Chitinase-3 like-protein-1: A potential predictor of cardiovascular disease (Review)

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Abstract. Chitinase-3 like-protein-1 (CHI3L1), a glycoprotein belonging to the glycoside hydrolase family 18, binds to chitin; however, this protein lacks chitinase activity. Although CHI3L1 is not an enzyme capable of degrading chitin, it plays significant roles in abnormal glucose and lipid metabolism, indicating its involvement in metabolic disorders. In addition, CHI3L1 is considered a key player in inflammatory diseases, with clinical data suggesting its potential as a predictor of cardiovascular disease. CHI3L1 regulates the inflammatory response of various cell types, including macrophages, vascular smooth muscle cells and fibroblasts. In addition, CHI3L1 participates in vascular remodeling and fibrosis, contributing to the pathogenesis of cardiovascular disease. At present, research is focused on elucidating the role of CHI3L1 in cardiovascular disease. The present systematic review was conducted to comprehensively evaluate the effects of CHI3L1 on cardiovascular cells, and determine the potential implications in the occurrence and progression of cardiovascular disease. The present study may further the understanding of the involvement of CHI3L1 in cardiovascular pathology, demonstrating its potential as a therapeutic target or biomarker in the management of cardiovascular disease.

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Contents

1. Introduction

Cardiovascular disease remains the predominant cause of morbidity and mortality worldwide, accounting for almost one-third of global mortality (1). Despite advancements in diagnosis and treatment, effectively managing the progression of cardiovascular disease and enhancing patient outcomes in a timely manner continue to present significant challenges (2). Therefore, the early prediction and diagnosis of cardiovascular disease are crucial for the development of effective treatment options.

Previous studies have highlighted the significant role of chronic inflammation in the progression of cardiovascular disease (3-5). At present, research is focused on establishing treatment targets and regulating inflammation to enhance cardiovascular outcomes (6-8). Chitinase-3-like protein 1 (CHI3L1) is a pro-inflammatory protein that plays a role in the development of chronic inflammatory diseases in multiple systems, including the nervous, digestive and respiratory systems. CHI3L1 exhibits potential as a biomarker for various inflammatory diseases (9-11). Results of previous studies revealed that CHI3L1 is closely associated with inflammatory cardiovascular disease, such as atherosclerosis (AS), highlighting its potential as a predictive marker for cardiovascular disease (12,13) (Fig. 1). The present article systematically reviewed the role of CHI3L1 in the occurrence and development of cardiovascular disease.

2. CHI3L1 is associated with cardiovascular disease risk factors

Biological characteristics of CHI3L1. CHI3L1, also known as breast regression protein 39 in mice and YKL-40 in

humans, belongs to the glycoside hydrolase 18 family and is categorized as a non-enzymatic chitinase-like protein. In humans, CHI3L1 is encoded by the CHI3L1 gene located on chromosomes 1q31-1q32. The gene consists of 7,498 base pairs and 10 exons, with genomic DNA that is ~8 kbp in length (14). The name 'YKL-40' reflects the molecular weight of the protein, at ~40 kDa, and the presence of the first three amino acids in the N-terminal sequence; namely, tyrosine (Y), lysine (K) and leucine (L) (15,16). Crystal diffraction studies revealed that CHI3L1 contains two distinct domains; namely, a (β/α)8-barrel domain, with a carbohydrate binding cleft of ~43 amino acids at the end of the β chain, and a second domain composed of an α helix and six inverted parallel β strands (17). This structural analysis suggested that CHI3L1 interacts with heparin and different cytokines, such as interleukin-13 receptor α2 (IL-13Rα2), CD44 (18). Despite its ability to bind to chitin, CHI3L1 lacks chitinase activity due to mutations in two critical catalytic residues, rendering it incapable of breaking down chitin or any other carbohydrates (19,20). CHI3L1 is secreted by various cell types, including macrophages, neutrophils, chondrocytes, synoviocytes, osteoblasts and smooth muscle cells (SMCs) (15). Although the specific function of CHI3L1 remains to be elucidated, this protein has been implicated in various biological processes, including cell proliferation, tissue remodeling, extracellular matrix (ECM) turnover, inflammation and fibrosis (21).

CHI3L1 is closely associated with inflammation and regulates the occurrence of inflammatory responses (22). A previous study using CHI3L1-/-mice revealed that CHI3L1 promoted the activation and enrichment of CD4+T cells and macrophages, subsequently regulating the TH2 inflammatory response. In addition, CHI3L1 promotes the production of the TH2 inflammatory factor, IL-13 (23). In addition, CHI3L1 induced macrophages to secrete monocyte chemotactic protein-1 (MCP-1), C-X-C motif chemokine ligand 2 (CXCL2), matrix metalloproteinase 9 (MMP-9) and other pro-inflammatory factors, promoting tumor growth and metastasis in a mouse model of breast cancer (24). In addition to promoting the production of inflammatory cytokines, CHI3L1 acts as an inflammatory target molecule that is regulated by a variety of other cytokines and hormones (25). For example, inflammatory factors; namely, TNF-α and IL-1, induce the expression of CHI3L1 in chondrocytes through the NF-κB signaling pathway (26,27). Thus, CHI3L1 demonstrates potential as a biomarker and therapeutic target. In Alzheimer's disease, the level of CHI3L1 in cerebrospinal fluid (CSF) is considered a biomarker of early neuroinflammation, which may be indicative of stress-induced neurotoxicity (28,29). CHI3L1 is also associated with the degree of liver inflammation and fibrosis; thus, exhibiting potential as a therapeutic target (10).

Metabolic diseases. Type 2 diabetes mellitus (T2D), caused by obesity and insulin resistance, is characterized by abnormal lipid metabolism, which effects the occurrence of cardiovascular disease (30,31). Clinical data suggests that obese patients with T2D exhibit elevated CHI3L1 serum levels (Fig. 1) (32). Notably, elevated CHI3L1 levels are associated with insulin resistance in T2D (33,34). In addition, plasma CHI3L1 is associated with fasting plasma glucose and plasma IL-6 levels (35) and the development of coronary artery disease in patients with asymptomatic T2D (36).

Adiponectin is a colloidal protein secreted by adipose tissue, with a molecular weight of 29 kDa. Plasma adiponectin not only plays a role in obesity-related insulin resistance, but also stimulates the phosphorylation and activation of AMP kinase. Thus, adiponectin produces anti-inflammatory effects and protects endothelial cells (37). Results of a previous study revealed that CHI3L1 and adiponectin expression levels were elevated in patients with asymptomatic T1D in a European Mediterranean population, thus highlighting the potential of these proteins as markers of early inflammation in diabetic patients (38).

Collectively, these results reveal that CHI3L1 may be involved in insulin resistance, metabolic syndrome characterized by obesity and cardiovascular and metabolic disorders (39,40). Further research is required to fully elucidate the mechanisms underlying these associations and to explore the potential of CHI3L1 as a therapeutic target or biomarker for T1D/T2D and the associated complications.

Vascular inflammation. Vascular inflammation is also a common cause of numerous cardiovascular diseases (41). Giant cell arteritis (GCA) is the most common systemic vasculitis in adults (42), and macrophages mediate the destruction and formation of blood vessels (43,44). Abdominal aortic aneurysm is a vascular inflammatory disease characterized by inflammatory cell infiltration, neovascularization, and the production of various proteases and cytokines. The formation of abdominal aortic aneurysm is associated with the degeneration of aortic elastic mediators, and vascular rupture is considered the most serious complication (45). Serum levels of CHI3L1 are elevated in patients with GCA and abdominal aortic aneurysm (43,44,46).

AS is also a vascular inflammatory disease. The lesion site is infiltrated by inflammatory cells, such as macrophages and T lymphocytes, and pro-inflammatory cytokines produced by these immune cells are a key cause of plaque rupture. In addition, results of previous studies reveal that regulating the gene expression of inflammatory factors affects the occurrence and development of AS (47,48). Results of previous studies also emphasize that AS progression is closely associated with CHI3L1 expression levels. Thus, CHI3L1 exhibits potential as a marker of coronary AS severity and plaque instability (49,50). Results of previous studies demonstrate that serum CHI3L1 expression levels are associated with arterial wall fibrosis and arterial stiffness (51-53). These findings support the notion that CHI3L1 upregulates abnormal lipid metabolism and vascular inflammation, which are risk factors for cardiovascular disease. Collectively, these results suggest that CHI3L1 may play a role in accelerating the development of cardiovascular disease through promoting the progression of these risk factors.

3. CHI3L1 is involved in regulating the function of vascular-related cells

CHI3L1 exhibits potential as a predictor of cardiovascular disease. Previous research indicates that CHI3L1 serum levels may affect the risk of adverse cardiovascular outcomes and mortality (54). Results of a previous study using clinical data reveal that CHI3L1 levels are elevated in patients with cardiovascular disease and these elevated levels are often associated

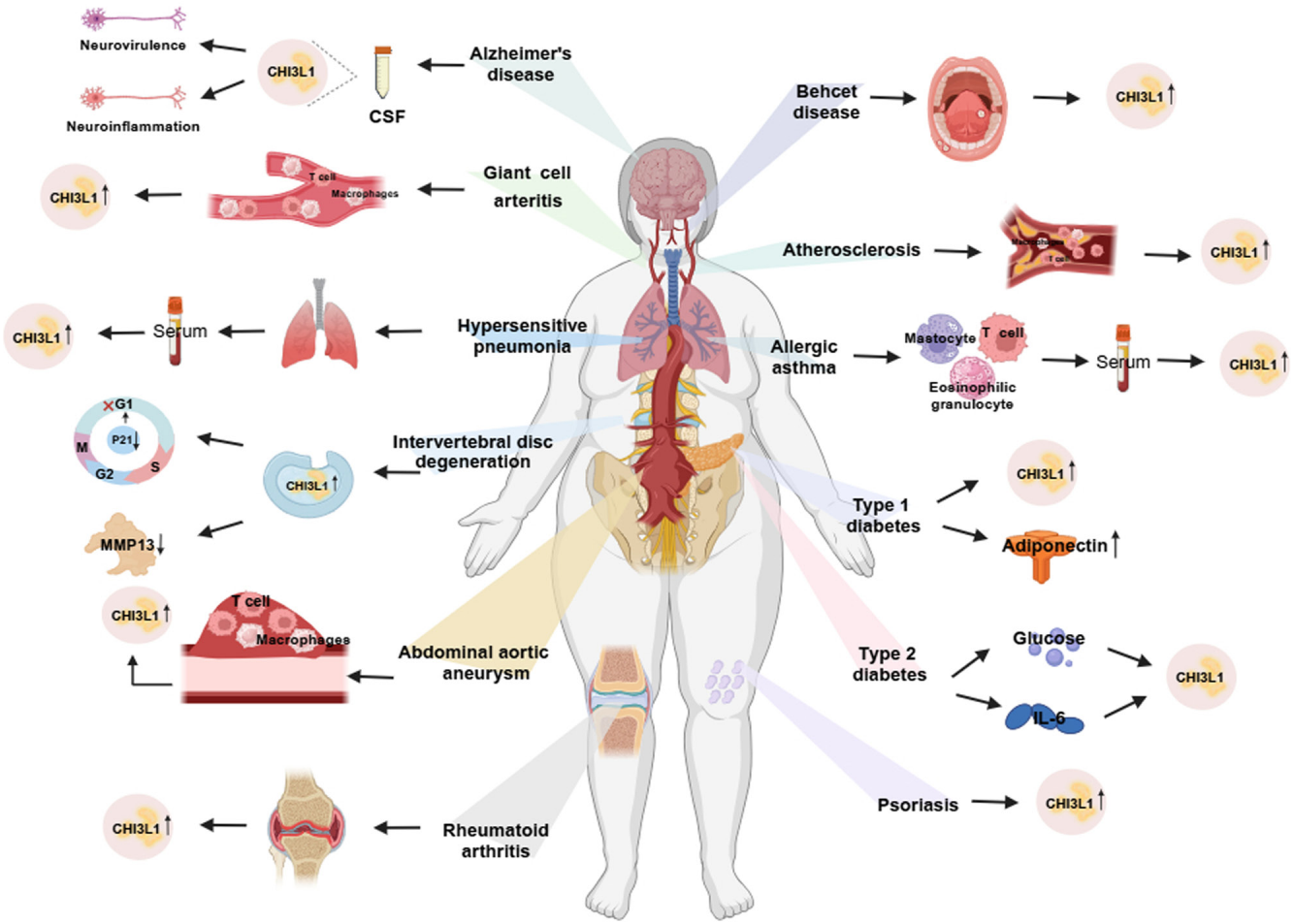

Figure 1. CHI3L1 is associated with a variety of diseases. CHI3L1 expression is increased in various inflammatory diseases affecting different systems. In Alzheimer's disease, elevated CHI3L1 expression levels in cerebrospinal fluid contribute to neurotoxicity and neuroinflammation. In intervertebral disc degeneration, CHI3L1 reduces the expression of P21 and MMP-13, thereby protecting nucleus pulposus cells. Immune cells release CHI3L1 to regulate cardiovascular-associated tissue cells, which may exacerbate disease, such as abdominal aortic aneurysm and giant cell arteritis. CHI3L1 also affects glucose metabolism and the production of inflammatory factors, such as IL-6, which may increase the risk of cardiovascular disease, including type 1 and type 2 diabetes. In addition to adiponectin, CHI3L1 exhibits potential as a marker for diabetes. In addition, elevated levels of serum CHI3L1 are observed in inflammatory diseases, such as hypersensitivity pneumonitis, allergic asthma, psoriasis and rheumatoid arthritis. CHI3L1, chitinase-3 like-protein-1; CSF, cerebral spinal fluid.

with disease progression (55). In addition, CHI3L1 is associated with mortality in individuals with cardiovascular disease (56). Serum CHI3L1 levels are increased in patients with essential hypertension, which is positively correlated with the incidence of hypertension in pre-hypertensive subjects (57). Monitoring CHI3L1 serum levels may aid in predicting the occurrence of cardiovascular events in patients with hypertension during long-term follow-up for 7.89±0.12 years (58). Results of previous studies also reveal that increased CHI3L1 serum levels in patients with aortic stenosis and peripheral artery disease are associated with a poor prognosis (59,60). Notably, CHI3L1 levels are elevated during the acute phase of ischemic stroke and are independently associated with recurrent stroke, complex vascular events and adverse functional outcomes (61). In patients with atrial fibrillation, CHI3L1 is highly expressed in epicardial tissue. Thus, serum CHI3L1 levels may be used to predict the recurrence of atrial fibrillation and may be associated with atrial fibrosis (62,63). Assessment of serum CHI3L1 may exhibit potential in identifying the risk of future cardiovascular events in additional diseases, such as essential thrombocythemia and polycythemia vera (64). In addition, CHI3L1 may affect the progression of coronary artery disease (CAD), affecting the stability of the fibrous cap of atherosclerotic plaques and the occurrence of complications. Thus, CHI3L1 may exhibit potential as significant indicator for the early diagnosis of CAD (65,66). Results of a previous study demonstrated a strong correlation between CHI3L1 levels and the progression of cardiovascular disease (67). These levels not only allow for the monitoring of disease progression, but also offer effective prediction of mortality caused by cardiovascular events, showcasing the potential of CHI3L1 as a valuable predictor of cardiovascular disease. Results of previous studies also highlight the effect of CHI3L1 on cardiovascular disease through the regulation of cardiovascular-related cells. In disease models of AS and pulmonary hypertension, CHI3L1 is closely associated with functions in specific cells, including macrophages and SMCs (25,55,68,69).

CHI3L1 and macrophages. During the maturation of macrophages, the expression of CHI3L1 is upregulated due to the

binding of nuclear transcription factor sp1 to the promoter of the CHI3L1 gene. Thus, CHI3L1 is considered a marker of macrophage maturation (70).

Results of a previous study indicated that individuals with Prader-Willi syndrome (PWS), a neurodevelopmental disorder, exhibit an increased risk of obesity and cardiovascular disease (71). The occurrence of PWS is associated with compromised macrophage suppression and increased ECM remodeling. Notably, patients with PWS exhibit elevated levels of MMP-9 and myeloperoxidase, along with reduced levels of macrophage inhibitory factor. In addition, patients with PWS exhibit elevated CHI3L1 expression levels, highlighting the potential association between CHI3L1 and macrophages (72). CHI3L1 expression has been detected in CD68+ macrophages and circulating monocytes in GCA, mediated by B cells (25). Cytokines produced by B cells promote the transformation of macrophages into pro-inflammatory phenotypes, and results of this study also demonstrated that CHI3L1, IL-6, IL-1β, TNF-α and MMP-9 expression levels were significantly increased (43). In GCA, CHI3L1 is mainly derived from CD206+MMP9+ macrophage subsets. As an upstream regulator of MMP-9+ macrophages, CHI3L1 binds to the IL-13Rα2, which is highly expressed in the vascular wall of GCA layers. Notably, IL-13Rα2 mediates tissue destruction and angiogenesis. In macrophages, CHI3L1 knockdown rescues the aforementioned effects (44). In M1 macrophages, IL-6 decreases the expression of microRNA (miR)-24-1, and upregulates the expression of CHI3L1 and inflammatory mediators, TNF-α and C-C motif chemokine ligand 2 (CCL2)\MCP-1 during the progression of vascular inflammation. IL-6 mediates these effects through RelA (p65)/Nfkb1 (p50). In addition, upregulated CHI3L1 and its downstream inflammatory factor, CCL2, promote SMC migration through JNK and ERK phosphorylation pathways, stimulates the expression of vascular endothelial cell adhesion molecules, such as vascular cell adhesion molecule-1, intercellular cell adhesion molecule-1 and P-selectin and enhances the adhesion function of monocytes (Fig. 2) (46).

The formation of plaque following accumulation of fat and/or fibrous material in the lining of the arteries is a major feature of AS, which involves the phagocytosis of plasma lipoproteins deposited in the lining of the arteries, with macrophages transforming them into foam cells (73). Serum CHI3L1 is significantly elevated in patients with symptomatic carotid AS (74). The initiation factor of AS, oxidized low-density lipoprotein (OX-LDL), also stimulates macrophages to secrete CHI3L1. These results suggest that CHI3L1 may play a role in the development of vascular diseases characterized by macrophage/monocyte accumulation and activation (Fig. 2) (25). Results of a previous study reveal that CHI3L1 gene knockout suppresses the expression of pro-inflammatory mediators, decreases plaque lipid and macrophage levels, and increases collagen and SMC content in ApoE (-/-) mice (75). In addition, CHI3L1 inhibits the activation of Caspase-9 and decreases the apoptosis of macrophages, resulting in plaque fiber cap damage (76).

MCP-1 is a chemokine secreted by adipose tissue that induces monocyte migration and macrophage infiltration and participates in the formation of atheromatous lipostreaks and the development of unstable plaques (77). Results of previous studies demonstrate that patients with obesity may exhibit increased CHI3L1 expression levels (78). However, CHI3L1 expression levels are reduced following weight loss in these patients. These results indicate that increased CHI3L1 expression levels induced the excessive accumulation of macrophages in obese patients, leading to a sub-inflammatory state and the occurrence of AS and other diseases (39,79,80).

Collectively, these results demonstrate that CHI3L1 is not only secreted by macrophages, but also acts on macrophages, facilitating macrophage activation and inflammation. This, in turn, leads to damage in cardiac vascular tissue. Thus, CHI3L1 may play a key role in the advancement of AS. Targeted elimination of CHI3L1 may delay the pathological progression of AS, highlighting its potential as a specific target in the treatment of AS, through the inhibition of inflammation.

CHI3L1 and endothelial cells. Results of a previous study reveal that CHI3L1 stimulated the chemotaxis and migration of human umbilical cord vascular endothelial cells (81). Sun *et al* (68) demonstrate that CHI3L1 inhibits endothelial cell apoptosis during vascular remodeling in pulmonary hypertension, by co-binding to the transmembrane protein 219 (TMEM219) receptor and the corresponding IL-13Rα2 receptor. In addition, CHI3L1 upregulates oxygen regulatory protein through the peroxisome proliferator-activated receptor (PPAR)-δ-dependent pathway, reducing lipopolysaccharide (LPS)-induced phosphorylation of NFκB and inhibiting the expression of endothelial cell adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin (Fig. 2) (82). Results of a previous study revealed that CHI3L1 and Lp-PLA2 RNAi in combination are superior to Lp-PLA1 or CHI3L1 RNAi alone in the treatment of AS (83). In a transgenic mouse model of amyloid precursor protein, miR-342-3p targeted the CHI3L13'-untranslated region (UTR) to inhibit CHI3L1 expression in endothelial cells, thereby inhibiting IL-6-induced monocyte-endothelial cell adhesion and platelet-derived growth factor (PDGF-BB)-induced cell migration and proliferation (Fig. 2) (69). Notably, CHI3L1 regulates endothelial cells to promote tumor angiogenesis. Small interfering RNA-mediated CHI3L1 knockdown inhibits tumor growth rate and blood vessel density in the glioblastoma U87 cell line. Anti-VEGF antibody exerts no effect on CHI3L1-mediated endothelial angiogenesis; thus confirming that CHI3L1 promotes tumor blood vessel formation as an angiogenic factor, independent of VEGF (84,85). In xenograft experiments, CHI3L1 expressed by tumor-derived mural cells (GSDCs) activates neural cadherin/β-catenin/smooth muscle α actin (SMA) and VE-cadherin/β between GSDC and endothelial cells. The catenin/actin pathway plays a role in mediating intercellular adhesion and permeability, enhancing the interaction between GSDCs and endothelial cells and stabilizing the vascular network. Results of a previous study reveal that CHI3L1 silencing in GSDCs leads to a significant reduction in tumor blood vessel density and stability, ultimately inhibiting tumor growth (86). In osteoblastoma cell lines; namely, MG-63 and U87, mouse monoclonal anti-CHI3L1 antibodies effectively inhibit the CHI3L1-induced activation of MAPK and ERK (1/2), thereby inhibiting the tube formation of microvascular endothelial cells (87). CHI3L1 also interacts with TGF-β to increase endothelial cell permeability and promote endothelial-to-mesenchymal transition (EMT). The treatment

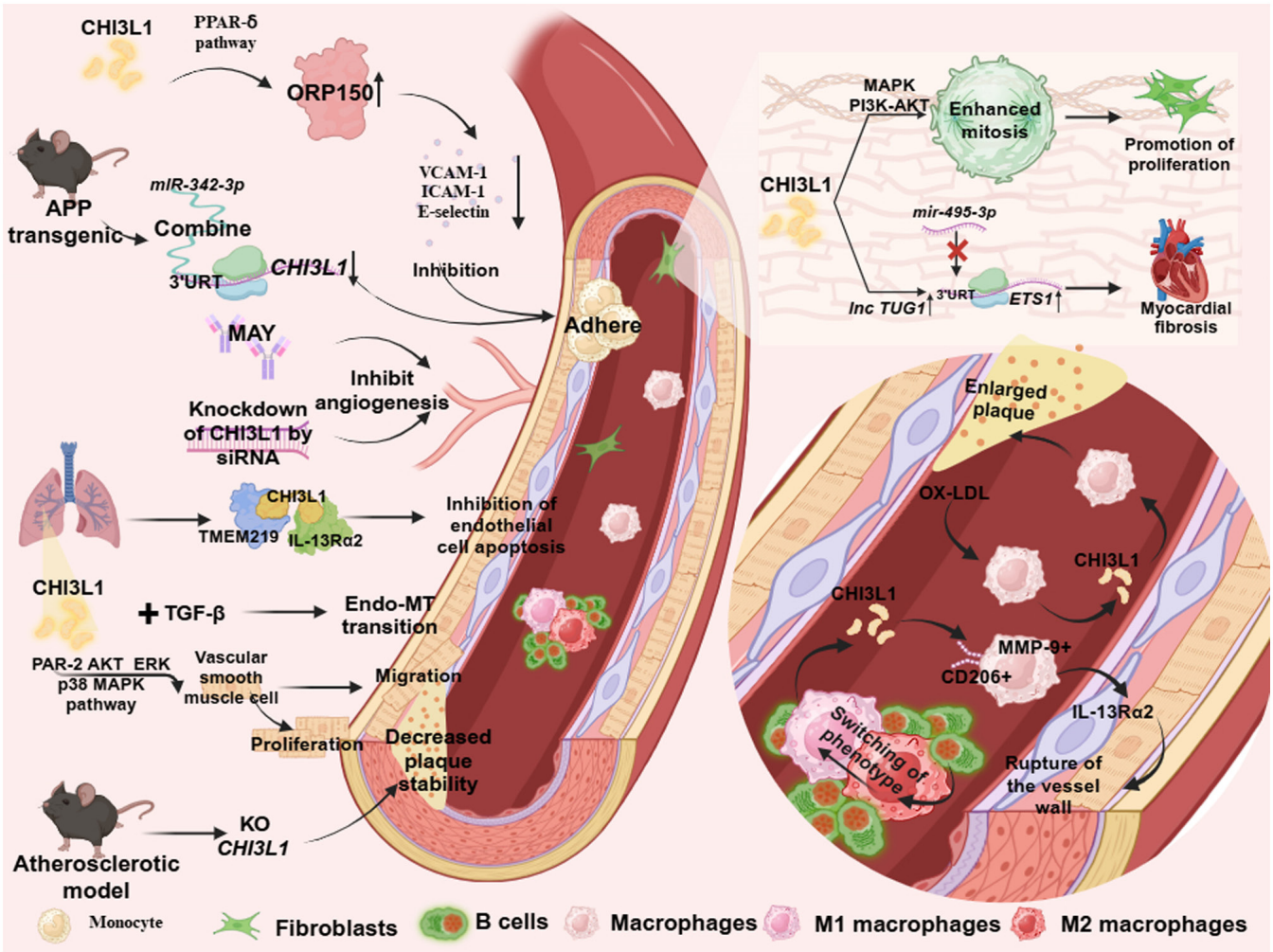

Figure 2. CHI3L1 regulates the function of vascular-associated cells. In giant cell arteritis, MMP-9 and CHI3L1 secreted by CD206+ macrophages mediated vascular rupture by binding to IL-13Rα2. In a model of pulmonary hypertension, CHI3L1 inhibits endothelial cell apoptosis through the co-binding of TMEM219 receptor and IL-13Rα2 receptor and acts with TGF-β to mediate EMT. CHI3L1 upregulates ORP150 through the PPAR-pathway, inhibits the expression of endothelial cell adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin, and weakens the adhesion between endothelial cells and monocytes. In APP transgenic mice, endothelial cell microRNA-342-3p binds to the CHI3L1 3'-untranslated region to inhibit CHI3L1 expression, thereby inhibiting the adhesion between endothelial cells and monocytes. In addition, both antibody-mediated and small interfering RNA-induced CHI3L1 knockdown inhibits endothelial angiogenesis. In asthma bronchial remodeling, CHI3L1 promotes smooth muscle cell proliferation and migration through PAR-2, AKT, ERK and p38-dependent mechanisms and the MAPK pathway. In atherosclerosis, CHI3L1 may enlarge plaques and increase plaque stability. CHI3L1 mediates mitosis through MAPK and PI3K-AKT signaling pathways, stimulates fibroblast growth and promotes mouse cardiomyocyte fibrosis through regulating the long non-coding RNA TUG1/microRNA-1-495-3p/ETS1 axis. CHI3L1, chitinase-3 like-protein-1; IL-13Rα2, interleukin-13 receptor α2, TMEM219, transmembrane protein 219; EMT, endothelial-to-mesenchymal transition; ORP 150, 150-kDa oxygen-regulated protein; PPAR, Peroxisome proliferator-activated receptor; ICAM-1, intercellular cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; APP, amyloid precursor protein; MAY, monoclonal anti-YKL-40 antibody; TMEM, transmembrane; EMT, endothelial-to-mesenchymal transition; TUG1, taurine upregulated 1; ETS1, ETS proto-oncogene 1; ox-LDL, oxidized low-density lipoprotein.

of bovine pulmonary artery endothelial cells with CHI3L1 in combination with TGF-β downregulates VE-cadherin in vascular endothelial cells and reduces the expression of α-SMA, a mesenchymal cell marker (Fig. 2) (68). Thus, CHI3L1 may play a role in promoting tumor angiogenesis and in mediating endothelial cell apoptosis and EMT. Targeting CHI3L1 may inhibit tumor growth, thus highlighting the potential of this protein in the development of novel treatment strategies.

CHI3L1 and fibroblasts. Fibrosis is a tissue repair response that relies on fibroblast activation and is characterized by the excessive accumulation of ECM components, such as collagen and fibronectin (88). CHI3L1 stimulates fibroblast growth in a dose-dependent manner through MAPK and PI3K-AKT signaling pathways. Results of a previous study reveal that CHI3L1 mediates mitotic reactions, stimulates the proliferation of connective tissue cells and participates in fibrosis (89). During the wound healing process in diabetic foot ulcer, fibroblasts overexpressing CHI3L1 are enriched and M1-type macrophages are polarized (90). Notably, CHI3L1 is associated with atrial fibrosis in patients with atrial fibrillation (62). Results of a previous study reveal that CHI3L1 affects the degree of fibrosis in mouse cardiomyocytes by modulating the long non-coding (lnc)RNA TUG1/miR-1-495-3p/ETS proto-oncogene 1 (ETS1) axis. CHI3L1 increases the expression of lncRNA TUG1 and reduces the expression of miR-495-3p, thereby weakening the targeted binding of miR-495-3p to the 3'UTR sequence of the

ETS1 gene. Thus, ETS1 gene expression levels are increased in mice, ultimately leading to increased levels of myocardial fibrosis (Fig. 2) (91). Collectively, these studies revealed that CHI3L1 may play a crucial role in the advancement of fibrosis in cardiovascular patients; thus highlighting its potential in the development of novel treatment options for fibrosis.

CHI3L1 and SMCs. CHI3L1 participates in the morphological and phenotypic transformation of SMCs (92). During bronchial remodeling in patients with asthma, CHI3L1 stimulates IL-8 expression through PAR-2, AKT, ERK and P38-dependent mechanisms and promotes the proliferation and migration of bronchial SMCs (93,94). Although pulmonary artery SMCs do not express CHI3L1, CHI3L1 interacts with the G-protein-coupled receptor, chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), expressed by vascular SMCs. Thus, CHI3L1 promotes the proliferation of vascular SMCs and the formation of fibrosis during pulmonary hypertension vascular remodeling (68). TGF-β, a stimulator of hypoxia and fibrosis, also upregulates the expression of CRTH2, which exerts synergistic effects with CHI3L1 (68). Results of a previous study demonstrate that CHI3L1 and α-SMA co-localize in unstable plaques and CHI3L1 inhibits vascular SMC proliferation. In apo-/-mouse, CHI3L1 gene knockout results in a decrease in α-SMA+ cells localized in the plaque cap region and decreases plaque stability (95,96) (Fig. 2). In addition, in the presence of the atherosclerotic stimulant OX-LDL, large tumor suppressor kinase 2 (LATS2) expression levels are increased in human carotid SMCs. In addition, LATS2 knockdown *in vitro* inhibits the expression of the macrophage marker, advanced glycation end-product receptor 3 (LGALS3), and inflammatory cytokines, such as IL-6 and IL-1β. Results of a previous study highlights that CHI3L1 may reduce the expression of LATS2 and homologous domain-associated protein kinase 2 (96). These results reveal the role of CHI3L1 in the transition to a synthetic phenotype and in inhibiting SMC proliferation in atherosclerosis. Notably, the regulatory effect of CHI3L1 on SMCs varies depending on the disease; thus, further investigations are required to elucidate the specific underlying mechanisms.

Collectively, these results suggest that CHI3L1 may play a role as a crucial mediator in the development and progression of cardiovascular disease. Prolonged nicotine consumption exacerbates inflammatory responses through upregulation of CHI3L1, thereby heightening the risk and advancement of abdominal aortic aneurysm. Notably, this may be associated with reduced microRNA-24 expression (97). In male patients with end-stage renal disease, CHI3L1 expression is associated with vascular calcification, indicating the sex-specific role of CHI3L1 as a novel marker for cardiovascular disease that may affect the development of cardiovascular comorbidities (22). Through proteomics and Mendelian randomization, results of a previous study reveal that CHI3L1 acts as a circulating protein that is causally associated with the treatment of heart failure. Thus, CHI3L1 may exhibit potential in the treatment of heart failure (98).

CHI3L1 is not only associated with the development of cardiovascular disease, but also serves as a valuable indicator for monitoring the prognosis of patients. Notably, CHI3L1 may affect disease progression by modulating the functional status of cells associated with the cardiovascular system. As a novel predictor of cardiovascular disease, CHI3L1 exhibits potential as a target for disease management.

4. CHI3L1 regulates molecules involved in cardiovascular disease

CHI3L1 and chemokines. As signaling proteins, chemokines bind to corresponding receptors on the cell surface, to play key roles in angiogenesis and in the regulation of leukocyte adhesion and migration (99). Notably, CHI3L1 gene expression is negatively correlated with the expression of CCL2/MCP-1. Interference with the CHI3L1 gene inhibits the occurrence of inflammation in AS (83). In addition, CHI3L1 induces the secretion of IL-8 and CCL2 in macrophages, promoting the migration of macrophages and endothelial cells (100). In lung macrophages, CHI3L1 promotes CXCL2 production. Results of a previous study also demonstrate that CHI3L1 promotes the expression of LPS-treated macrophage angiogenesis factors, leading to further increases in angiogenesis (101).

CHI3L1 and adhesion molecules. As an inflammatory molecule, CHI3L1 is used in combination with VCAM-1 and ICAM-1 to evaluate the occurrence of vascular inflammation (102). Serum CHI3L1, VCAM-1 and ICAM-1 are significantly increased in vascular endothelial injury and vascular inflammation induced by high cholesterol (103). Results of a previous study reveal that CHI3L1 promotes a decline in endothelial barrier function by reducing the expression of VE-cadherin (68). During the formation of tumor blood vessels, CHI3L1 stimulates endothelial cells to upregulate the membrane receptor sydecan-1 protein to coordinate integrin αvβ3, triggering a signaling cascade of focal adhesion kinase and ERK-1/2; thus promoting angiogenesis (104). Proteoglycan also plays a key role in regulating cell adhesion and migration. Notably, CHI3L1 binds to proteoglycans, such as chitosaccharides and hyaluronic acid; thus playing a regulatory role in a variety of diseases (105).

CHI3L1 and ILs. ILs play a key role in inflammatory response and regulate the progression of AS (106). In high-cholesterol rats with vitamin D deficiency, IL-6 and CHI3L1 levels are simultaneously increased, promoting vascular inflammation (103). Results of a previous study reveal that CHI3L1 specifically binds to IL-13Rα2, increases the phosphorylation of ERK1/2 and JNK, promotes the recruitment of members of the activator protein-1 family in the nucleus, targets the MMP family and degrades the ECM (107). In lung tissue and airway remodeling, IL-13 upregulates the expression of CHI3L1 and plays a key role in the inflammatory response (108).

CHI3L1 and MMPs. MMPs are a class of zinc-dependent endoproteases secreted by endothelial cells, vascular SMCs, fibroblasts, macrophages and neutrophils. MMP expression levels are associated with vascular remodeling and stiffening and plaque stability (109). In AS, MMP-7 regulates the function of macrophages, leading to the generation of atherosclerotic unstable plaques. MMP-2, MMP-9, MMP-13,

MMP-35 and MMP-42 increase the risk of plaque rupture through degradation of arterial elastin and increasing vascular calcification, leading to further AS development (109,110). Results of a previous study demonstrated that both MMP-9 and CHI3L1 were independent risk factors for unstable plaque formation (111). Mechanical stress, including shear force, is involved in vascular remodeling through the regulation of MMPs. Results of a previous study reveal that vascular inflammatory factor MMP-8 expression levels are decreased in a model of AS, following CHI3L1 gene knockout (83).

5. Conclusions

Results of previous studies reveal that CHI3L1 is closely associated with the occurrence and development of cardiovascular disease; thus stressing the potential of CHI3L1 in predicting the prognosis of patients and the management of disease. However, the present study possesses limitations. The regulatory function of CHI3L1 in SMCs in atherosclerotic diseases is associated with cell-cell interactions and the atherosclerotic microenvironment. Additional negative feedback pathways may play a role in CHI3L1 synthesis and secretion and these were not investigated in the present study. In addition, results of previous studies were inconsistent in demonstrating the role of CHI3L1 in cells, which may be due to differing disease processes and experimental environments. However, CHI3L1 may promote plaque formation in the early stage of AS, inhibit plaque progression in the late stage and improve plaque stability. Through the analysis of clinical samples, results of a previous study revealed that CHI3L1 serum levels are elevated in patients with cardiovascular disease, suggesting that CHI3L1 may promote the development of cardiovascular disease. Thus, further experiments are required to determine the mechanisms underlying CHI3L1 in the prevention and treatment of cardiovascular disease.

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Availability of data and materials

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Authors' contributions

ZQ, YL, YR and DX wrote and revised the manuscript, and constructed the figures. ZG and MC conceived the study and revised the manuscript. Data authentication is not applicable. All authors have 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.

References

1. Al-Mallah MH, Sakr S and Al-Qunaibet A: Cardiorespiratory fitness and cardiovascular disease prevention: An update. Curr Atheroscler Rep 20: 1, 2018.
2. Mensah GA, Fuster V and Roth GA: A Heart-Healthy and Stroke-Free world: Using data to inform global action. J Am Coll Cardiol 82: 2343-2349, 2023.
3. Dhande IS and Doris PA: Genomics and inflammation in cardiovascular disease. Compr Physiol 11: 2433-2454, 2021.
4. Weber BN, Giles JT and Liao KP: Shared inflammatory pathways of rheumatoid arthritis and atherosclerotic cardiovascular disease. Nat Rev Rheumatol 19: 417-428, 2023.
5. Forteza MJ, Berg M, Edsfeldt A, Sun J, Baumgartner R, Kareinen I, Casagrande FB, Hedin U, Zhang S, Vuckovic I, *et al*: Pyruvate dehydrogenase kinase regulates vascular inflammation in atherosclerosis and increases cardiovascular risk. Cardiovasc Res 119: 1524-1536, 2023.
6. Chen R, Zhang H, Tang B, Luo Y, Yang Y, Zhong X, Chen S, Xu X, Huang S and Liu C: Macrophages in cardiovascular diseases: Molecular mechanisms and therapeutic targets. Signal Transduct Target Ther 9: 130, 2024.
7. Wagenhauser MU, Mulorz J, Krott KJ, Bosbach A, Feige T, Rhee YH, Chatterjee M, Petzold N, Böddeker C, Ibing W, *et al*: Crosstalk of platelets with macrophages and fibroblasts aggravates inflammation, aortic wall stiffening, and osteopontin release in abdominal aortic aneurysm. Cardiovasc Res 120: 417-432, 2024.
8. Kinoshita D, Suzuki K, Yuki H, Niida T, Fujimoto D, Minami Y, Dey D, Lee H, McNulty I, Ako J, *et al*: Sex-Specific association between perivascular inflammation and plaque vulnerability. Circ Cardiovasc Imaging 17: e016178, 2024.
9. Ham HJ, Lee YS, Koo JK, Yun J, Son DJ, Han SB and Hong JT: Inhibition of Amyloid-β (Aβ)-Induced cognitive impairment and neuroinflammation in CHI3L1 knockout mice through down-regulation of ERK-PTX3 pathway. Int J Mol Sci 25: 5550, 2024.
10. Kui L, Kim AD, Onyuru J, Hoffman HM and Feldstein AE: BRP39 regulates neutrophil recruitment in NLRP3 Inflammasome-Induced liver inflammation. Cell Mol Gastroenterol Hepatol 17: 481-497, 2024.
11. Ferrigno I, Verzellesi L, Ottone M, Bonacini M, Rossi A, Besutti G, Bonelli E, Colla R, Facciolongo N, Teopompi E, *et al*: CCL18, CHI3L1, ANG2, IL-6 systemic levels are associated with the extent of lung damage and radiomic features in SARS-CoV-2 infection. Inflamm Res 73: 515-530, 2024.
12. Song M, Zhang G, Shi H, Zhu E, Deng L and Shen H: Serum YKL-40 in coronary heart disease: Linkage with inflammatory cytokines, artery stenosis, and optimal cut-off value for estimating major adverse cardiovascular events. Front Cardiovasc Med 10: 1242339, 2023.
13. Reilly CS, Borges AH, Baker JV, Safo SE, Sharma S, Polizzotto MN, Pankow JS, Hu X, Sherman BT, Babiker AG, *et al*: Investigation of causal effects of protein biomarkers on cardiovascular disease in persons with HIV. J Infect Dis 227: 951-960, 2023.
14. Czestkowski W, Krzeminski L, Piotrowicz MC, Mazur M, Pluta E, Andryianau G, Koralewski R, Matyszewski K, Olejniczak S, Kowalski M, *et al*: Structure-Based discovery of High-Affinity small molecule ligands and development of tool probes to study the role of Chitinase-3-Like protein 1. J Med Chem 67: 3959-3985, 2024.
15. Junker N, Johansen JS, Hansen LT, Lund EL and Kristjansen PE: Regulation of YKL-40 expression during genotoxic or microenvironmental stress in human glioblastoma cells. Cancer Sci 96: 183-190, 2005.
16. Zhao T, Su Z, Li Y, Zhang X and You Q: Chitinase-3 like-protein-1 function and its role in diseases. Signal Transduct Target Ther 5: 201, 2020.

17. Fusetti F, Pijning T, Kalk KH, Bos E and Dijkstra BW: Crystal structure and carbohydrate-binding properties of the human cartilage glycoprotein-39. J Biol Chem 278: 37753-37760, 2003.
18. Zhao H, Huang M and Jiang L: Potential roles and future perspectives of Chitinase 3-like 1 in macrophage polarization and the development of diseases. Int J Mol Sci 24: 16149, 2023.
19. Coffman FD: Chitinase 3-Like-1 (CHI3L1): A putative disease marker at the interface of proteomics and glycomics. Crit Rev Clin Lab Sci 45: 531-562, 2008.
20. Suzuki K, Okawa K, Ohkura M, Kanaizumi T, Kobayashi T, Takahashi K, Takei H, Otsuka M, Tabata E, Bauer PO and Oyama F: Evolutionary insights into sequence modifications governing chitin recognition and chitinase inactivity in YKL-40 (HC-gp39, CHI3L1). J Biol Chem 300: 107365, 2024.
21. Yu JE, Yeo IJ, Han SB, Yun J, Kim B, Yong YJ, Lim YS, Kim TH, Son DJ and Hong JT: Significance of chitinase-3-like protein 1 in the pathogenesis of inflammatory diseases and cancer. Exp Mol Med 56: 1-18, 2024.
22. Laucyte-Cibulskiene A, Ward LJ, Ebert T, Tosti G, Tucci C, Hernandez L, Kautzky-Willer A, Herrero MT, Norris CM, Pilote L, *et al*: Role of GDF-15, YKL-40 and MMP 9 in patients with end-stage kidney disease: Focus on sex-specific associations with vascular outcomes and all-cause mortality. Biol Sex Differ 12: 50, 2021.
23. Kwak EJ, Hong JY, Kim MN, Kim SY, Kim SH, Park CO, Kim KW, Lee CG, Elias JA, Jee HM and Sohn MH: Chitinase 3-like 1 drives allergic skin inflammation via Th2 immunity and M2 macrophage activation. Clin Exp Allergy 49: 1464-1474, 2019.
24. Libreros S, Garcia-Areas R, Shibata Y, Carrio R, Torroella-Kouri M and Iragavarapu-Charyulu V: Induction of proinflammatory mediators by CHI3L1 is reduced by chitin treatment: Decreased tumor metastasis in a breast cancer model. Int J Cancer 131: 377-386, 2012.
25. Lee CG, Da Silva CA, Dela Cruz CS, Ahangari F, Ma B, Kang MJ, He CH, Takyar S and Elias JA: Role of chitin and chitinase/chitinase-like proteins in inflammation, tissue remodeling, and injury. Annu Rev Physiol 73: 479-501, 2011.
26. Ling H and Recklies AD: The chitinase 3-like protein human cartilage glycoprotein 39 inhibits cellular responses to the inflammatory cytokines interleukin-1 and tumour necrosis factor-alpha. Biochem J 380: 651-659, 2004.
27. Recklies AD, Ling H, White C and Bernier SM: Inflammatory cytokines induce production of CHI3L1 by articular chondrocytes. J Biol Chem 280: 41213-41221, 2005.
28. Connolly K, Lehoux M, O'Rourke R, Assetta B, Erdemir GA, Elias JA, Lee CG and Huang YA: Potential role of chitinase-3-like protein 1 (CHI3L1/YKL-40) in neurodegeneration and Alzheimer's disease. Alzheimers Dement 19: 9-24, 2023.
29. Cicognola C, Mattsson-Carlgren N, van Westen D, Zetterberg H, Blennow K, Palmqvist S, Ahmadi K, Strandberg O, Stomrud E, Janelidze S and Hansson O: Associations of CSF PDGFRβ with aging, Blood-Brain barrier damage, neuroinflammation, and Alzheimer disease pathologic changes. Neurology 101: e30-e39, 2023.
30. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, *et al*: Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: A case-control study. Lancet 366: 1640-1649, 2005.
31. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ and Patterson CC: Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia 46: 760-765, 2003.
32. Kwon Y, Kim JH, Ha EK, Jee HM, Baek HS, Han MY and Jeong SJ: Serum YKL-40 levels are associated with the atherogenic index of plasma in children. Mediators Inflamm 2020: 8713908, 2020.
33. Kyrgios I, Galli-Tsinopoulou A, Stylianou C, Papakonstantinou E, Arvanitidou M and Haidich AB: Elevated circulating levels of the serum acute-phase protein YKL-40 (chitinase 3-like protein 1) are a marker of obesity and insulin resistance in prepubertal children. Metabolism 61: 562-568, 2012.
34. Catalan V, Gomez-Ambrosi J, Rodriguez A, Ramírez B, Rotellar F, Valentí V, Silva C, Gil MJ, Salvador J and Frühbeck G: Increased circulating and visceral adipose tissue expression levels of YKL-40 in obesity-associated type 2 diabetes are related to inflammation: Impact of conventional weight loss and gastric bypass. J Clin Endocrinol Metab 96: 200-209, 2011.
35. Nielsen AR, Erikstrup C, Johansen JS, Fischer CP, Plomgaard P, Krogh-Madsen R, Taudorf S, Lindegaard B and Pedersen BK: Plasma YKL-40: A BMI-independent marker of type 2 diabetes. Diabetes 57: 3078-3082, 2008.
36. Kim HM, Lee BW, Song YM, Kim WJ, Chang HJ, Choi DH, Yu HT, Kang E, Cha BS and Lee HC: Potential association between coronary artery disease and the inflammatory biomarker YKL-40 in asymptomatic patients with type 2 diabetes mellitus. Cardiovasc Diabetol 11: 84, 2012.
37. Fisman EZ and Tenenbaum A: Adiponectin: A manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? Cardiovasc Diabetol 13: 103, 2014.
38. Aguilera E, Serra-Planas E, Granada ML, Pellitero S, Reverter JL, Alonso N, Soldevila B, Mauricio D and Puig-Domingo M: Relationship of YKL-40 and adiponectin and subclinical atherosclerosis in asymptomatic patients with type 1 diabetes mellitus from a European Mediterranean population. Cardiovasc Diabetol 14: 121, 2015.
39. Deng Y, Li G, Chang D and Su X: YKL-40 as a novel biomarker in cardio-metabolic disorders and inflammatory diseases. Clin Chim Acta 511: 40-46, 2020.
40. Perumalsamy S, Huri HZ, Abdullah BM, Mazlan O, Wan Ahmad WA and Vethakkan S: Genetic markers of insulin resistance and atherosclerosis in type 2 diabetes mellitus patients with coronary artery disease. Metabolites 13: 427, 2023.
41. Sanchez-Madrid F and Sessa WC: Spotlight on mechanisms of vascular inflammation. Cardiovasc Res 86: 171-173, 2010.
42. Haaversen AB, Brekke LK, Bakland G, Rodevand E, Myklebust G and Diamantopoulos AP: Norwegian society of rheumatology recommendations on diagnosis and treatment of patients with giant cell arteritis. Front Med (Lausanne) 9: 1082604, 2022.
43. Graver JC, Jiemy WF, Altulea DHA, van Sleen Y, Xu S, van der Geest KSM, Verstappen GMPJ, Heeringa P, Abdulahad WH, Brouwer E, *et al*: Cytokine producing B-cells and their capability to polarize macrophages in giant cell arteritis. J Autoimmun 140: 103111, 2023.
44. van Sleen Y, Jiemy WF, Pringle S, van der Geest KSM, Abdulahad WH, Sandovici M, Brouwer E, Heeringa P and Boots AMH: A distinct macrophage subset mediating tissue destruction and neovascularization in giant cell arteritis: Implication of the YKL-40/Interleukin-13 receptor α 2 axis. Arthritis Rheumatol 73: 2327-2337, 2021.
45. Haque K and Bhargava P: Abdominal aortic aneurysm. Am Fam Physician 106: 165-172, 2022.
46. Maegdefessel L, Spin JM, Raaz U, Eken SM, Toh R, Azuma J, Adam M, Nakagami F, Heymann HM, Chernogubova E, *et al*: miR-24 limits aortic vascular inflammation and murine abdominal aneurysm development. Nat Commun 5: 5214, 2014.
47. Kong P, Cui ZY, Huang XF, Zhang DD, Guo RJ and Han M: Inflammation and atherosclerosis: Signaling pathways and therapeutic intervention. Signal Transduct Target Ther 7: 131, 2022.
48. Liang G, Wang S, Shao J, Jin YJ, Xu L, Yan Y, Günther S, Wang L and Offermanns S: Tenascin-X Mediates Flow-Induced suppression of EndMT and atherosclerosis. Circ Res 130: 1647-1659, 2022.
49. Michelsen AE, Rathcke CN, Skjelland M, Holm S, Ranheim T, Krohg-Sørensen K, Klingvall MF, Brosstad F, Oie E, Vestergaard H, *et al*: Increased YKL-40 expression in patients with carotid atherosclerosis. Atherosclerosis 211: 589-595, 2010.
50. Sciborski K, Kuliczkowski W, Karolko B, Bednarczyk D, Protasiewicz M, Mysiak A and Negrusz-Kawecka M: Plasma YKL-40 levels correlate with the severity of coronary atherosclerosis assessed with the SYNTAX score. Pol Arch Intern Med 128: 644-648, 2018.
51. Xu Q, Sun L, Wang Y, Wang R, Jia Y, Guo D, Shi M, Yang P, Zhang Y and Zhu Z: Causal effects of YKL-40 on ischemic stroke and its subtypes: A 2-Sample mendelian randomization study. J Am Heart Assoc 12: e029000, 2023.
52. Kjaergaard AD, Bojesen SE, Johansen JS and Nordestgaard BG: Elevated plasma YKL-40 levels and ischemic stroke in the general population. Ann Neurol 68: 672-680, 2010.
53. Ma WH, Wang XL, Du YM, Wang YB, Zhang Y, Wei DE, Guo LL and Bu PL: Association between human cartilage glycoprotein 39 (YKL-40) and arterial stiffness in essential hypertension. BMC Cardiovasc Disord 12: 35, 2012.
54. Schroder J, Jakobsen JC, Winkel P, Hilden J, Jensen GB, Sajadieh A, Larsson A, Ärnlöv J, Harutyunyan M, Johansen JS, *et al*: Prognosis and reclassification by YKL-40 in stable coronary artery disease. J Am Heart Assoc 9: e014634, 2020.

55. Wu S, Hsu LA, Cheng ST, Teng MS, Yeh CH, Sun YC, Huang HL and Ko YL: Circulating YKL-40 level, but not CHI3L1 gene variants, is associated with atherosclerosis-related quantitative traits and the risk of peripheral artery disease. Int J Mol Sci 15: 22421-22437, 2014.
56. Wallentin L, Eriksson N, Olszowka M, Grammer TB, Hagström E, Held C, Kleber ME, Koenig W, März W, Stewart RAH, *et al*: Plasma proteins associated with cardiovascular death in patients with chronic coronary heart disease: A retrospective study. PLoS Med 18: e1003513, 2021.
57. Xu T, Zhong C, Wang A, Guo Z, Bu X, Zhou Y, Tian Y, HuangFu X, Zhu Z and Zhang Y: YKL-40 is a novel biomarker for predicting hypertension incidence among prehypertensive subjects: A population-based nested case-control study in China. Clin Chim Acta 472: 146-150, 2017.
58. Çetin M, Erdoğan T, Kırış T, Özer S, Çinier G, Emlek N, Durak H and Şatıroğlu Ö: Elevated serum YKL40 level is a predictor of MACE during the long-term follow up in hypertensive patients. Clin Exp Hypertens 42: 271-274, 2020.
59. Arain F, Abraityte A, Bogdanova M, Solberg OG, Michelsen AE, Lekva T, Aakhus S, Holm S, Halvorsen B, Finsen AV, *et al*: YKL-40 (Chitinase-3-Like protein 1) serum levels in aortic stenosis. Circ Heart Fail 13: e006643, 2020.
60. Hobaus C, Tscharre M, Herz CT, Pesau G, Wrba T, Koppensteiner R and Schernthaner GH: YKL-40 levels increase with declining ankle-brachial index and are associated with long-term cardiovascular mortality in peripheral arterial disease patients. Atherosclerosis 274: 152-156, 2018.
61. Chen XL, Li Q, Huang WS, Lin YS, Xue J, Wang B, Jin KL and Shao B: Serum YKL-40, a prognostic marker in patients with large-artery atherosclerotic stroke. Acta Neurol Scand 136: 97-102, 2017.
62. Wang Q, Shen H, Min J, Gao Y, Liu K, Xi W, Yang J, Yin L, Xu J, Xiao J and Wang Z: YKL-40 is highly expressed in the epicardial adipose tissue of patients with atrial fibrillation and associated with atrial fibrosis. J Transl Med 16: 229, 2018.
63. Michelakakis N, Neroutsos GJ, Perpinia AS, Farmakis D, Voukouti EG, Karavidas AJ, Parissis J, Georgiakaki MT and Pyrgakis VN: Chitinase-3-like protein-1 (YKL-40) before and after therapy in supraventricular arrhythmias. J Cardiovasc Med (Hagerstown) 18: 650-654, 2017.
64. Krečak I, Gverić-Krečak V, Lapić I, Rončević P, Gulin J, Fumić K, Krečak F, Holik H and Duraković N: Circulating YKL-40 in Philadelphia-negative myeloproliferative neoplasms. Acta Clin Belg 76: 32-39, 2021.
65. Xing Y, Guo J, Gai L, Liu B and Luo D: Serum YKL-40 is associated with the severity of coronary artery disease and hypertension. Asian J Surg 43: 1121-1122, 2020.
66. Song CL, Bin L, Diao HY, Wang JH, Shi YF, Lu Y, Wang G, Guo ZY, Li YX, Liu JG, *et al*: Diagnostic value of serum YKL-40 level for coronary artery disease: A Meta-Analysis. J Clin Lab Anal 30: 23-31, 2016.
67. Zheng JL, Lu L, Hu J, Zhang RY, Zhang Q, Chen QJ and Shen WF: Increased serum YKL-40 and C-reactive protein levels are associated with angiographic lesion progression in patients with coronary artery disease. Atherosclerosis 210: 590-595, 2010.
68. Sun X, Nakajima E, Norbrun C, Sorkhdini P, Yang AX, Yang D, Ventetuolo CE, Braza J, Vang A, Aliotta J, *et al*: Chitinase 3 like 1 contributes to the development of pulmonary vascular remodeling in pulmonary hypertension. JCI Insight 7: e159578, 2022.
69. Jung YY, Kim KC, Park MH, Seo Y, Park H, Park MH, Chang J, Hwang DY, Han SB, Kim S, *et al*: Atherosclerosis is exacerbated by chitinase-3-like-1 in amyloid precursor protein transgenic mice. Theranostics 8: 749-766, 2018.
70. Rehli M, Niller HH, Ammon C, Langmann S, Schwarzfischer L, Andreesen R and Krause SW: Transcriptional regulation of CHI3L1, a marker gene for late stages of macrophage differentiation. J Biol Chem 278: 44058-44067, 2003.
71. Thomas C, Mandilaras G, Rabenhorst D, Oberhoffer FS, Fischer M, Haas NA and Fernandez Rodriguez S: Vagal asystoles in a boy with Prader-Willi syndrome. Pediatrics 152: e2022058216, 2023.
72. Hope S, Naerland T, Olav Kolset S, Ueland T, Andreassen OA and Nordstrom M: Systemic immune profile in Prader-Willi syndrome: Elevated matrix metalloproteinase and myeloperoxidase and reduced macrophage inhibitory factor. Orphanet J Rare Dis 18: 185, 2023.
73. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, Tokgözoğlu L and Lewis EF: Atherosclerosis. Nat Rev Dis Primers 5: 56, 2019.
74. Boot RG, van Achterberg TA, van Aken BE, Renkema GH, Jacobs MJ, Aerts JM and de Vries CJ: Strong induction of members of the chitinase family of proteins in atherosclerosis: Chitotriosidase and human cartilage gp-39 expressed in lesion macrophages. Arterioscler Thromb Vasc Biol 19: 687-694, 1999.
75. Gong Z, Xing S, Zheng F and Xing Q: Increased expression of chitinase 3-like 1 in aorta of patients with atherosclerosis and suppression of atherosclerosis in apolipoprotein E-knockout mice by chitinase 3-like 1 gene silencing. Mediators Inflamm 2014: 905463, 2014.
76. Huan W, Yandong L, Chao W, Sili Z, Jun B, Mingfang L, Yu C and Lefeng Q: YKL-40 aggravates early-stage atherosclerosis by inhibiting macrophage apoptosis in an Aven-dependent Way. Front Cell Dev Biol 9: 752773, 2021.
77. de Lemos JA, Morrow DA, Sabatine MS, Murphy SA, Gibson CM, Antman EM, McCabe CH, Cannon CP and Braunwald E: Association between plasma levels of monocyte chemoattractant protein-1 and long-term clinical outcomes in patients with acute coronary syndromes. Circulation 107: 690-695, 2003.
78. Ahangari F, Sood A, Ma B, Takyar S, Schuyler M, Qualls C, Dela Cruz CS, Chupp GL, Lee CG and Elias JA: Chitinase 3-like-1 regulates both visceral fat accumulation and asthma-like Th2 inflammation. Am J Respir Crit Care Med 191: 746-757, 2015.
79. Hempen M, Kopp HP, Elhenicky M, Höbaus C, Brix JM, Koppensteiner R, Schernthaner G and Schernthaner GH: YKL-40 is elevated in morbidly obese patients and declines after weight loss. Obes Surg 19: 1557-1563, 2009.
80. Kopp HP, Kopp CW, Festa A, Krzyzanowska K, Kriwanek S, Minar E, Roka R and Schernthaner G: Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. Arterioscler Thromb Vasc Biol 23: 1042-1047, 2003.
81. Malinda KM, Ponce L, Kleinman HK, Shackelton LM and Millis AJ: Gp38k, a protein synthesized by vascular smooth muscle cells, stimulates directional migration of human umbilical vein endothelial cells. Exp Cell Res 250: 168-173, 1999.
82. Jung TW, Park HS, Choi GH, Kim D, Jeong JH and Lee T: Chitinase-3-like protein 1 ameliorates atherosclerotic responses via PPARdelta-mediated suppression of inflammation and ER stress. J Cell Biochem 119: 6795-6805, 2018.
83. Zhang H, Zhou W, Cao C, Zhang W, Liu G and Zhang J: Amelioration of atherosclerosis in apolipoprotein E-deficient mice by combined RNA interference of lipoprotein-associated phospholipase A2 and YKL-40. PLoS One 13: e0202797, 2018.
84. Ngernyuang N, Yan W, Schwartz LM, Oh D, Liu YB, Chen H and Shao R: A heparin binding motif rich in arginine and lysine is the functional domain of YKL-40. Neoplasia 20: 182-192, 2018.
85. Shao R, Hamel K, Petersen L, Cao QJ, Arenas RB, Bigelow C, Bentley B and Yan W: YKL-40, a secreted glycoprotein, promotes tumor angiogenesis. Oncogene 28: 4456-4468, 2009.
86. Francescone R, Ngernyuang N, Yan W, Bentley B and Shao R: Tumor-derived mural-like cells coordinate with endothelial cells: Role of YKL-40 in mural cell-mediated angiogenesis. Oncogene 33: 2110-2122, 2014.
87. Faibish M, Francescone R, Bentley B, Yan W and Shao R: A YKL-40-neutralizing antibody blocks tumor angiogenesis and progression: A potential therapeutic agent in cancers. Mol Cancer Ther 10: 742-751, 2011.
88. Henderson NC, Rieder F and Wynn TA: Fibrosis: From mechanisms to medicines. Nature 587: 555-566, 2020.
89. Recklies AD, White C and Ling H: The chitinase 3-like protein human cartilage glycoprotein 39 (HC-gp39) stimulates proliferation of human connective-tissue cells and activates both extracellular signal-regulated kinase- and protein kinase B-mediated signalling pathways. Biochem J 365: 119-126, 2002.
90. Theocharidis G, Thomas BE, Sarkar D, Mumme HL, Pilcher WJR, Dwivedi B, Sandoval-Schaefer T, Sîrbulescu RF, Kafanas A, Mezghani I, *et al*: Single cell transcriptomic landscape of diabetic foot ulcers. Nat Commun 13: 181, 2022.
91. Sun Y, Shan X, Guo J, Liu X and Ma D: CHI3L1 promotes myocardial fibrosis via regulating lncRNA TUG1/miR-495-3p/ETS1 axis. Apoptosis 28: 1436-1451, 2023.
92. Shackelton LM, Mann DM and Millis AJ: Identification of a 38-kDa heparin-binding glycoprotein (gp38k) in differentiating vascular smooth muscle cells as a member of a group of proteins associated with tissue remodeling. J Biol Chem 270: 13076-13083, 1995.

93. Bara I, Ozier A, Girodet PO, Carvalho G, Cattiaux J, Begueret H, Thumerel M, Ousova O, Kolbeck R, Coyle AJ, *et al*: Role of YKL-40 in bronchial smooth muscle remodeling in asthma. Am J Respir Crit Care Med 185: 715-722, 2012.
94. Tang H, Sun Y, Shi Z, Huang H, Fang Z, Chen J, Xiu Q and Li B: YKL-40 induces IL-8 expression from bronchial epithelium via MAPK (JNK and ERK) and NF-κB pathways, causing bronchial smooth muscle proliferation and migration. J Immunol 190: 438-446, 2013.
95. Lambert J and Jorgensen HF: Vascular smooth muscle cell phenotypic switching and plaque stability: A role for CHI3L1. Cardiovasc Res 117: 2691-2693, 2021.
96. Tsantilas P, Lao S, Wu Z, Eberhard A, Winski G, Vaerst M, Nanda V, Wang Y, Kojima Y, Ye J, *et al*: Chitinase 3 like 1 is a regulator of smooth muscle cell physiology and atherosclerotic lesion stability. Cardiovasc Res 117: 2767-2780, 2021.
97. Mulorz J, Spin JM, Mulorz P, Wagenhäuser MU, Deng A, Mattern K, Rhee YH, Toyama K, Adam M, Schelzig H, *et al*: E-cigarette exposure augments murine abdominal aortic aneurysm development: Role of Chil1. Cardiovasc Res 119: 867-878, 2023.
98. Henry A, Gordillo-Maranon M, Finan C, Schmidt AF, Ferreira JP, Karra R, Sundström J, Lind L, Ärnlöv J, Zannad F, *et al*: Therapeutic targets for heart failure identified using proteomics and mendelian randomization. Circulation 145: 1205-1217, 2022.
99. Sadeghi M, Dehnavi S, Asadirad A, Xu S, Majeed M, Jamialahmadi T, Johnston TP and Sahebkar A: Curcumin and chemokines: Mechanism of action and therapeutic potential in inflammatory diseases. Inflammopharmacology 31: 1069-1093, 2023.
100. Kawada M, Seno H, Kanda K, Nakanishi Y, Akitake R, Komekado H, Kawada K, Sakai Y, Mizoguchi E and Chiba T Chitinase 3-like 1 promotes macrophage recruitment and angiogenesis in colorectal cancer. Oncogene 31: 3111-3123, 2012.
101. Libreros S, Garcia-Areas R, Keating P, Carrio R and Iragavarapu-Charyulu VL: Exploring the role of CHI3L1 in 'pre-metastatic' lungs of mammary tumor-bearing mice. Front Physiol 4: 392, 2013.
102. Janelidze S, Mattsson N, Stomrud E, Lindberg O, Palmqvist S, Zetterberg H, Blennow K and Hansson O: CSF biomarkers of neuroinflammation and cerebrovascular dysfunction in early Alzheimer disease. Neurology 91: e867-e877, 2018.
103. Kocabas R: Effect of Vitamin D on YKL-40: Rat hypercholesterolemia model. Korean Circ J 53: 92-102, 2023.
104. Francescone RA, Scully S, Faibish M, Taylor SL, Oh D, Moral L, Yan W, Bentley B and Shao R: Role of YKL-40 in the angiogenesis, radioresistance, and progression of glioblastoma. J Biol Chem 286: 15332-15343, 2011.
105. Kognole AA and Payne CM: Inhibition of mammalian glycoprotein YKL-40: identification of the physiological ligand. J Biol Chem 292: 2624-2636, 2017.
106. Henein MY, Vancheri S, Longo G and Vancheri F: The role of inflammation in cardiovascular disease. Int J Mol Sci 23: 12906, 2022.
107. Chen Y, Zhang S, Wang Q and Zhang X: Tumor-recruited M2 macrophages promote gastric and breast cancer metastasis via M2 macrophage-secreted CHI3L1 protein. J Hematol Oncol 10: 36, 2017.
108. Lee CG, Hartl D, Lee GR, Koller B, Matsuura H, Da Silva CA, Sohn MH, Cohn L, Homer RJ, Kozhich AA, *et al*: Role of breast regression protein 39 (BRP-39)/chitinase 3-like-1 in Th2 and IL-13-induced tissue responses and apoptosis. J Exp Med 206: 1149-1166, 2009.
109. Olejarz W, Lacheta D and Kubiak-Tomaszewska G: Matrix metalloproteinases as biomarkers of atherosclerotic plaque instability. Int J Mol Sci 21: 3946, 2020.
110. Liu SF, Nambiar Veetil N, Li Q, Kucherenko MM, Knosalla C and Kuebler WM: Pulmonary hypertension: Linking inflammation and pulmonary arterial stiffening. Front Immunol 13: 959209, 2022.
111. Jiao Y, Qin Y, Zhang Z, Zhang H, Liu H and Li C: Early identification of carotid vulnerable plaque in asymptomatic patients. BMC Cardiovasc Disord 20: 429, 2020.