). Because CCL7 is a ligand for the CCR2 receptor, it is crucial for the recruitment of inflammatory monocytes (28). Stabilin-1 can be a mediator of myeloid cell recruitment, which is induced by regulation of the expression of CCL7 and CXCL10. Moreover, it is a regulatory factor in the early immune cell influx during inflammation.

For successful infection to take place, Lm must be able to evade immune clearance mechanisms by controlling the expression and function of immune proteins. Research has shown that infection of mice with the pathogenic form of Lm leads to suppression of the expression of Stabilin-1 in macrophages, endothelial cells and spleen tissue (13). Notably, the infection caused by Lm results in the translocation of Stabilin-1 proteins from host cell membranes to the intracellular compartment (13).

Future studies should aim to more precisely identify the virulence factors of Lm that control Stabilin-1 expression and distribution, determine the synergistic impact of Stabilin-1 with other receptors, such as scavenger receptor-A and macrophage receptor with collagenous structure, in Lm infection and investigate the possibility of a novel approach using Stabilin-1 to increase immune protection against infection (13).

Sepsis. The low pH environment induced by sepsis can upregulate the expression of Stabilin-1 through the Ets-2 and JNK signalling pathways (17). Stabilin-1 mediates the phagocytosis of apoptotic endothelial cells by macrophages through binding to PS, clears apoptotic cells in the inflammatory microenvironment, prevents their lysis and release of proinflammatory factors such as IL-1β, IL-6 and TNF-α, and creates conditions for the regeneration of vascular endothelial cells, thereby maintaining vascular homeostasis (26). Furthermore, Stabilin-1 can prevent tissue damage from excessive inflammatory responses by regulating the activation state of phagocytic cells. In the early stage of sepsis, Stabilin-1 may exert a protective effect by inhibiting Th1-type immune responses and downregulating excessive inflammatory activation, whereas in the later stage, it primarily exerts a protective effect by maintaining vascular barrier function (25). Hepatocellular nuclear factor 4α(HNF4A) is a transcription factor that is notably downregulated in the lung tissue and alveolar macrophages of septic mice; HNF4A promotes the transcriptional expression of nuclear receptor co activator 2 (NCOA2) by directly binding to its promoter region; NCOA2, as a co activator of glucocorticoid receptor (GR), can bind to GR monomers or homodimers, enhancing GR mediated gene transcription regulation (92). Studies have shown that HNF4A promotes the polarization of macrophages towards the M2 phenotype by upregulating the NCOR2/GR/Stabilin-1 axis, thereby alleviating sepsis-related lung injury (92).

High mobility group box 1 (HMGB1) is an important proinflammatory mediator in sepsis (93), which can bind competitively to PS on the surface of apoptotic cells, interfering with the recognition of PS by Stabilin-1 and thus inhibiting the phagocytosis of macrophages (94,95). This constitutes a vicious cycle in sepsis: Increased HMGB1 release inhibits Stabilin-1-mediated phagocytosis, resulting in the accumulation of apoptotic cells and increased release of proinflammatory factors, thus exacerbating the inflammatory

response. These findings identify a new target for sepsis treatment. Neutralizing antibodies against HMGB1 have been shown to effectively relieve the functional inhibition of Stabilin-1 by HMGB1, and improve vascular integrity and survival rate in mice with sepsis (96).

Cancer. TAMs, which represent the greatest number of innate immune cells in the tumour microenvironment (TME), are highly prone to differentiate into proinflammatory M1 or anti-inflammatory M2 macrophages in response to signals from the TME (97). In the majority of cancers, these cells have been shown to comprise mainly the M2 macrophage subset, with the ability to facilitate tumour progression through the secretion of immunosuppressive cytokines and support tumour angiogenesis (98). Various studies have shown that infiltrates of Stabilin-1$^+$ TAMs are strongly associated with cancer aggressiveness and poor patient survival rates in different types of cancer (7,99,100). A notable negative effect on patient survival rates has been observed to be related to the infiltration of CD68$^+$Stabilin-1$^+$ macrophages in breast cancer (99). In addition, high numbers of Stabilin-1$^+$ TAMs have been shown to predict adverse cancer progression outcomes in patients with early-stage gastric adenocarcinoma (7). In colorectal cancer, the presence and number of Stabilin-1$^+$ TAMs could be used as a prognostic marker for disease staging; a high number of Stabilin-1$^+$ TAMs within tumours in patients with stage IV disease is associated with shortened survival (100). Similar phenomena have been reported in bladder cancer and acute myeloid leukaemia (AML) confirming the ubiquitous role of Stabilin-1$^+$ TAMs in promoting cancer (101,102).

Mechanistic functions include promoting the phenotypic polarization of macrophages to the M2 phenotype. On the basis of experimental studies in animals with Stabilin-1 KO, the phenotypic polarization of TAMs shifts from the M2 phenotype to the M1 phenotype, indicating the secretion of the inflammatory factors IL-1β, TNF-α and IL-12p70, as well as the expression of the chemokines CCL3 and CCL4 (11,16,101,103,104). On the other hand, the high expression level of Stabilin-1 suppresses the antitumour efficacy mediated by T cells through the inhibition of antigen presentation and a reduction in the expression levels of the major histocompatibility complex, further exacerbating the augmentation of the immunosuppressive microenvironment through the activation of Tregs (105). Furthermore, Stabilin-1 serves a role in metabolic and functional plasticity-regulating processes in macrophages through the modulation of the mTOR pathway and the composition of the lysosome population (11,106).

Stabilin-1 is produced by the lymphatic endothelial cells and vascular endothelial cells of tumour vessels. It promotes the lymphatic and haematogenous metastasis of tumour cells by facilitating the interaction between tumour cells and endothelial cells (107,108). In squamous cell carcinoma of the head and neck and breast cancer, a positive association has been identified between metastatic potential and the density of Stabilin-1$^+$ lymphatic vessels (106,109). In liver metastatic melanoma, Stabilin-1 enhances tumour angiogenic remodelling by modifying Postn and TGF-β1 expression to induce immune cell infiltration (110). The aforementioned evidence indicates that Stabilin-1 serves a regulatory role in promoting tumour metastasis via modification of the tumour angiogenesis-metastasis cascade. The matrix metalloproteinase (MMPs) family comprises a vast number of endopeptidases with varied substrate specificities (111). By hydrolysing intraprotein peptide bonds, MMPs can dismantle the vast majority of proteins that make up connective tissue, such as collagen, elastin, cellulose, gelatine and casein (112). Abnormal expression levels of MMPs are commonly observed during tumour neovascularization, and tumour invasion or metastasis (113,114). MMPs enhance angiogenesis through multiple mechanisms, increasing the bioavailability of proangiogenic mediators bound to the ECM, and promoting endothelial cell migration and detachment from the surrounding growing blood vessels (115,116). Stabilin-1 can regulate the expression balance of MMPs and tissue inhibitors of metalloproteinases, affecting the degradation and remodelling of the ECM (117).

The primary or acquired resistance of some patients to immune checkpoint inhibitors [such as anti-programmed death-1 (PD-1)/cytotoxic T-lymphocyte-associated protein 4 antibodies] limits their clinical application, and enrichment of Stabilin-1$^+$ TAMs is among the key mechanisms leading to resistance (118). The best-known immune escape mechanism used by tumour cells is mediated by the PD-1/programmed death ligand 1 (PD-L1) pathway. PD-1 is a-type I transmembrane glycoprotein that is a member of the B7/CD28 receptor family and is expressed on T lymphocytes in humans. Following T-cell receptor (TCR) activation, PD-1 interacts with PD-L1 and PD-L2, which are expressed on antigen-presenting cells or non-hemopoietic tissues, in an attempt to stimulate proinflammatory cytokines; this is termed the 'PD-L1/PD-1 axis'. The PD-1/PD-L1 system is an immune regulatory mechanism mediated by intracellular inhibitory signalling (119). Stabilin-1$^+$ TAMs inhibit the function of CD8$^+$ T cells through the secretion of IL-10 and TGF-β, while upregulating the expression of PD-L1 on tumour cells and forming an immunosuppressive microenvironment that dampens the effects of immunotherapy (120). Tumour inflammation can lead to the production of Stabilin-1 as a soluble form of Clever-1 (sClever-1) following a serine protease-mediated cleavage process along the IFN-γ/LPS signalling pathway (106). As an isolated immunosuppressive mediator, sClever-1 selectively interacts with the insulin-like growth factor 2 receptor (IGF2R) surface receptor on activated T cells via a mannose-6-phosphate (M6P) interaction (106) and thereby suppresses Y394 phosphorylation of the tyrosine-protein kinase Lck in the TCR signalling pathway, impairing Th1 cell expansion and promoting the differentiation of FoxP3$^+$ suppressor CD8$^+$ T cells (106). Moreover, sClever-1 has been reported to interact with or bind to extracellular vesicles (EVs) derived from macrophages and further improve the suppressive effect on T cells by targeting T cells through EV delivery, decreasing its responsiveness to anti-PD-1 treatment (106).

In addition to immune regulation, Stabilin-1 can directly affect the biological properties of tumour cells. In AML, Stabilin-1 facilitates the polarization of M2 macrophages through the activation of the IKK/NF-κB signalling pathway, increases the apoptosis of tumour cells, suppresses cell proliferation and increases the chemoresistance of tumour cells (101). In papillary thyroid carcinoma, Stabilin-1 acts as a

shield against immune tolerance to support tumour cell proliferation through the regulation of $CD4^+$/$CD8^+$ T cells (103). Furthermore, Stabilin-1 participates in ECM tissue remodelling by abolishing the tumour suppressor factor SPARC from the TME to indirectly support tumour cell invasion and migration (121,122).

5. Conclusions and future perspectives

An imbalance in inflammation and disruption of tissue homeostasis are the key mechanisms involved in the development and progression of different chronic diseases. Uncovering key regulatory factors may serve an essential role in the development of effective strategies for anti-inflammatory therapeutic intervention (1,6). Stabilin-1, a functional immune regulator and scavenger receptor with different functions, has shown high potential in regulating different immune events and various inflammatory diseases related to non-specific immunity, specific immunity and other processes. The intricate mechanisms related to its multifunctional modulation are inadequately understood, and have an important role in uncovering different unanswered questions regarding its therapeutic potential.

In the process of innate immunity, Stabilin-1 has been reported to favour M2 macrophage polarization and mediate the recruitment of monocytes via interaction with fibronectin (24,26). However, in cells other than macrophages, such as SECs and lymphatic endothelial cells, the details of how ligand binding triggers the intracellular signalling of Stabilin-1 remain unknown. In SECs, Stabilin-1 suppresses the TLR4 pathway by mediating LPS clearance (62). However, whether this process involves cross-talk with other signalling molecules, such as negative regulators of NF-κB or specific post-translational modifications, including phosphorylation and ubiquitination of Stabilin-1, has not been reported. On this basis, it may be speculated that, in SECs, by binding to the LPS-HDL complex, Stabilin-1 can recruit the adaptor protein Gulp1 through its NPxF motif, and then inhibit the dimerization and nuclear translocation of NF-κB by activating the MAPKp38 pathway, thus suppressing the proinflammatory response mediated by TLR4 (18,49). In the future, researchers may consider detecting the interaction between Stabilin-1/Gulp1 protein and NF-κB regulatory protein through co-immunoprecipitation, and changes in NF-κB activity can be measured in SECs with Stabilin-1 overexpression or knockout under LPS stimulation. In adaptive immunity, Stabilin-1 modulates the migration of distinctive immune cells (75,76). Nevertheless, the mechanism through which Stabilin-1 participates in the process of transendothelial migration in Tregs, B cells and lymphatic endothelial cells is not fully understood. Several reports have shown that Stabilin-1 binds to the GGA protein SNX17, and inhibits Stabilin-1 intracellular trafficking (54,55). Therefore, the proposed hypothesis is that in lymphatic endothelial cells, after binding to Tregs/B-cell surface ligands, Stabilin-1 may form a complex with GGA1 and integrin αvβ3, promoting cytoskeleton rearrangement through the Rac1 pathway and mediating transendothelial migration (48). This hypothesis may be confirmed by analysing transendothelial migration of lymphatic endothelial cells with GGA1 or integrin αvβ3 knockdown *in vitro*, as well as by detecting changes in the binding ability of Stabilin-1 to Tregs/B cells. In the case of chronic liver disease, Stabilin-1 displays a dual mechanism, which can facilitate immune evasion in tumours and inhibit fibrosis of the liver simultaneously (76,87). On the basis of the current findings, the multiligand binding property might be associated with the mechanism of its duality, although the crucial ligands and pathways involved in regulating its functionality are still unknown. Because Stabilin-1 can facilitate the clearance of oxidative stress products, such as MDA-LDL, and recruit Tregs, it may be hypothesized that in the early phase of chronic injury in the liver, relatively high expression of MDA-LDL in the microenvironment markedly promotes the scavenger function of Stabilin-1, thus passively inhibiting liver fibrosis (16). In the subsequent phase of injury, the abundant expression of surface ligands on Tregs may enhance the immune regulatory capabilities of Stabilin-1, thus leading to tumour progression (78). This hypothesis could be substantiated through the examination of the expression levels of MDA-LDL and surface ligands on Tregs in the distinct stages of chronic inflammation in the liver, in addition to analysing the functionality of Stabilin-1 following the blocking of respective ligands.

In sepsis, HMGB1 and Stabilin-1 constitute a vicious cycle in the HMGB1-Stabilin-1 pathway, increasing the degree of inflammation. Nevertheless, he regulatory role of Stabilin-1 gene expression under low pH conditions in sepsis remains unknown (94,95). Because low pH in sepsis can induce Stabilin-1 gene upregulation through the Ets-2 and JNK pathways, it may be hypothesized that HMGB1 further augments the gene transcription process of Stabilin-1 through increased phosphorylation of Ets-2 and JNK, which could negatively regulate Stabilin-1 gene transcription and control excessive inflammation for homeostasis (17). This assumption could be proven by assessing changes in Ets-2 and JNK phosphorylation in HMGB1-treated macrophages in a low pH environment and investigating Stabilin-1 gene promoter transcription through a luciferase gene reporter assay.

In tumours, Stabilin-1^+ TAMs promote immune escape through the inhibition of T-cell function, and the secretion of sClever-1 further enhances immune suppression (105,106,120). However, the exact mechanism through which sClever-1 controls the IGF2R-Lck pathway in T cells remains unclear. It may be proposed that sClever-1 can bind to IGF2R on the surface of activated T cells through M6P, inducing the internalization and degradation of Lck and thus suppressing the phosphorylation of Lck at the Y394 site and hindering T-cell activation (106). This hypothesis could be confirmed by detecting the degree of degradation of Lck in T cells treated with sClever-1, as well as the degree of recovery after the overexpression of Lck.

In conclusion, Stabilin-1 is known to act as an immunoregulatory scavenger receptor in the inflammatory microenvironment and in tissue homeostasis. In-depth research into the underlying mechanisms of Stabilin-1 activity may not only strengthen the theoretical basis of immunological regulation in inflammation, but also offer new targets for and approaches to different inflammation-related illnesses.

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Authors' contributions

DLC and STQ conceptualized and designed the research, outlined the manuscript and prepared the manuscript. STQ searched for literature and wrote an early version of this manuscript, and participated in the writing of the current review, focusing on the relationship between Stabilin-1 and inflamation-related diseases. XLX contributed to the design and writing of the original manuscript, and drew the illustrations. XTY participated in the writing and editing of the original manuscript. YTW and CC contributed to the editing of the manuscript and reviewed the literature. CYY translated the manuscript and helped edit the review. Data authentication is not applicable. All authors read and approved the final manuscript.

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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