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Significance of chitinase-3-like protein 1 in the pathogenesis of inflammatory diseases and cancer

Ji Eun Yu[1,6], In Jun Yeo[1,2,6], Sang-Bae Han[1], Jaesuk Yun[1], Bongcheol Kim[3], Yoon Ji Yong[4], Young-soo Lim[4], Tae Hun Kim[5], Dong Ju Son[1]✉ and Jin Tae Hong[1]✉

Chitinase-3-like protein 1 (CHI3L1) is a secreted glycoprotein that mediates inflammation, macrophage polarization, apoptosis, and carcinogenesis. The expression of CHI3L1 is strongly upregulated by various inflammatory and immunological diseases, including several cancers, Alzheimer's disease, and atherosclerosis. Several studies have shown that CHI3L1 can be considered as a marker of disease diagnosis, prognosis, disease activity, and severity. In addition, the proinflammatory action of CHI3L1 may be mediated via responses to various proinflammatory cytokines, including tumor necrosis factor-α, interleukin-1β, interleukin-6, and interferon-γ. Therefore, CHI3L1 may contribute to a vast array of inflammatory diseases. However, its pathophysiological and pharmacological roles in the development of inflammatory diseases remain unclear. In this article, we review recent findings regarding the roles of CHI3L1 in the development of inflammatory diseases and suggest therapeutic approaches that target CHI3L1.

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INTRODUCTION

Although several studies on chitinase-3-like 1 (CHI3L1) have been published, a systematic review of the various features and functions of this protein is lacking. In this review article, we provide information based on an analysis of the available data using an Open Targets Platform[1–3] and other data-analysis platforms to assess the significance of CHI3L1 as a target molecule in several inflammatory diseases. We also provide further information regarding the interacting target of CHI3L1 obtained using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING), which is a comprehensive web-based platform that lists known and predicted protein–protein interactions[4–9]. Furthermore, we discuss recent findings related to the roles of CHI3L1 in the development of several inflammatory diseases, as well as in therapeutic approaches.

Using the Open Targets Platform, we found that several cancers, neurological diseases, pulmonary diseases, cardiovascular diseases, and rheumatoid arthritis, among others, are critically associated with CHI3L1 (Fig. 1). Thus, here, we discuss the significant roles of CHI3L1 in the development of cancers (lung, liver, and colon), neurological diseases (Alzheimer's disease, schizophrenia, etc.), cardiovascular diseases, and rheumatoid arthritis; moreover, we provide some information pertaining to the significance of CHI3L1 in the most common autoimmune disease among Korean children, i.e., atopy.

PROPERTIES OF CHITINASE-LIKE PROTEINS

The most studied mammalian chitinases are chitotriosidase (CHIT1) and acidic mammalian chitinase (AMCase), which are both true chitinases, whereas CHI3L1, chitinase-3-like 2 (CHI3L2), oviductal glycoprotein 1 (OVGP1), and stabilin-1 interacting chitinase like protein (S1-CLP) have the ability to bind chitin but not to degrade it. The properties of CLPs, including CHI3L1, are summarized in Table 1.

Among them, CHI3L1 has been called YKL-40 in humans and breast regression protein 39 (BRP-39) in mice[10]. CHI3L1 is derived from the three N-terminal amino acids present on the secreted form and its molecular mass. Since its initial detection in the culture supernatant of the MG63 osteosarcoma cell line, it has been subsequently discovered in human chondrocytes, synoviocytes, and vascular smooth muscle cells[11–13]. CHI3L1 protein shows high conservation among species, with homologies of 73.3% in mice, 79.6% in rats, 96.6% in monkeys, and 83.8% in sheep. CHI3L1 is a 40-kDa glycoprotein with heparin, chitin, and collagen-binding properties. It acts as a lectin due to its preserved carbohydrate-binding domain, but its ligands are still unknown[14–17]. CHI3L1 is strongly expressed by macrophages in inflammatory diseases, such as rheumatoid arthritis, asthma, liver cirrhosis, encephalitis, stroke, multiple sclerosis, and glioblastoma[18–27]. It is noteworthy that CHI3L1 has the ability to bind to multiple receptors, such as the receptor for advanced glycation end products (RAGE), syndecan-1/αVβ3, interleukin 13 receptor alpha 2 (IL-13Rα2), and VEGFR2, and this binding leads to the activation of several signals related to inflammasome activation, neuronal inflammation, tumor metastasis and invasion, angiogenesis, apoptosis, carcinogenesis, Aβ accumulation, vascular smooth muscle cell activation, endothelial cell inflammation and atherogenesis (Fig. 2)[28–30].

[1]College of Pharmacy and Medical Research Center, Chungbuk National University, 194-31, Osongsaengmyeong 1-ro, Osong-eup, Cheongju-si, Chungbuk 28160, Republic of Korea. [2]College of Pharmacy, Kyungpook National University, 80 Daehakro, Bukgu, Daegu 41566, Republic of Korea. [3]Senelix Co. Ltd., 25, Beobwon-ro 11-gil, Songpa-gu, Seoul 05836, Republic of Korea. [4]PRESTI GEBIOLOGICS Co. Ltd., Osongsaengmyeong 1-ro, Osong-eup, Cheongju-si, Chungbuk 28161, Republic of Korea. [5]Autotelic Bio Inc., Osongsaengmyeong 1-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungbuk 28160, Republic of Korea. [6]These authors contributed equally: Ji Eun Yu, In Jun Yeo.
✉email: sondj@chungbuk.ac.kr; jinthong@chungbuk.ac.kr

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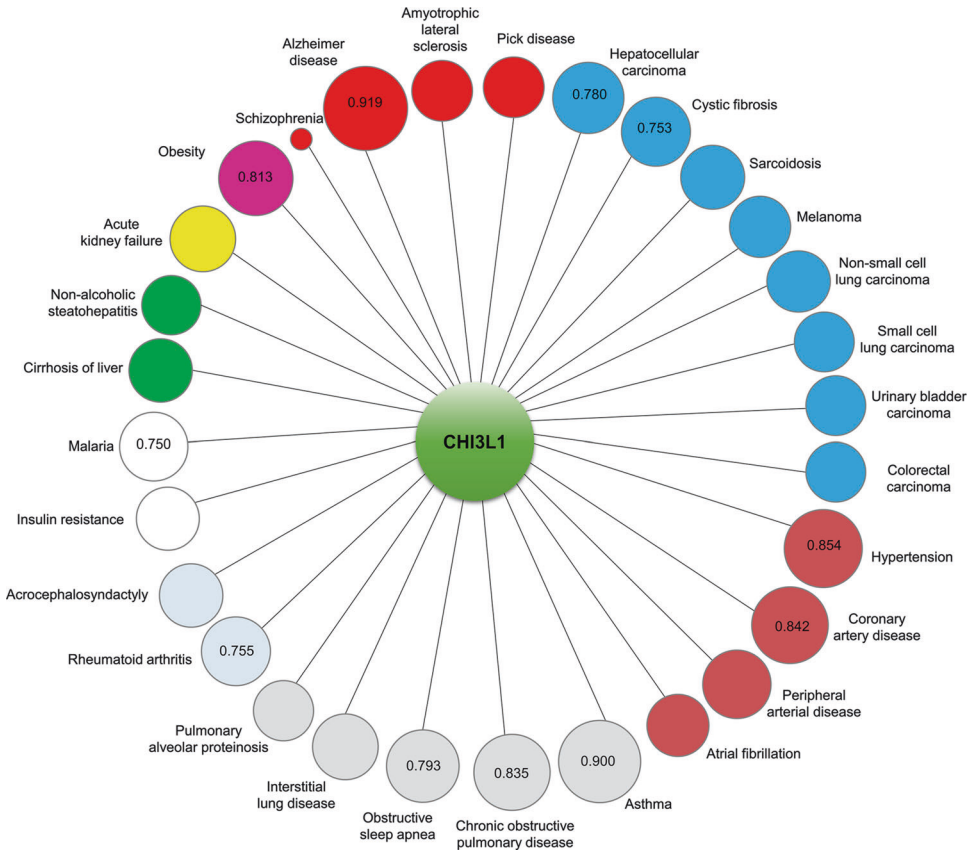

Fig. 1 Relationship between CHI3L1 and various diseases. The circle sizes are determined based on text-mining scores. The values in the circle symbols are the text-mining scores determined via Open Targets Platform analysis.

Table 1. Properties of CLP isoforms.

	CHI3L1	CHI3L2	OVGP1	S1-CLP
Biological activities	**Carbohydrate and chitin binding**	**Carbohydrate and chitin binding**	**Saccharides and oligosaccharides binding**	**Oligosaccharide, chitin and protein binding**
Expressing cells	Neutrophils, synoviocytes, monocytes/ macrophages, osteoclasts, endothelial cell, hepatic stellate cells, smooth muscle cells, and many cancer cells	Synovial fibroblasts, human cartilage chondrocytes, and cancer cells	Oviductal epithelial cell	Macrophages, monocytes, lymphocytes, and sinusoidal endothelial cells, cancer cells
Possible functions	Regulation of cell proliferation, adhesion, migration, and activation Activation of macrophages Regulation of immune-response in inflammation and cancer	Cartilage biogenesis Type II collagen expression Regulation of immune-response	Supportive role in fertilization and embryo development	A ligand for the multifunctional receptor stabilin-1, macrophage inflammatory regulator, pathogen sensing, endotoxin neutralization
Associated diseases	Pneumonia, rheumatoid arthritis, breast cancer, colon cancer, ovarian carcinoma, hepatocellular carcinoma, lung cancer, atherosclerosis, atopy, liver fibrosis, depression, schizophrenia, and Alzheimer's disease, Parkinson disease, obesity, diabetes, asthma etc.	Rheumatoid arthritis, Osteoarthritis, Alzheimer's disease, renal, glioma and breast cancer	Ovarian cancers, mucinous carcinomas' hypertension, endometriosis	Rheumatoid arthritis, osteoarthritis chronic obstructive pulmonary disease, sarcoidosis

INVOLVEMENT OF CHI3L1 IN CANCERS

Lung cancer

CHI3L1 is known to play a significant role in the development and progression of lung cancer, promoting tumor cell invasion and metastasis. It is upregulated in lung cancer tissues and associated with a poor prognosis in patients with the disease[31–38]. Studies in mice have shown elevated CHI3L1 expression in non-small cell lung cancer (NSCLC) tissues compared to normal lung tissues, and high CHI3L1 levels are correlated with reduced survival in NSCLC patients[39–41]. Moreover, the inhibition of CHI3L1 expression or activity has been shown to reduce lung tumor growth and size, while its overexpression promotes the growth, migration, and invasion of lung cancer cell lines[42–46].

CHI3L1 has also been reported to have a proinflammatory function, which is thought to contribute to tumor growth and progression. CHI3L1 activates immune cells (macrophages and

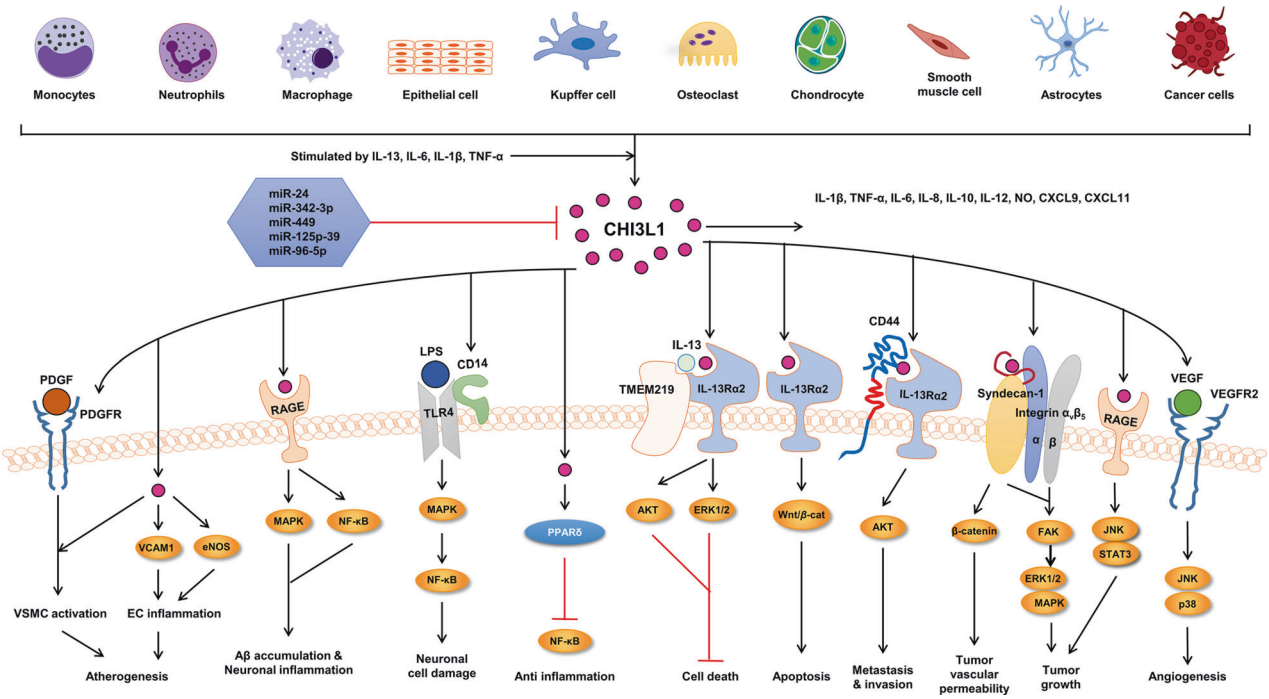

Fig. 2 The role of CHI3L1 in signaling pathways for the development of various diseases. Various cells, such as monocytes, neutrophils, macrophages, epithelial cells, Kupffer cells, osteoclasts, chondrocytes, smooth muscle cells, astrocytes, and cancer cells, produce CHI3L1 by the stimulation of several interleukins, such as IL-13, IL-6, IL-1β, and TNF-α. CHI3L1 expression is inhibited by miR-24, miR-342-3p, miR-449, miR125p-39, and miR-96-5p. The activated cells can release (or produce) IL-1β, TNF-α, IL-6, IL-8, IL-10, IL-12, NO, CXCL9, and CXCL11. In the development of atherogenesis, CHI3L1 directly induces PDGF and PDGFR expression to activate VSMCs and/or directly induces VCAM1 and eNOS expression in the cytosol to cause EC inflammation. In the development of neurodegenerative diseases, CHI3L1 activates the MAPK and NF-κB signaling pathways to induce Aβ accumulation and neuronal inflammation via RAGE in either astrocytes or neurons. In neuronal cells, CHI3L1 activity leads to increased expression of CD14 and TLR4 through the MAPK and NF-κB signaling pathways to damage neurons. In cancer development, several receptors and signaling pathways are involved in these processes. CHI3l1 binds to its receptor IL-13Rα2 by associating with TMEM219 directly or by physically interacting with CD44. The TMEM219-dependent pathway prevents cell death by activating the ERK1/2 and AKT pathways, but direct interaction with IL-13Rα2 causes apoptosis through activation of Wnt/β-catenin. Physical interaction with CD44 activates the AKT pathway to induce metastasis and invasion. The membrane receptors syndecan-1 and integrin $\alpha_v\beta_5$ trigger CHI3L1 signaling pathways, causing tumor vascular permeability and growth by activating the β-catenin, FAK, and ERK 1/2 (MAPK) pathways. CHI3L1 also binds to RAGE and thus activates the FAK and STAT3 pathways, inducing tumor growth. In addition, CHI3L1 elevates the expression of VEGF and its receptor to cause angiogenesis via the activation of the JNK and p38 signaling pathways.

neutrophils) and recruits them to the tumor site, where they release proinflammatory cytokines and chemokines, promoting inflammation and supporting cancer cell survival[31,37,38,42–46]. CHI3L1 also directly stimulates cancer cells to produce proinflammatory cytokines (IL-6, IL-8, and TGF-β)[28,46–49]. CHI3L1 can activate TGF-β signaling by binding to its receptor, thus leading to the production of proinflammatory cytokines and the recruitment of immune cells, which can promote tumor growth and metastasis[28]. CHI3L1 recruits and polarizes tumor-associated macrophages (TAMs) toward an M2-like phenotype, suppressing antitumor immune responses and promoting angiogenesis[31,50]. M2 TAMs inhibit cytotoxic T cells (CTLs) and natural killer cell activity, impairing tumor cell elimination. CHI3L1 promotes lung cancer progression by inhibiting CTL activation, increasing T-cell exhaustion, and promoting lung metastasis through the modulation of T-cell costimulatory and immune checkpoint molecules (ICOS, ICOSL, CD28, CTLA-4, and PD-L1)[51]. It also negatively regulates Th1 differentiation and enhances Th2 differentiation via IFN-γ signaling[46]. Additionally, CHI3L1 targets IL-13Rα2, activating the PI3K/Akt pathway to increase lung cancer cell proliferation, migration, and invasion[46,48,49,52]. Overall, the interactions of CHI3L1 contribute to inflammation, tumor growth, and survival in lung cancer.

To determine whether CHI3L1 is actually a viable candidate therapeutic approach (as a potential drug target) in lung cancer, we examined the association between CHI3L1 and lung cancer using the Open Targets Platform. The text-mining score of NSCLC and CHI3L1 was 0.669, which indicates a high association (Fig. 3 and Table 2). In addition, the text-mining score of CHI3L1 and small cell lung carcinoma was 0.653 (Table 2). If we sum the text-mining scores listed for NSCLC and small cell lung cancer, lung cancer may be the top disease related to CHI3L1. The text-mining scores of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), which have been widely studied as well-known NSCLC diagnostic marker proteins, were 0.891 and 0.790, respectively. However, the overall association score for the association between CHI3L1 and NSCLC was 0.083, whereas the overall association scores of EGR and VEGF were 0.854 and 0.602, respectively (Table 2). Despite the limited information on its genetic or functional aspects compared with EGFR or VEGFA, CHI3L1 had a relatively high text-mining score. Consequently, further genetic or functional studies of CHI3L1 in NSCLC are needed. Next, we used STRING to identify target proteins associated with CHI3L1. Proteins were classified based on this approach to identify proteins associated with CHI3L1 in lung cancer, which could suggest potential target proteins that are functionally related to CHI3L1. As a result of the STRING analysis, the proteins associated with CHI3L1 in lung cancer were identified in the order of VEGFA, TNF Receptor Superfamily Member 10a (TNFRSF10A), IL-13Rα2, chitinase-domain-containing 1 (CHID), IL-13, Transmembrane Protein 219 (TMEM219), IL-6, and C-reactive protein (CRP) (Fig. 4a upper panel). Next, we investigated the

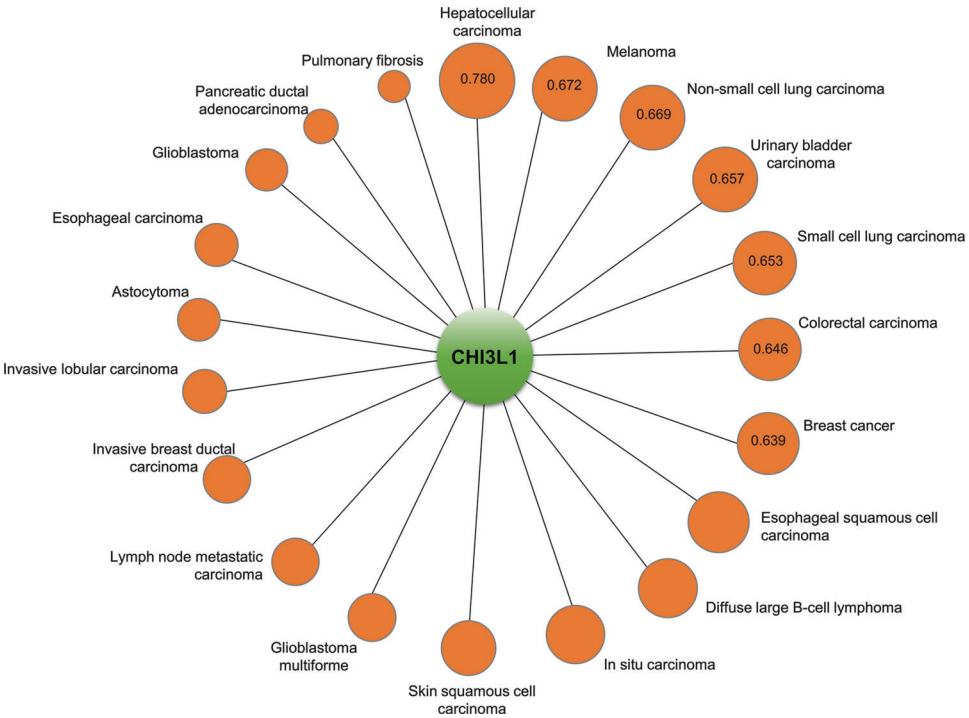

Fig. 3 The relationship between CHI3L1 and cancers. The circle sizes are determined based on text-mining scores. The values in the circle symbols are the text-mining scores determined via Open Targets Platform analysis.

signaling pathways involving CHI3L1 and its target proteins. The signaling pathway between CHI3L1 and its target proteins in NSCLC is illustrated in the lower panel of Fig. 4a. Based on the preliminary findings from the Open Targets Platform and STRING analyses, CHI3L1 exhibits interesting potential as a candidate biomarker for further investigation in lung cancer prediction. Our previous study found that K284-6111 and Ebractenoid F, which are small-molecule inhibitors of CHI3L1 activity, yielded promising results in preclinical studies regarding the inhibition of the growth and metastasis of lung cancer cells[52,53]. Anti-CHI3L1 antibodies specifically target CHI3L1 and prevent it from interacting with its receptors, thereby inhibiting its signaling pathways and lung tumor growth[31]. VEGF and EGFR antibodies and programmed cell death protein 1 inhibitors include bevacizumab, ramucirumab, cetuximab, nivolumab, and pembrolizumab. The standard dosage of these antibodies and inhibitors is 2−15 mg/kg twice a week for 3−4 weeks[54–58]. These antibodies at the indicated doses afford a tumor growth inhibition of approximately 50%. However, our previous study showed that the injection of 0.5 mg/ml of an anti-CHI3L1 antibody twice a week for 4 weeks reduced lung tumor growth by more than 80%. Overall, given the strong evidence linking CHI3L1 to lung cancer formation and progression, targeting this protein may be a promising strategy for the development of new therapies and diagnostic tools for this deadly disease.

Liver cancer

CHI3L1 has also been shown to be involved in the development and progression of liver cancer. In fact, CHI3L1 is expressed at the highest level in the liver among all tissues examined. Previous studies have reported that CHI3L1 is upregulated in patients with liver tumors and that high CHI3L1 expression is associated with a poor prognosis and decreased survival rates[59–63]. The overexpression of CHI3L1 was shown to increase tumor growth, whereas CHI3L1 knockdown inhibited the growth and invasion capacity of hepatocellular carcinoma (HCC) tumors in mice. CHI3L1 was also upregulated in several HCC cells[64].

CHI3L1 promotes an inflammatory response in liver cancer cells by activating signaling pathways that induce the production of proinflammatory cytokines, such as IL-6 and TNF-α. This can contribute to tumor growth and progression by triggering angiogenesis, cell proliferation, and cell survival. A study explored whether a combination of three inflammatory biomarkers (CHI3L1, IL-6, and CRP) along with carcinoembryonic antigen and carbohydrate antigen 19-9 could predict the prognosis in patients with liver metastases after resection[62]. Moreover, another study found that CHI3L1 increased the TNF-α-induced proliferation, migration, and invasion of liver cancer cells[65]. Furthermore, CHI3L1 regulates signaling pathways in liver cancer that are involved in tumor growth and progression. In fact, CHI3L1 can modulate TGF-β signaling in liver cancer through the regulation of SMAD Family Member-2 (SMAD-2) and SMAD-3[64]. Therefore, targeting CHI3L1 may inhibit liver tumor growth and metastasis.

As stated above, targeting CHI3L1 may have therapeutic potential in liver cancer. We used the Open Targets Platform to validate the link between CHI3L1 and liver cancer. The text-mining scores of CHI3L1, EGFR, and VEGF in hepatocellular carcinoma were 0.780, 0.393, and 0.785, respectively, indicating a higher association of CHI3L1 and VEGF in the disease than for EGFR (Table 2). The overall association scores of CHI3L1, EGFR, and VEGF were 0.095, 0.389 and 0.581, respectively (Table 2). CHI3L1 had lower overall association scores than EGFR and VEGF because there is less genetic and functional evidence for CHI3L1. The high text-mining score of CHI3L1 suggests a significant association with liver cancer, similar to those of the representative marker proteins EGFR and VEGF. Subsequently, a target protein connected to CHI3L1 in liver cancer was discovered using STRING analysis, which revealed that the following proteins were linked to CHI3L1 in liver cancer: VEGFA, IL-13Rα2, TGF-β1, matrix metalloproteinase (MMP)-9, IL-6, cluster of differentiation 14 (CD14), S100 Calcium Binding Protein A6 (S100A6), and S100A4 (Fig. 4b upper panel). The lower panel of Fig. 4b illustrates the liver cancer signaling pathway between CHI3L1 and its target proteins. Overall, the

Table 2. Text mining score and overall association score of cancer types associated with CHI3L1, EGFR, and VEGF on the Open Targets Platform.

CHI3L1-cancer			EGFR-cancer			VEGF-cancer		
Name	**Text Mining**	**Overall Association Score**	**Name**	**Text Mining**	**Overall Association Score**	**Name**	**Text Mining**	**Overall Association Score**
Hepatocellular carcinoma	0.780	0.095	Non-small cell lung carcinoma	0.891	0.854	Non-small cell lung carcinoma	0.790	0.602
Melanoma	0.672	0.082	Lung cancer	0.813	0.755	Breast cancer	0.786	0.605
Non-small cell lung carcinoma	0.669	0.083	Glioblastoma multiforme	0.795	0.729	Hepatocellular carcinoma	0.785	0.581
Urinary bladder carcinoma	0.657	0.080	Lung adenocarcinoma	0.788	0.728	Neoplasm	0.784	0.569
Small cell lung carcinoma	0.653	0.079	Head and neck squamous cell carcinoma	0.767	0.691	Glioblastoma multiforme	0.779	0.596
Colorectal carcinoma	0.646	0.079	Neoplasm	0.716	0.622	Renal cell carcinoma	0.750	0.535
Breast cancer	0.639	0.078	Squamous cell carcinoma	0.701	0.607	Multiple myeloma	0.653	0.135
Esophageal squamous cell carcinoma	0.628	0.076	Breast cancer	0.699	0.612	Melanoma	0.641	0.330
Diffuse large B-cell lymphoma	0.608	0.074	Squamous cell lung carcinoma	0.683	0.624	Lung adenocarcinoma	0.594	0.366
In situ carcinoma	0.604	0.073	Breast carcinoma	0.674	0.632	Cancer	0.571	0.150
Skin squamous cell carcinoma	0.565	0.069	Metastatic colorectal cancer	0.638	0.555	Esophageal adenocarcinoma	0.554	0.103
Glioblastoma multiforme	0.494	0.069	Pancreatic carcinoma	0.604	0.625	Osteosarcoma	0.538	0.117
Lymph node metastatic carcinoma	0.490	0.060	Glioma	0.595	0.572	Esophageal squamous cell carcinoma	0.532	0.115
Invasive breast ductal carcinoma	0.489	0.059	Lung carcinoma	0.578	0.564	Glioblastoma	0.526	0.114
Invasive lobular carcinoma	0.456	0.055	Colorectal adenocarcinoma	0.573	0.682	Intrahepatic cholangiocarcinoma	0.525	0.111
Esophageal carcinoma	0.447	0.054	Thyroid carcinoma	0.572	0.455	Acute myeloid leukemia	0.521	0.113
Astrocytoma	0.439	0.055	Brain cancer	0.562	0.437	Nonpapillary renal cell carcinoma	0.520	0.113
Glioblastoma	0.435	0.053	Brain neoplasm	0.556	0.428	Squamous cell carcinoma	0.517	0.131
Pancreatic ductal adenocarcinoma	0.355	0.046	Head and neck malignant neoplasia	0.517	0.646	Adenomyosis	0.513	0.087
Pulmonary fibrosis	0.331	0.040	Colorectal carcinoma	0.515	0.445	Triple-negative breast cancer	0.500	0.133

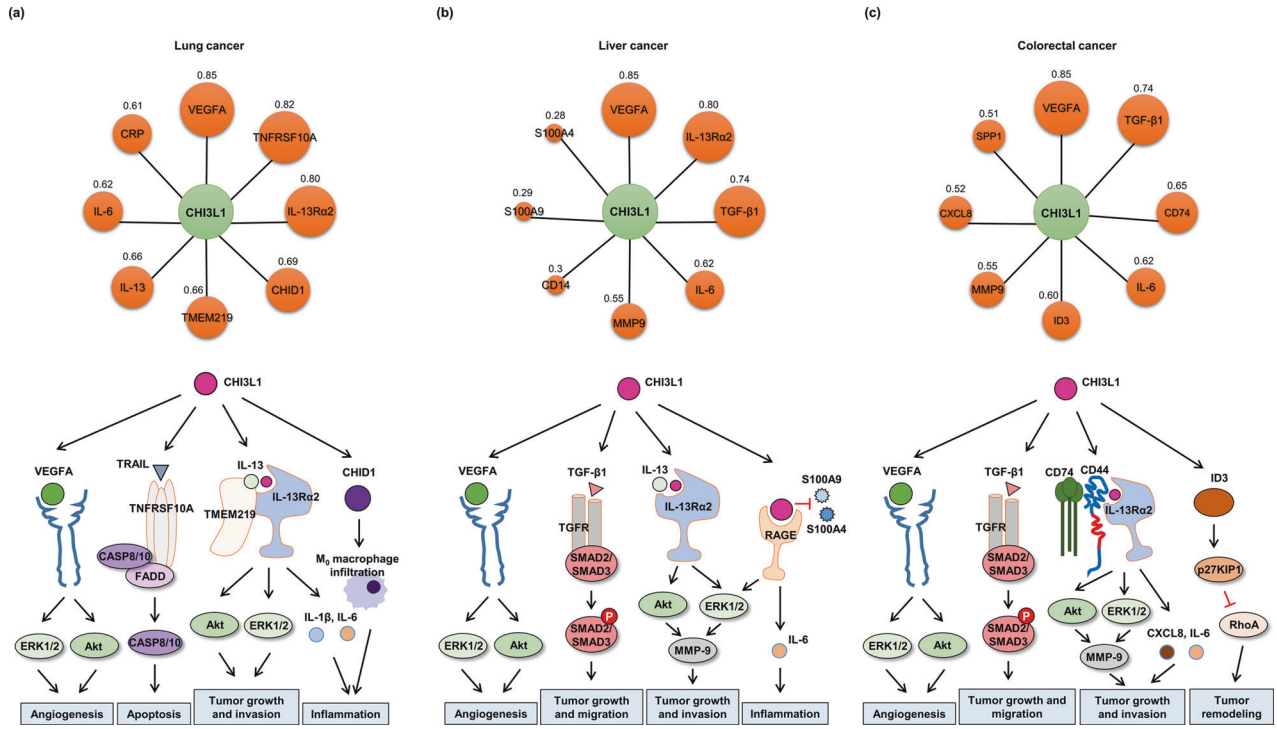

Fig. 4 The interaction network between CHI3L1 and its target proteins and the roles of CHI3L1 in signaling pathways for the development of cancers. a Lung cancer. Upper panel: The circle sizes are determined based on the score. The values in the circle symbols are the scores determined by STRING analysis. Lower panel: In lung cancer, elevated CHI3L1 levels are linked to increased VEGF expression, promoting angiogenesis and tumor progression. CHI3L1 upregulates VEGF through pathways such as ERK1/2 and Akt. CHI3L1 inhibits apoptosis through interactions with the TRAIL signaling pathway, involving TNFRSF10A and CASP8/CAS10. CHI3L1 can bind to TMEM219 and promote tumor growth and invasion by activating Erk1/2 and Akt signaling. CHI3L1 regulates the IL-13 signaling pathway through IL-13Rα2, leading to increased secretion of cytokines, such as IL-1β and IL-6, which can influence inflammation in lung cancer. There have been no reported associations between CHI3L1 and CHID1. However, it has been observed that CHID1 increases M0 macrophage infiltration. **b** Liver cancer, upper panel; the circle sizes are determined based on the score. The values in the circle symbols are the scores determined by STRING analysis. Lower panel: Elevated CHI3L1 levels increase VEGFA expression through the ERK1/2 and Akt pathways, promoting angiogenesis in liver cancer. CHI3L1 may promote tumor growth and migration by interacting with TGF-β1 and TGFR, thereby activating the SMAD2/SMAD3 signaling pathway. CHI3L1 interacts with IL-13 and IL-13Rα2 to activate the IL-13 signaling pathway, including the AKT and ERK1/2 pathways. Additionally, CHI3L1 affects MMP9, promoting tumor invasion and metastasis. CHI3L1 interacts with RAGE, leading to an increase in IL-6 secretion and inflammation. On the other hand, CHI3L1 may negatively regulate S100A9 and S100A4, which means that its interaction with S100A9 and S100A4 results in a reduction in the proinflammatory effects of S100A9 and S100A4 in liver cancer. **c** Colorectal cancer. Upper panel: The circle sizes are determined based on the score. The values in the circle symbols are the scores determined by STRING analysis. Lower panel: CHI3L1 leads to an increase in VEGF/VEGFA expression through the activation of the ERK1/2 and Akt pathways, promoting angiogenesis and tumor progression in colorectal cancer. CHI3L1 has the potential to enhance tumor growth and migration by interacting with TGF-β1 and TGFR, which subsequently activates the SMAD2/SMAD3 signaling pathway. CHI3L1 interacts with CD44 and IL-13Ra2, activating pathways such as AKT and ERK1/2, which in turn promote tumor growth and invasion. Additionally, CHI3L1 affects MMP-9, contributing to tumor invasion. Furthermore, CHI3L1 induces the secretion of CXCL8 and IL-6, which are proinflammatory cytokines that can also play a role in tumor progression and invasion. The relationship between CHI3L1 and ID3 is not well established. However, the interplay between ID3-induced p27KIP1 and RhoA inhibition can contribute to tumor remodeling in colorectal cancer.

association between CHI3L1 and these target proteins in liver cancer suggests that CHI3L1 plays an important role in liver cancer progression and metastasis and that targeting CHI3L1 is a potential therapeutic approach for liver cancer.

Colorectal cancer

CHI3L1 is upregulated in colon tumor tissues and has been proposed as a potential biomarker of colorectal cancer. CHI3L1 is significantly upregulated in patients with colorectal cancer compared with healthy individuals[66,67]. Moreover, overexpressing CHI3L1 in colorectal cancer cells was shown to enhance colon tumor growth in mice[68]. Furthermore, CHI3L1 overexpression significantly enhanced the proliferation of SW480 cells. Conversely, the knockdown of CHI3L1 by RNA interference or neutralization by an anti-CHI3L1 antibody strongly suppressed the CHI3L1-induced migration and tube formation of human colorectal cancer cells[68].

CHI3L1 also regulates the expression of proinflammatory cytokines in colorectal cancer. Previous studies have shown that CHI3L1 can stimulate the migration and invasion of cancer cells by modulating the tumor microenvironment[68,69]. CHI3L1 treatment significantly increases the secretion of IL-8, monocyte chemoattractant protein-1, and VEGFA from cancer-associated fibroblasts[69]. Another study showed that the upregulation of these cytokines and angiogenic factors by CHI3L1 was mediated by the activation of the MAPK signaling pathways[68]. In addition, secreted CHI3L1 activates the NF-κB signaling pathways in cancer cells and macrophages, thus leading to a protumor tumor microenvironment characterized by activated M2 macrophages[50]. In addition, CHI3L1 overexpression leads to a reduction in S100A9 expression, increases cell sensitivity to cetuximab and promotes cell proliferation by downregulating p53 and upregulating EGFR[70].

Colorectal cancer is the fourth most common cancer in Korea, after thyroid, lung, and stomach cancer. In addition, multiple studies have found that Koreans have the highest rate of colorectal cancer in the world. We investigated the relationship between CHI3L1 and colorectal cancer using the Open Targets

Platform. The text-mining scores of CHI3L1, EGFR, and VEGF were 0.646, 0.638, and 0.307, respectively (Table 2). The overall association scores of CHI3L1, EGFR and VEGF with colorectal cancer were 0.079, 0.555, and 0.596, respectively. While drugs targeting EGFR and VEGFA have been extensively studied for colorectal cancer, there are currently no reported drugs for this disease targeting CHI3L1. Therefore, further research on the development of drugs targeting CHI3L1 in colorectal cancer is necessary. Next, we analyzed the target proteins of CHI3L1 in colorectal cancer. We identified several potential CHI3L1 target proteins, including VEGFA, TGF-β1, Cluster of Differentiation 74 (CD74), IL-6, inhibitor of DNA binding 3 (ID3), MMP9, CXCL8, and SPP1, in this type of cancer (Fig. 4c upper panel). The signaling pathway between CHI3L1 and its target proteins in colorectal cancer is depicted in the lower panel of Fig. 4c. The putative target proteins of CHI3L1 in colorectal cancer are involved in diverse biological processes related to the development and progression of the disease.

INVOLVEMENT OF CHI3L1 IN NEUROLOGICAL DISEASES

The expression of CHI3L1 is increased in patients with various neurological diseases, including Alzheimer's disease (AD), amyotrophic lateral sclerosis, multiple sclerosis, and schizophrenia (SCZ)[71]. According to the comprehensive Open Targets Platform and text-mining scores, AD is the neurological disease most strongly associated with the *CHI3L1* gene. In addition, ALS and SCZ are also associated with the *CHI3L1* gene in the neurological disease category. CHI3L1 is widely expressed in all regions of the human brain and is particularly found in activated microglia and astrocytes, making it a potential biomarker for neurological diseases[72]. The intricate interactions of the immune system with the brain hold significant therapeutic potential in neurological diseases, and CHI3L1 has emerged as a promising therapeutic target in this context. This section describes the associations and related target genes of CHI3L1 in neurological diseases.

Alzheimer's disease

CHI3L1 is a putative marker of neuroinflammation and has potential prognostic utility as a preclinical biomarker of AD[73]. The increased plasma concentration of CHI3L1 in patients with early AD suggests its usefulness as an early diagnostic indicator[74–77]. The upregulation of CHI3L1 is linked to the immune activation of microglia and neuronal death, and it is also responsive to hippocampal neuron injury[78,79]. In addition, increased expression of CHI3L1 in both healthy women and in brain regions affected by late-onset Alzheimer's disease indicates a possible explanation for the higher prevalence of AD in women than in men[80–83]. Recent research has shown that CHI3L1 plays a role in the formation of amyloid plaques, which are a hallmark of AD pathology[72]. CHI3L1 is primarily expressed in astrocytes in the brains of AD patients and is linked to neuroinflammation in the white matter and cognitive decline[84,85].

CHI3L1 is upregulated in the hippocampus of 9-month-old 5xFAD mice, which are AD model animals expressing human amyloid beta precursor protein[86] and presenilin 1 (*PSEN1*) transgenes[87]. The activation of NF-κB has been observed in the brains of AD patients, and disrupting the NF-κB pathway decreases β-site APP-cleaving enzyme 1 expression and Aβ generation, leading to memory deficits and reduced neurogenesis in vivo[88–90]. Therefore, targeting CHI3L1 is a potential therapy for AD by reducing neuroinflammation. Furthermore, animal studies have shown that the knockout of CHI3L1 proteins can significantly decrease AD pathogenesis, suppress glial phagocytic activation, and reduce amyloid accumulation[72].

Several candidate genes and signals associated with CHI3L1 and AD have been proposed. Increased levels of CHI3L1, APOE, and visinin-like 1 (VSNL1) in the cerebrospinal fluid (CSF) have been associated with AD[91,92]. IL-1β and IL-6, which can upregulate CHI3L1 in astrocytes through STAT3-dependent signaling, have also been implicated in neuroinflammatory dementias[93]. Evidence indicates a shared neuroinflammatory profile among neurodegenerative dementias, where levels of CHI3L1, CHIT1, and GFAP are significantly increased in AD[94]. These findings suggest that several genes are associated with CHI3L1-related neuroinflammation and AD. The inhibition of CHI3L1 using K284-6111 has been reported to block this process, prevent neuroinflammation, and attenuate cognitive impairments[95,96].

We also investigated the relationship between CHI3L1 and AD using the Open Targets Platform. The text-mining score of CHI3L1 (0.919) was the highest score, and the overall association score (0.133) was the second highest score among the neurological diseases (Fig. 5a and Table 3). These data suggest that CHI3L1 is a significant target for AD. The text-mining and overall association scores of other AD targets, such as APP (0.995; 0.824), were consistent (Table 3). These data indicate the necessity for the study of genetic function and drug development for CHI3L1. Next, we analyzed the target proteins of CHI3L1 in AD using the STRING system. We identified several potential CHI3L1 target proteins, including APP, PSEN1, APOE, IL-1β, VSNL1, TNF, IL-6, and GFAP, in AD (Fig. 6a upper panel). The lower panel of Fig. 6a depicts the signaling pathway between CHI3L1 and its target proteins in AD. These putative target proteins of CHI3L1 in AD are involved in diverse biological processes that contribute to neurodegenerative processes.

Schizophrenia

Schizophrenia, which affects approximately 1% of the population, is a prevalent mental disorder. Schizophrenia results from a combination of genetic, environmental, and neurobiological factors; however, its specific mechanism and function remain unclear. On multiple discovery platforms (such as DisGeNET and the Open Targets Platform), SCZ has been found to be most strongly associated with CHI3L1. For example, CHI3L1 was shown to be upregulated in the hippocampus of patients with SCZ[97]. Since then, clinical studies have shown that single-nucleotide polymorphisms (SNPs) of the *CHI3L1* gene are associated with the risk of SCZ[98,99]. Specifically, the G allele of a SNP in the *CHI3L1* gene has been found to be linked to a higher expression of the CHI3L1 protein in the serum of patients with SCZ[100]. However, this genetic association between the *CHI3L1* gene and SCZ has failed to be confirmed in Japanese and Chinese populations[101]. Therefore, there is a lack of in vivo and in vitro studies to demonstrate the relationship between CHI3L1 and SCZ.

Several studies have reported that CHI3L1 is involved in inflammatory and immune responses, including the regulation of inflammatory cytokines and the proliferation and activation of immune cells[102,103]. The importance of inflammation in the risk of developing SCZ has been increasingly recognized[104–106]. The AKT1–GSK3β pathway, which is related to oxidative stress and inflammation, has been suggested to be relevant to the expression of CHI3L1 in SCZ[107]. CHI3L1 induces the production of inflammatory cytokines, whereas AKT signaling is activated by PI3K through SCZ-associated cytokine receptors, colony stimulating factor 2 receptor subunit alpha, and IL-13Rα2[108,109]. The overexpression of CHI3L1, together with other proteins (SERPINA3, IFITM 1, IFITM2, and CD14), has been associated with prefrontal dysfunction in SCZ[110,111]. In first-episode psychosis, increased plasma levels of MCP-1 and CHI3L1 were suggestive of immune reactions in SCZ[112]. We also recently reported that the transmembrane inflammatory cytokine TNF-α may be significant for the development of SCZ[113]. A recent study indicated that CHI3L1 is associated with subsequent type 2 diabetes and low-grade chronic inflammation in patients with SCZ. We next investigated the relationship between CHI3L1 and SCZ using the Open Targets Platform. The text-mining score of CHI3L1 was 0.237 (Fig. 5a and

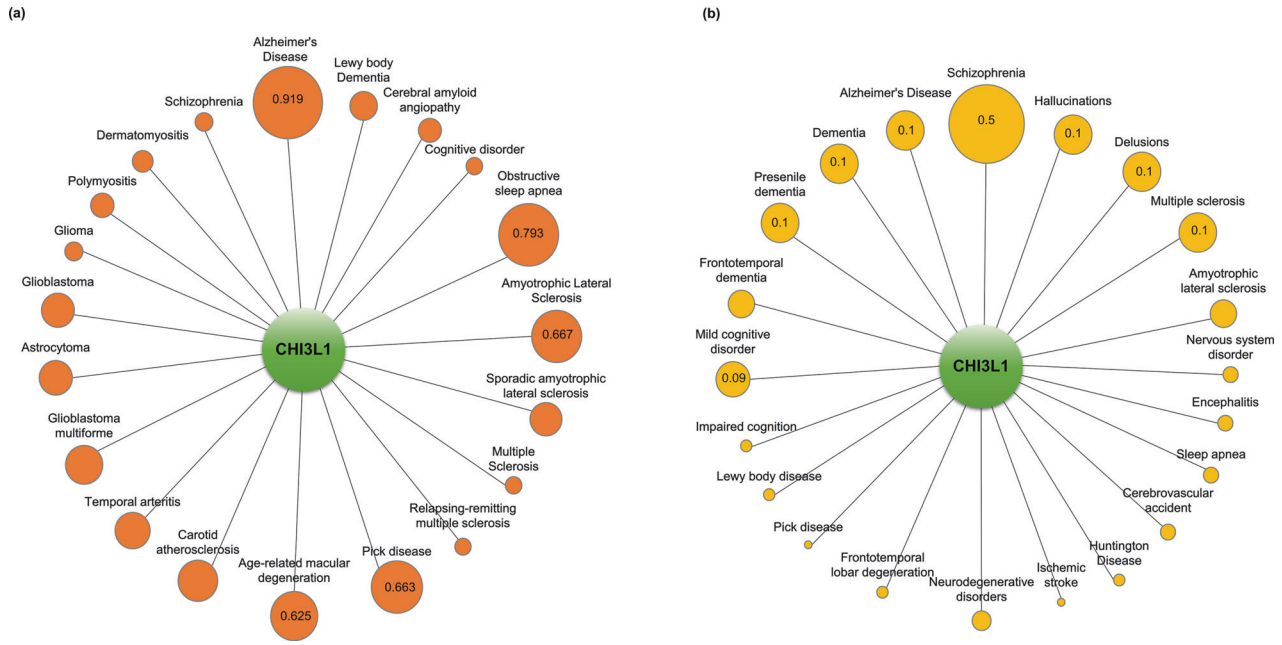

Fig. 5 The relationship between CHI3L1 and neurological diseases. a The circle sizes are determined based on the text-mining score. The values in circle symbols are the text-mining scores determined via Open Targets Platform analysis. **b** The circle sizes are determined based on the gda score. The values in the circle symbols are the gda scores determined via DisGeNET analysis.

Table 3). Moreover, the overall association score (0.377) was the highest score among neurological diseases. The DRD2 target may be the most promising target for the development of drugs for SCZ because it had the highest text-mining and overall association scores (0.942; 0.732) (Table 3). APP had a low overall association score (0.092), even though it showed a relatively high text-mining score (0.693), indicating that it has lower therapeutic potential as a target for SCZ than DRD2. Although CHI3L1 has a lower text mining score than APP, its overall association score is relatively high, indicating a potential for further research. In addition, we found that CHI3L1 was the most interesting target regarding the development of drugs for SCZ because, according to the DisGeNET analysis[114], the gene–disease association (gda) score of CHI3L1 was the highest for its relationship with SCZ (Fig. 5b). These data suggest that CHI3L1 is a potential target in SCZ. Next, we analyzed the target proteins of CHI3L1 in SCZ. As mentioned previously in this section, we identified several potential CHI3L1 target proteins, including AKT1, CD14, CRP, TNF, IL-1β, IL-6, S100A8, and S100A9, in SCZ (Fig. 6b upper panel). We showed the detailed signaling pathways between the target proteins and CHI3L1 (Fig. 6b lower panel).

Other neurological diseases

In addition, CHI3L1 has been associated with various other neurological diseases, i.e., Parkinson's disease (PD), amyotrophic lateral sclerosis, Huntington's disease, MS, progressive supranuclear palsy, and epilepsy. CHI3L1 has been implicated in neuroinflammation and dopaminergic neuron degeneration in PD[115]. Neuroinflammation was shown to predict nonmotor symptoms and cognitive decline in early PD stages[116]. CHI3L1 expression was shown to be increased in the brain tissues and CSF of LPS-induced PD rats along with inflammatory cytokine release[117]. In amyotrophic lateral sclerosis, CHI3L1 has been shown to promote astrocyte activation and motor neuron death[118]. In Huntington's disease, CHI3L1 has been suggested as a potential biomarker of disease progression[119]. In patients with MS, CHI3L1 is a promising biomarker of disability because of its elevated levels in the CSF[120]. Moreover, the CSF levels of CHI3L1 are strongly correlated with MS pathology and can distinguish between primary progressive MS and relapsing–remitting MS[121]. Elevated levels of CHI3L1 in the CSF were found to be associated with faster disease progression[122]. In turn, in progressive supranuclear palsy, CHI3L1 was found to be elevated in the CSF and brain tissues and was correlated with disease severity[123]. Finally, in epilepsy, CHI3L1 has been suggested to be a potential marker of seizure severity and epilepsy type[124]. Further studies are necessary to clarify the mechanisms by which CHI3L1 contributes to the pathogenesis of these diseases and its potential as a biomarker and therapeutic target.

INVOLVEMENT OF CHI3L1 IN CARDIOVASCULAR DISEASES

Cardiovascular disease (CVD) is a collective term for a group of disorders of the heart and blood vessels. These diseases are the largest cause of morbidity and premature death worldwide. Specifically, atherosclerosis is a chronic disorder that occurs in the arterial walls and is associated with endothelial dysfunction, foam cell formation, cholesterol deposition, inflammation, ECM synthesis, smooth muscle cell biological transition, and immature neovascularization of plaques in disease initiation and development[125–128]. In a previous histopathological study that was performed over 20 years ago, strongly upregulated expression of CHI3L1 was detected in distinct subtypes of macrophages in advanced atherosclerotic lesions via in situ hybridization[129]. Subsequently, several clinical studies have reported that an elevated serum CHI3L1 level compared with that of healthy controls is associated with an increased risk of hypertension, endothelial dysfunction, vascular injury, angiographic lesion progression, carotid atherosclerosis, peripheral artery disease, atherosclerosis, large-artery atherosclerotic stroke, coronary artery disease, and cardiovascular complications in patients with diabetes, heart or kidney transplant recipients, and patients with sleep apnea syndrome[86,130–151], suggesting CHI3L1 as a diagnostic marker for CVD. However, the pathophysiological importance of CHI3L1 for CVD, especially hypertension and atherosclerosis, and the correlation between CHI3L1 and its associated genes have not been sufficiently discussed. This section describes the present

Table 3. Text mining score and overall association score of neurological diseases associated with CHI3L1, APP, and DRD2 on the Open Targets Platform.

CHI3L1-neurological diseases			APP-neurological diseases			DRD2-neurological diseases		
Name	**Text Mining**	**Overall Association Score**	**Name**	**Text Mining**	**Overall Association Score**	**Name**	**Text Mining**	**Overall Association Score**
Alzheimer disease	0.919	0.113	Alzheimer disease	0.995	0.824	Schizophrenia	0.942	0.732
Obstructive sleep apnea	0.793	0.096	Neuroblastoma	0.931	0.113	Parkinson disease	0.826	0.636
Amyotrophic lateral sclerosis	0.667	0.081	Dravet syndrome	0.898	0.109	Alcohol dependence	0.779	0.611
Pick disease	0.663	0.081	Parkinson disease	0.774	0.094	Psychosis	0.757	0.624
Age-related macular degeneration	0.625	0.076	Experimental autoimmune encephalomyelitis	0.694	0.084	Alzheimer disease	0.668	0.428
Carotid atherosclerosis	0.525	0.064	Schizophrenia	0.693	0.092	Insomnia	0.648	0.097
Glioblastoma multiforme	0.493	0.069	Autism	0.690	0.083	Autism	0.631	0.624
Temporal arteritis	0.464	0.056	Cerebral amyloid angiopathy	0.689	0.361	Prolactin-producing pituitary gland adenoma	0.613	0.083
Astrocytoma	0.438	0.055	Brain ischemia	0.607	0.073	Glioblastoma	0.608	0.073
Glioblastoma	0.435	0.053	Glioblastoma	0.513	0.062	Attention deficit hyperactivity disorder	0.572	0.658
Sporadic amyotrophic lateral sclerosis	0.425	0.052	Familial Alzheimer disease	0.455	0.055	Experimental autoimmune encephalomyelitis	0.488	0.059
Lewy body dementia	0.365	0.044	Huntington disease	0.419	0.051	Lewy body dementia	0.425	0.051
Polymyositis	0.312	0.038	Nervous system disease	0.331	0.040	Conduct disorder	0.419	0.556
Cerebral amyloid angiopathy	0.305	0.037	Stroke	0.317	0.392	Huntington disease	0.417	0.393
Dermatomyositis	0.277	0.034	Age-related macular degeneration	0.291	0.035	Post-traumatic stress disorder	0.384	0.585
Glioma	0.238	0.029	Amyotrophic lateral sclerosis	0.289	0.050	Catalepsy	0.377	0.045
Schizophrenia	0.237	0.377	Fragile X syndrome	0.268	0.032	Dyslexia	0.364	0.044
Multiple sclerosis	0.221	0.027	Neurodegenerative disease	0.264	0.032	Cocaine dependence	0.330	0.469
Cognitive disorder	0.218	0.027	Tauopathy	0.228	0.027	Fabry disease	0.305	0.0371
Relapsing-remitting multiple sclerosis	0.213	0.026	Brain injury	0.226	0.027	Migraine disorder	0.282	0.590

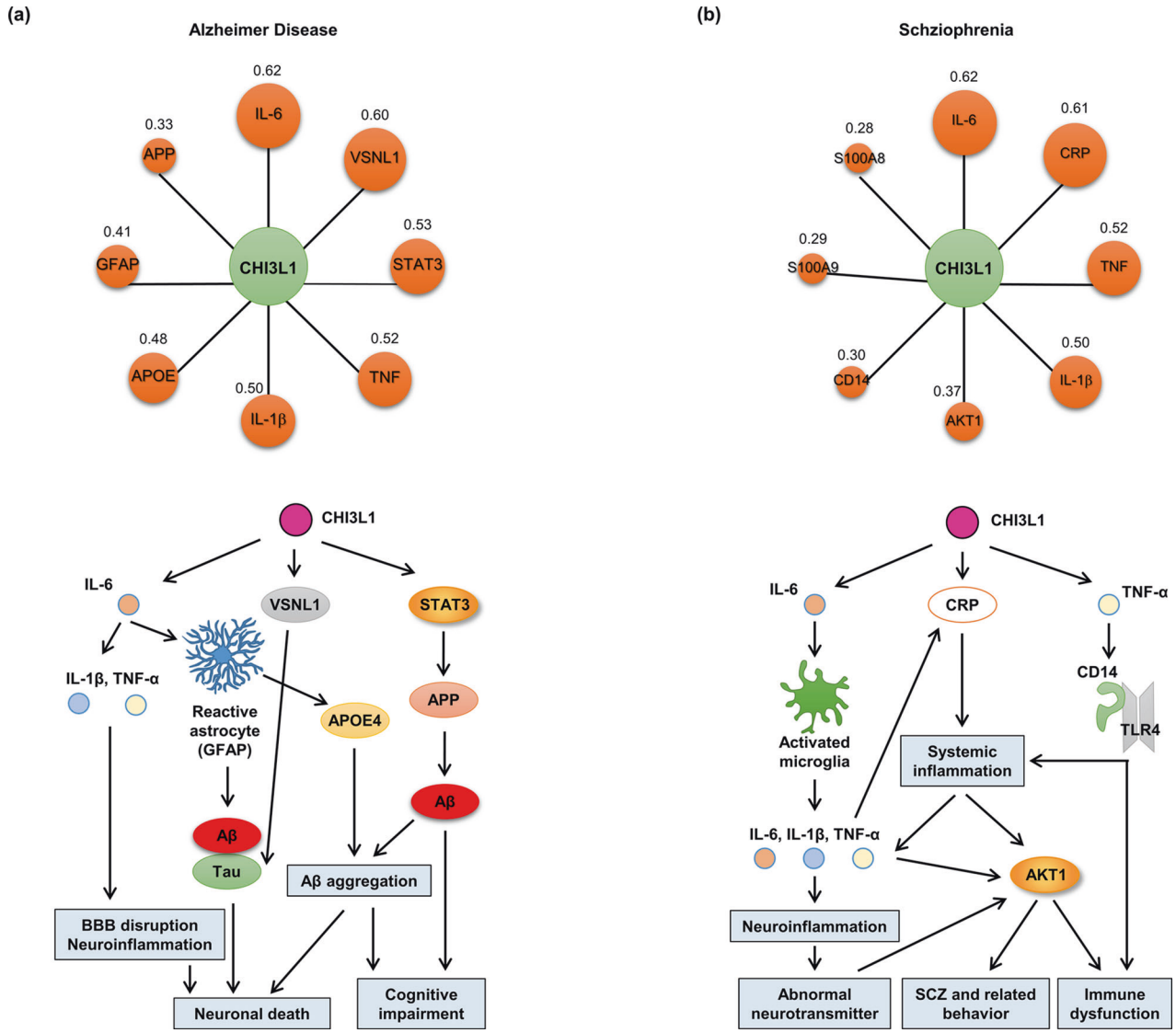

Fig. 6 The interaction network between CHI3L1 and its target proteins and the roles of CHI3L1 in signaling pathways for the development of neurological diseases. a Alzheimer's disease. Upper panel: The circle sizes are determined based on the score. The values in the circle symbols are the scores determined by STRING analysis. Lower panel: CHI3L1 regulates IL-6, inducing an increase in IL-1β and TNF-α. This pathway leads to the disruption of the blood–brain barrier (BBB) and triggers neuroinflammation, ultimately resulting in neuronal death. IL-6 activates astrocytes, and reactive astrocytes (with increased GFAP) induce Aβ aggregation and Tau phosphorylation. They can also induce Aβ aggregation through the ApoE4 pathway, ultimately leading to neuronal death and cognitive impairment. CHI3L1 downregulates VSNL1 and increases Tau phosphorylation. CHI3L1 activates STAT3 and increases APP expression in neuronal cells, resulting in Aβ aggregation and cognitive impairment. **b** Schizophrenia. Upper panel: The circle sizes are determined based on the score. The values in the circle symbols are the scores determined by STRING analysis. Lower panel: CHI3L1 regulates IL-6, inducing microglial activation. Activated microglia express IL-6, IL-1β, and TNF-α, which leads to neuroinflammation and triggers abnormal neurotransmitter signaling. Ultimately, this process results in schizophrenia and related behavioral and immune dysfunction. The association score between CHI3L1 and CRP is high, indicating a strong correlation. However, the specific interaction between these two factors has not yet been identified. CRP is increased by inflammatory cytokines (IL-6, IL-1β, and TNF-α) and induces systemic inflammation, leading to immune dysfunction via the AKT1 pathway. CHI3L1 regulates TNF-α and induces immune dysfunction through the CD14-TLR4 pathway.

knowledge about the role of CHI3L1 in CVD and discusses its relationship with target genes.

Hypertension

CHI3L1 was reported to be associated with the risk of hypertension. Several studies have demonstrated that CHI3L1 is associated with the severity of hypertension, insulin-resistant hypertension, portal hypertension, and several heart disease-related hypertension[152–157]. A population-based nested case–control study, a cohort study of 700 prehypertensive Chinese subjects and a 1:1 matched prospective cohort study with 507 Chinese subjects showed that CHI3L1 could be a biomarker for predicting the risk of hypertension[158]. A single-center prospective observational cohort study with 327 hypertensive patients showed elevated serum CHI3L1 levels[159]. Elevated circulating CHI3L1 levels are associated with hypertension in obstructive sleep apnea patients and cirrhotic portal hypertension (CPH), indicating the potential of CHI3L1 as a specific biomarker for hypertension[155,160]. CHI3L1 may serve as a diagnostic biomarker for systemic sclerosis with pulmonary arterial hypertension and pulmonary hypertension associated with bronchopulmonary dysplasia[152,156,161–165].

Although several recent clinical studies have shown that the range of CHI3L1 concentrations in healthy adults is approximately 30–60 ng/mL[130,133,134,143,148,149], to date, there is no precisely established normal range for the circulating levels of CHI3L1 in healthy individuals. With 121 chronic heart failure (CHF) patients, including hypertensive heart disease patients and 19 age-matched healthy controls, a study showed that serum CHI3L1 levels were significantly elevated in patients with hypertensive heart disease (205 ± 15 ng/mL) compared with healthy controls (163 ± 77 ng/mL)[166]. Ma et al. demonstrated that the serum CHI3L1 results of each group were as follows: nonmicroalbuminuric group, 61.63 ± 18.58 ng/ml; microalbuminuric group, 98.78 ± 19.83 ng/ml; and healthy controls, 37.85 ± 14.12 ng/ml[167]. In a study with 60 essential hypertension patients and 30 healthy subjects, serum CHI3L1 levels were significantly higher in the essential hypertension group than in the control group [51.7 (35.6–341.9) μg/L vs. 33.2 (23.3–167.3) μg/L]. These levels were also significantly higher in essential hypertension patients with metabolic syndrome than in essential hypertension patients without metabolic syndrome (152.3 μg/L vs. 94.2 μg/L). Thus, serum CHI3L1 levels might be used as a biomarker reflecting inflammation status in hypertensive patients.

Recent evidence has implicated CHI3L1 in patients with inflammatory diseases and cardiometabolic disorders, making it potentially useful to evaluate disease severity, prognosis and survival[152,168–171]. Using 40 age- and sex-matched dipper hypertensive patients and 40 nondipper hypertensive patients, it was found that nondippers had significantly increased epicardial adipose tissue (EAT) thickness and higher CHI3L1 and high-sensitivity CRP levels than dippers[172]. A study showed that bitransgenic mice that overexpressed human heme oxygenase-1, an anti-inflammatory gene, showed inhibited macrophage accumulation and activation, an induction of macrophage IL-10 expression, and the prevention of the development of hypoxia-induced pulmonary hypertension[173]. In a spontaneously hypertensive rat (SHR) animal model, it was identified that the gene expression levels of an inflammatory marker, CHI3L1, were higher in SHRs than in normotensive Wistar–Kyoto rats[174]. These studies suggest that neuroinflammation could be significantly associated with hypertension.

To determine whether CHI3L1 is actually a viable candidate therapeutic strategy as a potential drug target in CVD, we verified the association between CHI3L1 and CVD using the Open Targets Platform. As shown in Table 4, the text-mining score of CHI3L1 in hypertension was 0.854, which represented the highest association among the CVDs (Fig. 7a and Table 4). In turn, the text-mining scores of VCAM1 and ITGAX, which are widely studied and well-known genes in hypertension, were 0.706 and 0.149, respectively (Table 4). The overall association scores (0.104) were also highest among the CADs. In addition, the overall association scores with VCAM1 and ITGAX were also high (0.086 and 0.030). However, DisGeNET analysis showed that CHI3L1 was not closely related (Fig. 7b). Further studies regarding the drug target of CHI3L1 in hypertension are needed. STING analysis revealed that the following proteins were related to CHI3L1 in hypertension: VEGFA, IGF1, IL-13, IL-6, CRP, STAT3, TNF and CST2 (Fig. 8a upper panel). A detailed signaling pathway related to this is shown in Fig. 8a (lower panel).

Atherosclerotic vascular diseases

Serum CHI3L1 levels have been found to be elevated in atherosclerotic vascular diseases. In a study that included 89 patients with symptomatic or asymptomatic carotid atherosclerosis and 20 age-matched healthy controls, the serum CHI3L1 levels were significantly elevated in the patients with carotid atherosclerosis, particularly in symptomatic patients (114.9 ± 10.5 ng/mL), compared with the healthy controls (49.1 ± 3.2 ng/mL)[137]. Interestingly, a recent large-scale study of 302 patients with asymptomatic carotid atherosclerosis based on blood chemistry analysis combined with noninvasive cervical color Doppler ultrasound imaging revealed that high CHI3L1 levels (237.08 ± 67.24 ng/mL) were an independent risk factor for unstable plaque formation[138]. Furthermore, the serum CHI3L1 levels were significantly higher in patients with large-artery atherosclerosis (LLA) stroke than in healthy controls, suggesting that CHI3L1 is an independent prognostic biomarker for the prediction of the clinical outcomes of LLA stroke[146]. One study even suggested that the serum level of CHI3L1 may be a useful initial screening biomarker or subsequent risk indicator for atherosclerosis in children and adolescents[144]. These studies demonstrated that CHI3L1 is closely related to both the early and late phases of atherosclerotic vascular diseases.

A significant positive correlation was reported between CHI3L1 levels and the progression or severity of coronary artery disease. The serum CHI3L1 levels were markedly higher in patients with angiographic lesion progression (123.93 ± 74.01 ng/mL) compared with those without it (71.05 ± 55.14 ng/mL) and were significantly correlated with a change in lumen diameter stenosis and the cumulative coronary obstruction score, suggesting that an increased serum level of CHI3L1 is independently associated with lesion progression in patients with CAD[136]. Even higher levels of CHI3L1 have been documented in patients suffering from peripheral artery disease (PAD). A study involving 612 health-screened subjects found elevated circulating CHI3L1 levels in 86 subjects (406.7 ± 286.6 ng/mL) with PAD, and this finding was positively correlated with inflammatory biomarkers, suggesting that the level of circulating CHI3L1 is significantly associated with the risk of peripheral artery disease[139]. In addition, a recent study that included 365 PAD patients reported that baseline serum CHI3L1 levels were significantly associated with long-term cardiovascular mortality and all-cause mortality[140].

Atherosclerotic vascular disease is a chronic inflammatory disorder that affects the blood vessel walls, eventually leading to complete obstruction of the blood flow, myocardial infarction, ischemic stroke, and PAD[175,176]. The vascular endothelium is composed of a monolayer of endothelial cells (ECs) that line the lumen of the blood vessels and has emerged as a key regulator of vascular physiological roles, including tight junction function, vascular tone regulation, and cell adhesion and secretion[177,178]. The initiation of atherogenesis is accompanied by EC dysfunction, including vascular inflammation and infiltration, and the stimulating phenotypic change in vascular smooth muscle cells (VSMCs) that is involved in the early pathogenesis of the disease[179,180]. The involvement of CHI3L1 in inflammatory conditions and vascular processes implies that CHI3L1 plays an atherogenic role in endothelial dysfunction[181,182]. A recent study demonstrated that CHI3L1 induces endothelial inflammation and enhances platelet-derived growth factor (PDGF)-induced VSMC migration and proliferation[94]. Another study reported that CHI3L1 ameliorates LPS-induced atherosclerotic responses via PPARδ-mediated suppression of inflammation and endoplasmic reticulum stress and apoptosis, as studied using HUVECs and THP-1 cells[183]. Although the role of CHI3L1 in the pathogenesis of atherosclerotic vascular disease remains understudied, recent research findings suggest that targeting CHI3L1 may provide a novel therapeutic strategy for atherosclerosis.

As shown in Table 4, the text-mining scores of CHI3L1 in coronary artery disease, peripheral arterial disease, carotid atherosclerosis, and atherosclerosis were 0.842, 0.750, 0.525, and 0.511, respectively (Fig. 7a and Table 4). The text-mining scores of VCAM1, which is a widely studied and well-known gene in CVD, in atherosclerosis, cardiovascular disease, endothelial dysfunction, dilated cardiomyopathy, were 0.876, 0.851, 0.799, and 0.627, respectively. The text-mining scores of ITGAX, another well-known gene in CVD, atherosclerosis, Behcet's syndrome, coronary artery disease, and atrial fibrillation, were 0.798, 0.236, 0.148, and 0.146,

Table 4. Text mining score and overall association score of cardiovascular diseases associated with CHI3L1, VCAM1, and ITGAX on the Open Targets Platform.

CHI3L1-cardiovascular diseases			VCAM1-cardiovascular diseases			ITGAX-cardiovascular diseases		
Name	**Text Mining**	**Overall Association Score**	**Name**	**Text Mining**	**Overall Association Score**	**Name**	**Text Mining**	**Overall Association Score**
Hypertension	0.854	0.104	Atherosclerosis	0.876	0.106	Atherosclerosis	0.798	0.097
Coronary artery disease	0.842	0.102	Cardiovascular disease	0.851	0.104	Behcet's syndrome	0.236	0.029
Peripheral arterial disease	0.750	0.091	Endothelial dysfunction	0.799	0.097	Hypertension	0.149	0.030
Cardiovascular disease	0.707	0.086	Hypertension	0.706	0.086	Coronary artery disease	0.148	0.018
Atrial fibrillation	0.678	0.082	Dilated cardiomyopathy	0.627	0.076	Atrial fibrillation	0.146	0.018
Acute coronary syndrome	0.627	0.076	Duchenne muscular dystrophy	0.602	0.075	Mucocutaneous lymph node syndrome	0.122	0.015
Coronary stenosis	0.626	0.076	Arteriosclerosis	0.538	0.065	Atrial heart septal defect	0.076	0.009
Portal hypertension	0.608	0.074	Stroke	0.533	0.065	Vasculitis	0.065	0.008
Carotid atherosclerosis	0.525	0.064	Coronary artery disease	0.512	0.062	Myocarditis	0.064	0.008
Myocardial Ischemia	0.522	0.063	Vasculitis	0.341	0.042	Carotid atherosclerosis	0.061	0.007
Atherosclerosis	0.511	0.062	Heart failure	0.321	0.039	Abdominal Aortic Aneurysm	0.061	0.007
Temporal arteritis	0.464	0.056	Mucocutaneous lymph node syndrome	0.292	0.035	Congestive heart failure	0.061	0.007
Endothelial dysfunction	0.456	0.055	Systemic scleroderma	0.289	0.035	Arteritis	0.055	0.007
Cerebral amyloid angiopathy	0.305	0.037	Acute coronary syndrome	0.245	0.030	Cardiovascular disease	0.053	0.024
Systemic scleroderma	0.276	0.034	Rheumatic heart disease	0.230	0.028	Systemic scleroderma	0.041	0.005
Acute myocardial infarction	0.249	0.030	Atrial fibrillation	0.229	0.028	Thromboangiitis obliterans	0.036	0.004
Congestive heart failure	0.193	0.023	Pulmonary arterial hypertension	0.212	0.026	Aortic aneurysm	0.035	0.004
Idiopathic pulmonary arterial hypertension	0.188	0.023	Myocardial Ischemia	0.211	0.026	Acute myocardial infarction	0.031	0.004
Diabetic macular edema	0.182	0.022	Acute myocardial infarction	0.197	0.024	Thrombotic disease	0.030	0.004
Vascular dementia	0.155	0.019	Myocardial infarction	0.193	0.023	Coronary atherosclerosis	0.030	0.004

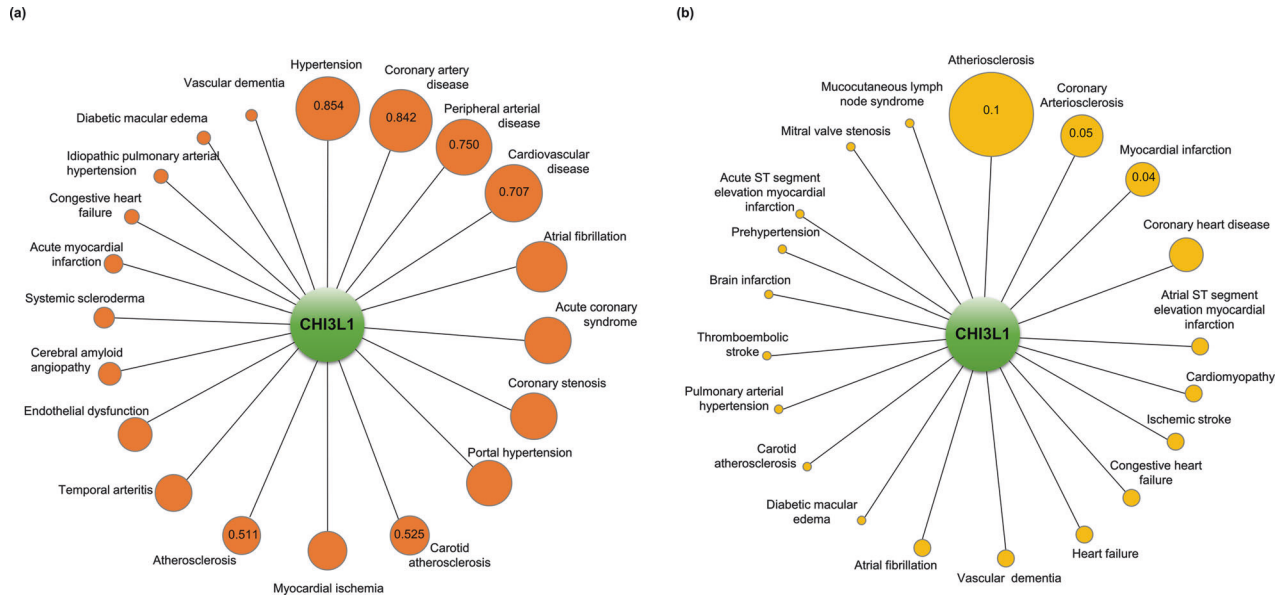

Fig. 7 The relationship between CHI3L1 and cardiovascular diseases. a The circle sizes are determined based on the text-mining score. The values in the circle symbols are the text-mining scores determined via Open Targets Platform analysis. **b** The circle sizes are determined based on the gda score. The values in the circle symbols are the gda scores determined via DisGeNET analysis.

respectively (Table 4). The overall association scores of CHI3L1 in coronary artery disease, peripheral arterial disease, carotid atherosclerosis, and atherosclerosis were 0.102, 0.091, 0.064, and 0.062, respectively, which are similar to the overall association scores of VCAM1 and ITGAX (Table 4). Moreover, DisGeNET analysis showed that arteriosclerosis had the highest association with CHI3L1 among CVDs, with a gda score of 0.1 (Fig. 7b). These data indicate that CHI3L1 is highly associated with atherosclerotic vascular diseases. STING analysis revealed that the following proteins were related to CHI3L1 in CVD: VEGFA, CCL2, HMOX1, Vesicle Associated Membrane Protein 8 (VAMP8), Caveolin 1 (CAV1), IL-6, Superoxide dismutase 2 (SOD2), and MMP-3 (Fig. 8b upper panel). The lower panel of Fig. 8b depicts the signaling pathway connecting CHI3L1 and its target proteins in atherogenesis. Overall, the association between CHI3L1 and these target proteins in CVD suggests that CHI3L1 plays a critical role in CVD, including atherosclerosis, and that targeting CHI3L1 may be a promising therapeutic approach for atherosclerotic vascular disease.

INVOLVEMENT OF CHI3L1 IN AUTOIMMUNE DISEASES

The development of other inflammatory diseases, such as rheumatoid arthritis (RA) and atopy, also involves the expression of CHI3L1. RA is an autoimmune disease that induces chronic inflammation of the joints. Several studies have suggested that CHI3L1 is a candidate autoantigen for inducing an autoimmune response in RA[184–189]. For example, patients with RA exhibited high levels of circulating CHI3L1, with high concentrations in synovial cells[190,191]. Moreover, cells that positively stained for major histocompatibility complex/human cartilage CHI3L1 complexes were observed in 61.5% of inflamed RA synovial samples compared with only 3.0% of the control samples in a specific and independent manner; therefore, CHI3L1 may be useful as a histological marker for the immunopathological diagnosis of RA[192].

Articular chondrocytes, synovial cells, infiltrated macrophages, and neutrophils can produce CHI3L1 in RA-affected joints. In RA, levels of proinflammatory mediators (MMP-3, IL-6, IFN-γ, and TNF-α) correlate with CHI3L1, and anti-rheumatic factor therapy reduces CHI3L1 levels in patients[193–196]. The treatment of cartilage explants from young bovine stifle joints with IL-1β and TNF-α increased the release of CHI3L1 in association with an innate immune and stress response by chondrocytes, which may play a role in the host defense against pathogens or may protect cells against stress-induced damage[197]. In addition, miR-24 reduced the osteoblast apoptosis, abnormal bone formation, and mineralization induced by *Staphylococcus aureus* by inhibiting the expression of CHI3L1[198]. In turn, CHI3L1 was detected in RA synovial fluid and tissue from patients with arthritis, and the synovial fluid of three out of 10 patients with spondylarthritis exhibited endogenous CHI3L1 expression[186]. In a serum analysis of 25 patients with RA, we found that CHI3L1 levels in patients with RA were significantly higher than the normal level, and the elevated levels did not deviate among the patients. We also found that the receiver operating characteristic curve of CHI3L1 yielded an AUC value of 0.955, which is slightly lower than the AUC values of the US FDA-recommended RA diagnostic factors, i.e., CRP (0.988) and cyclic citrullinated peptide (CCP, 0.995), but slightly higher than that of rheumatoid factor (0.865).

There are a few reports of CHI3L1 as a target for the treatment of atopy. In fact, the serum levels of CHI3L1 were found to be significantly increased in patients with atopy compared with healthy controls[199]. A recent study indicated that CHI3L1 KO reduced allergic skin inflammation through the inhibition of Th2-mediated inflammation and M2 macrophage activation[102]. Moreover, the g.-247C/T polymorphism located in the *CHI3L1* promoter region is associated with the risk of atopy in Korean children[200]. Previously, we found that suppressing CHI3L1 alleviated atopic dermatitis-like skin inflammation by inhibiting NF-κB-mediated ITGA5 expression in CHI3L1 knockout mice[201]. In addition, treatment with a CHI3L1 siRNA reduced the levels of these inflammatory cytokines in TNF-α/IFN-γ-treated cells. Additionally, the administration of a commercially available anti-CHI3L1 antibody significantly alleviated atopic symptoms, reducing atopy-related cytokines and inflammatory cell recruitment. The AUC value for CHI3L1 (0.932) was significantly higher than that for IL-4 (0.650), IL-13 (0.785), and IL-1β (0.790) in the serum analysis of 20 atopy patients. DUPIXENT@ is the first FDA-approved biologic therapy targeting IL-4Rα, thereby inhibiting IL-4 and IL-13 signaling and reducing type 2 inflammation. Finally, we found that the CHI3L1-inhibiting Compound K284-6111 completely

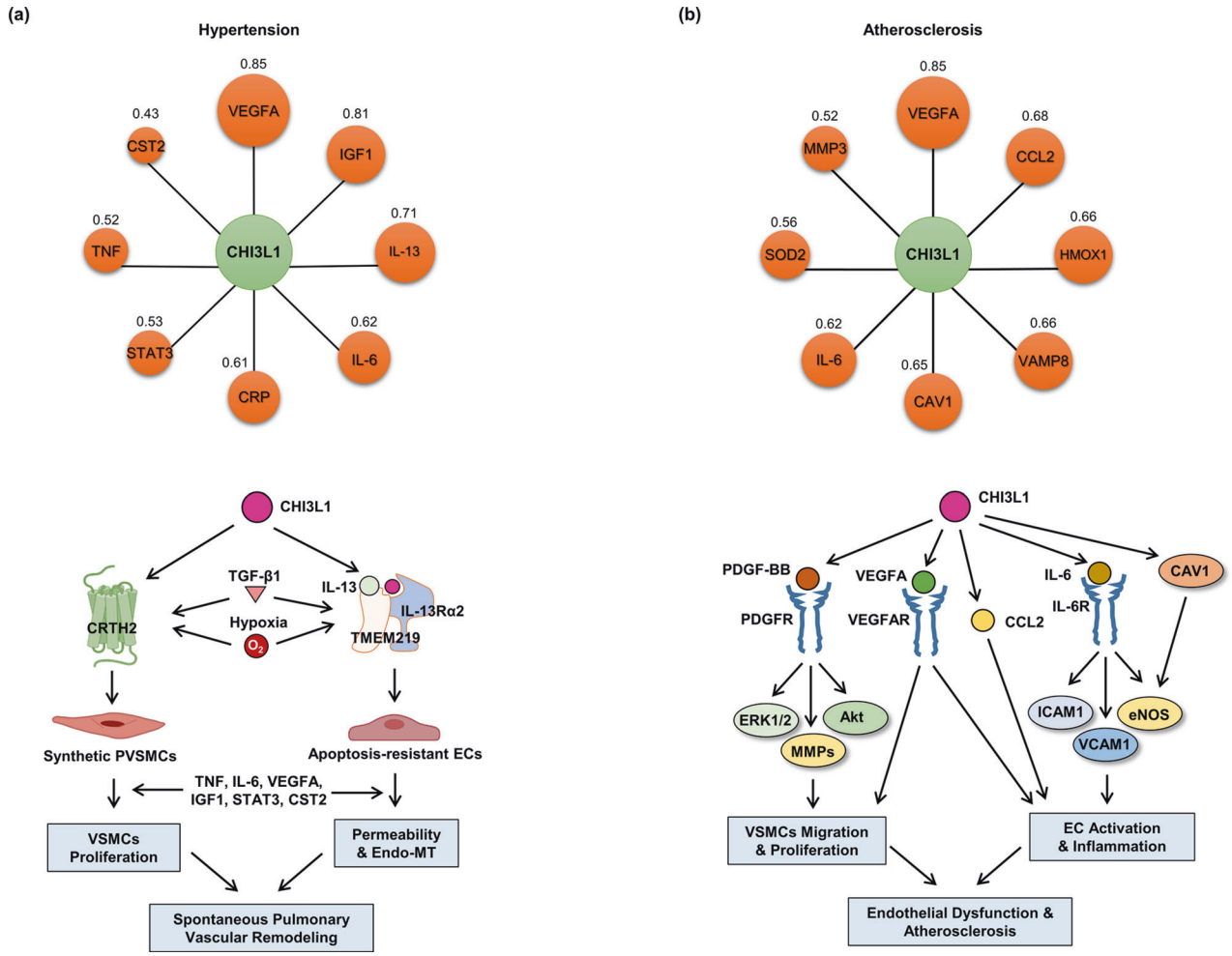

Fig. 8 The interaction network between CHI3L1 and its target proteins and the roles of CHI3L1 in signaling pathways for the development of cardiovascular diseases. a Hypertension. Upper panel: The circle sizes are determined based on the score. The values in the circle symbols are the scores determined by STRING analysis. Lower panel**:** In the development of hypertension, CHI3L1 stimulates pulmonary artery vascular smooth muscle proliferation through interaction with CRTH2, a G protein-coupled receptor. CHI3L1 binds with IL-13Rα2/TMEM219 and mediates anti-apoptotic effects in pulmonary arterial endothelial cell death through synergy with TGF-ß1 and hypoxia, promoting endothelial permeability and endo-MT transition. This causes spontaneous pulmonary vascular remodeling and hypertension. **b** Atherosclerosis. Upper panel: The circle sizes are determined based on the score. The values in the circle symbols are the scores determined by STRING analysis. Lower panel**:** In atherogenesis, CHI3L1 induces endothelial activation and inflammation through synergy with IL-6 and increases VEGFA and CCL2 levels. CHI3L1 potentiates PDGF-BB-induced vascular smooth muscle cell migration and proliferation and probably elevates the VEGFA signaling pathway. As a result, endothelial dysfunction and the onset of atherosclerosis are induced.

reduced atopy skin inflammation[202]. These findings suggest that CHI3L1 plays a role in the development of RA and atopy and is a good candidate therapeutic target for these inflammatory diseases.

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AUTHOR CONTRIBUTIONS

J.E.Y. and I.J.Y. performed the literature search and collected the information. S.B.H., J.Y., B.K., Y.J.Y., Y.S.L. and T.H.K. critically revised the manuscript. D.J.S. and J.T.H. supervised the entire project. J.E.Y., I.J.Y., D.J.S. and J.T.H. wrote the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Dong Ju Son or Jin Tae Hong.