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Review Articles

CHI3L1: From Inflammation to Cancer — A Molecular Hub in Multisystem Diseases and Novel Target for Precision Medicine

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Abstract

Chitinase-3-like protein 1 (CHI3L1) is a secreted glycoprotein critically involved in inflammation, tissue remodeling, and immune regulation. It plays a key role in the pathogenesis of numerous systemic diseases spanning the respiratory, cardiovascular, neurological, digestive, endocrine, immune, musculoskeletal, and reproductive systems. This review aims to systematically summarize recent advances in understanding the molecular mechanisms of CHI3L1 in disease progression and its functional roles across different organ systems. We highlight its emerging utility as a promising biomarker for early diagnosis and disease monitoring, as well as a novel therapeutic target. With ongoing mechanistic insights and improved detection methods, CHI3L1 holds significant potential to advance precision medicine for a wide spectrum of inflammatory and malignant conditions.

Keywords: CHI3L1; atherosclerosis; asthma; human physiological systems; triple-negative breast cancer; rheumatoid arthritis

1. Introduction

Chitinase-3-like protein 1 (CHI3L1) is a 40 kDa glycoprotein that belongs to the chitinase family but lacks enzymatic hydrolase activity toward chitin [1]. Secreted by diverse cell types, CHI3L1 is a pivotal mediator of tissue remodeling and inflammatory processes [2]. The protein's distinctive (β/α)8 TIM barrel structure is considered fundamental to its biological functions [1]. Mechanistic investigations have established that CHI3L1 elicits its physiological effects primarily via specific binding to the interleukin-13 receptor subunit alpha-2 (IL-13Rα2) [3]. Accumulating evidence underscores its significant pathophysiological implications across multiple organ systems, including the neurological, cardiovascular, respiratory, and immune systems. This review systematically synthesizes contemporary advances in understanding the multifaceted roles of CHI3L1 in multisystem diseases, with a specific focus on its molecular mechanisms in disease pathogenesis and progression. Furthermore, we critically evaluate its potential clinical utility as a dual-purpose diagnostic biomarker and therapeutic target.

2. Research Advances on CHI3L1 in Respiratory Diseases

Within the respiratory system, CHI3L1 functions as a critical regulatory factor in the pathogenesis of various conditions, including asthma, interstitial pneumonia, pulmonary fibrosis, and lung cancer. Clinical investigations have demonstrated significantly elevated serum CHI3L1 levels in patients

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with asthma and chronic obstructive pulmonary disease (COPD), which exhibit positive correlations with inflammatory markers such as IL-8, C-reactive protein, and IL-6. Mechanistic studies identify type 1, type 2, and type 17 interleukin-18 as among the most potent inducers of CHI3L1 expression [4]. Acting as a key modulator of Th2 inflammatory responses, CHI3L1 regulates M2 macrophage polarization and influences apoptosis in both Th2 cells and macrophages [1]. Recent in vivo studies have confirmed that specific knockout of CHI3L1 in murine lung tissues and bone marrow-derived dendritic cells (DCs) significantly attenuates airway hyperresponsiveness induced by respiratory syncytial virus (RSV) infection, indicating that CHI3L1 contributes to RSV-induced immune dysregulation by modulating DC function [5]. Furthermore, CHI3L1 promotes bronchial smooth muscle cell proliferation and migration through a protease-activated receptor-2 (PAR-2)-dependent mechanism[1]. Genetic association analyses indicate that the CHI3L1 single nucleotide polymorphism rs12141494 is significantly correlated with persistent airflow limitation and severe asthma [3]. Notably, CHI3L1 in pediatric asthma patients predominantly affects small airways, exhibiting a distinct functional pattern from that observed in adults [6]. In cystic fibrosis (CF) patients, serum CHI3L1 levels increase markedly with disease progression, although the precise molecular pathways underlying this phenomenon require further elucidation [3].

Pulmonary fibrosis is a chronic, progressive condition characterized by scarring of the lung parenchyma, clinically manifesting as dyspnea, non-productive cough, and, in severe cases, progression to respiratory failure. Accumulating evidence indicates a significant inverse correlation between CHI3L1 expression levels and clinical prognosis in patients with pulmonary fibrosis [7]. Although conventional understanding posits that CHI3L1 drives fibrotic progression primarily through M2 macrophage polarization [8], recent investigations have revealed a more complex mechanistic landscape. In bleomycin-induced murine models of pulmonary fibrosis, CHI3L1 interacts with CRTH2 (the Th2 cell chemoattractant receptor) both in vivo and in vitro, collaboratively amplifying fibrotic development [8][9]. Furthermore, CHI3L1 contributes substantially to vascular remodeling processes in pulmonary fibrogenesis [9], suggesting its involvement extends beyond inflammatory modulation to direct structural alterations in pulmonary architecture.

As a leading cause of cancer-related mortality worldwide, lung carcinogenesis is closely associated with CHI3L1 expression. Molecular biological investigations have established that CHI3L1 overexpression facilitates lung cancer cell proliferation and invasion by inducing autophagy via activation of the JNK signaling pathway [10]. Concurrently, intracellular CHI3L1 enhances cancer cell migratory capacity by modulating p53 expression and function [11]. The CHI3L1 inhibitor K284-6111 substantiates CHI3L1's role in tumor progression by effectively suppressing lung cancer metastasis and neoplastic growth through inhibition of the AKT signaling pathway. Clinical data analyses consistently demonstrate a positive correlation between CHI3L1 expression levels and lung cancer progression, alongside an inverse relationship with patient survival rates [10]. Therapeutically, humanized anti-CHI3L1 antibodies show promising efficacy by suppressing M2 macrophage polarization through STAT6-dependent phospholipase D signaling pathways, thereby significantly inhibiting tumor growth and metastasis [12]. Recent investigations further indicate that the natural compound efractenoid F concentration-dependently suppresses lung cancer cell growth by directly binding to CHI3L1 and subsequently blocking AKT signaling transduction [10].

Beyond the pathologies previously discussed, CHI3L1 demonstrates significant pathophysiological involvement in other respiratory disorders. In COVID-19, serum CHI3L1 levels have been established as a quantitative biomarker reflecting the degree of pulmonary injury [13]. Among rhinitis patients, elevated CHI3L1 concentrations are correlated with nasal mucosal remodeling, the subtyping of chronic rhinosinusitis with nasal polyps, and the

risk of postoperative recurrence [14]. Furthermore, circulating CHI3L1 levels have emerged as a reliable biomarker for evaluating disease severity in obstructive sleep apnea, demonstrating considerable potential for clinical stratification and management [15]. (Figure1)

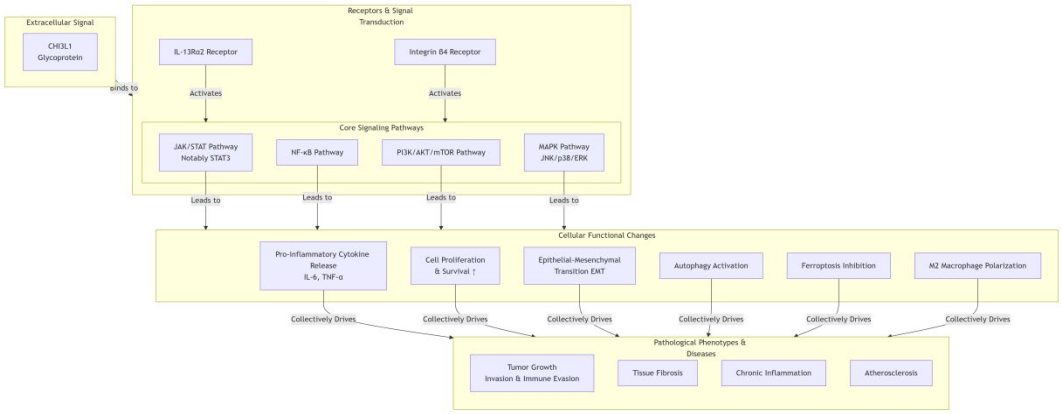

Figure 1：Flowchart of CHI3L1 Core Signaling Pathways and Their Roles in Disease

3. Research Advances on CHI3L1 in Cardiovascular Diseases

CHI3L1 has emerged as a significant biomarker in cardiovascular pathology, demonstrating potential as a therapeutic target across multiple conditions, including atherosclerosis, coronary artery disease, hypertension, and ischemic stroke [1]. In atherosclerosis, CHI3L1 contributes to disease progression through several distinct mechanisms:

(1) Plaque Stability Modulation: By upregulating Aven and subsequently suppressing caspase-9 activation, CHI3L1 inhibits programmed cell removal (PrCR) of macrophages, thereby accelerating atherosclerotic progression [16].

(2) Lesion Development Promotion: CHI3L1 activates inflammatory cells, promotes extracellular matrix degradation, and induces endothelial injury [1].

(3) Macrophage Function Regulation: Through downregulation of the ATF2-MFGE8 signaling axis, CHI3L1 impairs plaque stabilization [17].

(4) Diagnostic Utility: CHI3L1 expression levels exhibit a significant positive correlation with arterial plaque burden [16].

(5) Protective Regulation: By suppressing PPARδ-mediated endoplasmic reticulum stress and inflammatory responses, CHI3L1 attenuates LPS-induced atherosclerosis [3].

In coronary artery disease (CAD), serum CHI3L1 levels exhibit a positive correlation with disease severity, underscoring its potential utility as an auxiliary diagnostic marker [3]. A particularly significant finding is that acute coronary syndrome (ACS) accounts for approximately 90% of cardiovascular events in younger populations, with serum CHI3L1 levels remaining markedly elevated throughout the clinical course [18][19]. Prognostic studies further establish that CHI3L1 concentrations are strongly associated with both clinical outcomes and six-month survival rates in patients with ST-segment elevation myocardial infarction [20]. Moreover, CHI3L1 serves as an independent predictor of major adverse cardiovascular events following percutaneous coronary intervention (PCI) in myocardial infarction patients [21]. Recent mechanistic investigations have elucidated that neutrophil-derived CHI3L1 significantly exacerbates post-myocardial infarction cardiac dysfunction and inflammatory responses [22].

Hypertension, a condition affecting approximately 1.28 billion individuals globally, represents a predominant risk factor for cardiovascular morbidity. Genetic association studies indicate that the CHI3L1 polymorphism rs10399805 is significantly correlated with hypertension susceptibility in male populations; individuals with GA/AA genotypes demonstrate a 34% elevated disease risk compared

to GG genotype carriers [23]. Furthermore, elevated CHI3L1 levels are associated with a two-fold increase in venous thromboembolism risk [20]. Mechanistic investigations have elucidated that CHI3L1 promotes myocardial fibrosis by modulating the TUG1/miR-495-3p/ETS1 signaling axis. In patients with atrial fibrillation, CHI3L1 is specifically overexpressed within epicardial adipose tissue, where its expression—modulated by body mass index—correlates positively with the degree of atrial fibrosis [3].

In other cardiovascular pathologies, CHI3L1 constitutes an integral component of a core biomarker panel—alongside SPP1, IGFBP7, F11R, and Plaur—for the diagnosis and prognostic stratification of dilated cardiomyopathy with heart failure (DCM-HF) [24]. Furthermore, the serial assessment of serum CHI3L1 levels provides a valuable metric for monitoring therapeutic responsiveness in the management of heart failure [1].

4. Research Advances on CHI3L1 in Neurological Disorders

CHI3L1, predominantly secreted by activated astrocytes, fulfills a critical pathophysiological role in neurological diseases. Clinical studies indicate that CHI3L1 expression levels are positively correlated with biomarkers of neurodegeneration and synaptic injury, while elevated plasma concentrations serve as a predictive indicator for cognitive impairment and dementia risk [3]. Functioning as a regulatory hub for glial phagocytic activity, cerebrospinal fluid CHI3L1 levels demonstrate significant associations with both clinical progression and pathological severity in Alzheimer's disease (AD). Investigations in animal models confirm that CHI3L1 knockout reduces β-amyloid (Aβ) deposition and markedly improves spatial memory function [25]. In APP/PS1 transgenic mouse models, CHI3L1 deficiency not only diminishes amyloid plaque burden but also significantly upregulates expression of the microglial lysosomal marker CD68 surrounding plaques [3]. Mechanistically, CHI3L1 deficiency attenuates Aβ-induced memory deficits and neuroinflammation by suppressing the NF-κB and ERK-PTX3 signaling pathways, consequently reducing microglial release of inflammatory factors and M1 polarization [3]. Notably, CHI3L1 expression in the cerebellar tissue of AD patients exhibits distinct age- and sex-dependent variations. Furthermore, CHI3L1 contributes to Parkinson's disease pathology by sustaining a chronic neuroinflammatory microenvironment that promotes dopaminergic neuron loss, and emerging evidence also implicates CHI3L1 in the pathogenesis of amyotrophic lateral sclerosis [26].

As a pivotal regulator of neuroinflammation, CHI3L1 holds considerable value for clinical differential diagnosis. In multiple sclerosis (MS), the cerebrospinal fluid CHI3L1/CHI3L2 ratio serves as a discriminative biomarker for distinguishing progressive MS from the relapsing-remitting phenotype [3]. In neuromyelitis optica, CHI3L1 levels correlate with disease activity via a mechanism involving the suppression of the β-catenin signaling pathway following CHI3L1's engagement with Th2 cell surface chemotactic receptors [27]. Therapeutic targeting of this pathway facilitates neural repair and ameliorates cognitive impairment. Recent investigations demonstrate that the small-molecule compound K284-6111 exerts dual regulatory effects through concurrent CHI3L1 inhibition and ERK-dependent PTX3 pathway activation, significantly attenuating neuroinflammatory responses and improving memory dysfunction [28].

In primary brain tumors, CHI3L1 fulfills a central pathogenic role in glioblastoma, which constitutes approximately 80% of malignant brain neoplasms. Its tumor-promoting mechanisms primarily involve: (1) Binding to the ACTN4/NFKB1 complex to activate the NF-κB signaling pathway [29]; (2) Upregulating M2 tumor-associated macrophage infiltration via the PI3K/AKT/mTOR signaling axis [30]; (3) Enhancing transcriptional activity through interaction with the coiled-coil domain (CCD) of STAT3 [31][32]. Targeted therapeutic investigations demonstrate that inhibition of CHI3L1—for instance, through disruption of the CHI3L1-STAT3 interaction by hygromycin B—elicits substantial anti-

tumor effects, revealing considerable potential for clinical translation [32].

5. Research Advances on CHI3L1 in Digestive System Diseases

The liver, the largest parenchymal organ in the human body, executes a multitude of complex physiological functions. Research indicates that CHI3L1 is pivotal in hepatic inflammatory responses and fibrotic progression by regulating the activation, recruitment, and infiltration of immune cells. Mechanistic studies reveal that CHI3L1 sustains a persistent inflammatory microenvironment in the liver through NLRP3 inflammasome-mediated neutrophil accumulation [33]. Notably, CHI3L1 exhibits context-dependent regulatory functions across different liver injury models: in concanavalin A-induced hepatic injury, elevated CHI3L1 levels exacerbate liver damage, whereas CHI3L1 deficiency paradoxically aggravates tissue injury in acetaminophen-induced hepatotoxicity [1]. Emerging therapeutic strategies demonstrate that 5-aminolevulinate, through its interaction with CHI3L1, significantly ameliorates mitochondrial dysfunction and hepatocellular damage following hepatic ischemia-reperfusion injury, suggesting novel interventional targets for clinical management [34]. Clinical translational studies confirm that serum CHI3L1 levels serve as both diagnostic markers and independent risk factors for liver fibrosis in HBeAg-negative chronic hepatitis B patients [35]. In non-alcoholic fatty liver disease (NAFLD), macrophage-derived CHI3L1 has been established as a reliable biomarker for monitoring fibrotic progression [34].

Within the intestinal microenvironment, CHI3L1 significantly influences the colonization of Gram-negative bacteria in the mucosal layer, with its expression upregulated in response to gut microbiota stimulation [36]. Clinical observations reveal markedly elevated intestinal CHI3L1 expression in patients with celiac disease, a phenomenon potentially associated with gut dysbiosis, although the precise molecular mechanisms require further elucidation. Furthermore, CHI3L1 exacerbates intestinal inflammatory responses through interactions with bacterial chitin-binding proteins [34]. Emerging immunological research has identified CHI3L1 as a novel neutrophil autoantigen in inflammatory bowel disease, where the detection of CHI3L1-specific IgA and secretory IgA may provide a novel approach for serological diagnosis [37].

In the pathogenesis of gastrointestinal malignancies, the mechanistic role of CHI3L1 has attracted growing scientific interest. Recently developed fully human monoclonal CHI3L1 antibodies (nAbs) demonstrate multifaceted antitumor efficacy in animal models by suppressing oncogenic signaling pathways, attenuating cellular proliferation and migration, reducing fibrosis and angiogenesis within pancreatic and colorectal tumor microenvironments, and simultaneously restoring the antitumor functionality of immune cells [38]. Clinicopathological studies confirm the potential of CHI3L1 as a diagnostic biomarker for early gastric cancer, with its elevated expression significantly correlated with increased serum alpha-fetoprotein levels and advanced TNM stage III-IV progression [39]. In hepatocellular carcinoma, CHI3L1 expression exhibits a significant inverse relationship with patient survival rates. Molecular immunology research reveals that in gallbladder cancer, CHI3L1 promotes tumor immune evasion by dysregulating PD-L1 expression—enhancing its presentation on tumor cells while suppressing cytotoxic T-cell function [40]. Notably, CHI3L1 confers radiotherapeutic resistance in colorectal cancer by inhibiting ferroptosis via the p53/SLC7A11 axis, thereby facilitating tumor proliferation and metastasis and diminishing treatment efficacy [41]. Additionally, specific pathogenic bacteria such as Porphyromonas gingivalis accelerate colorectal carcinogenesis and immune escape by upregulating CHI3L1 expression in invariant natural killer T cells (iNKT) [42].

6. Research Advances on CHI3L1 in Urinary System Diseases

Clinical investigations have established that elevated CHI3L1 expression is significantly associated with various inflammatory conditions of the

kidneys and bladder. In renal pathology, urinary CHI3L1 serves not only as a sensitive biomarker for acute kidney injury but also correlates with the development of disease complications. Notably, CHI3L1 expression demonstrates progressive elevation with advancing stages of chronic kidney disease (CKD) and shows a specific association with cardiovascular complications exclusively in male patients with end-stage renal disease (ESRD) [43]. Furthermore, the detection of urinary CHI3L1 may offer a novel parameter for assessing donor kidney suitability in transplantation [3]. Regarding bladder disorders, studies indicate CHI3L1 involvement in the pathophysiology of inflammatory conditions such as bladder pain syndrome and interstitial cystitis, potentially through mechanisms that promote detrusor muscle fibrosis. This finding suggests that serum or urinary CHI3L1 levels could emerge as non-invasive diagnostic markers for bladder fibrosis [3]. Recent experimental evidence confirms that genetic suppression of CHI3L1 expression significantly impairs the proliferative capacity, metastatic potential, and gemcitabine resistance of bladder cancer cells [44]. Further analyses reveal substantial correlations between CHI3L1 expression levels and immune infiltration characteristics within the bladder cancer microenvironment [45]. Clinicopathological studies specifically highlight that elevated CHI3L1 derived from stromal cells—but not from epithelial cells—serves as an independent prognostic indicator in urothelial carcinoma, showing a positive correlation with the incidence of lymph node metastasis [45].

7. Research Advances on CHI3L1 in Endocrine System Diseases

CHI3L1 exerts significant pathophysiological influence across multiple endocrine disorders, including diabetes mellitus, obesity, insulin resistance, and thyroid diseases. In systemic glucose regulation, CHI3L1 modulates glucose homeostasis through dual complementary mechanisms: activation of AMP-activated protein kinase (AMPK) and concomitant regulation of the PI3K/AKT signaling pathway, collectively contributing to elevated plasma glucose concentrations [20]. Clinical studies demonstrate that increased serum CHI3L1 levels in diabetic patients are positively correlated with albuminuria severity [3]. During the progression of diabetic nephropathy, sustained hyperglycemia induces tubular injury, proteinuria, and progressive renal functional decline. CHI3L1 levels exhibit significant associations with both the rate of renal function deterioration and all-cause mortality in diabetic populations [46].

Diabetic foot syndrome, a severe complication of diabetes, is characterized by pathological features including hyperglycemia-induced peripheral neuropathy, microcirculatory impairment, and infection-delayed wound healing. Mechanistic investigations reveal that CHI3L1 contributes to impaired wound repair by modulating fibroblast proliferation and migratory capacity [47]. In cardiovascular complications, CHI3L1 serves not only as a diagnostic biomarker and therapeutic target for diabetic vasculopathy but also predicts coronary artery disease risk in asymptomatic type 2 diabetes patients [1][3]. Genetic association studies confirm that the CHI3L1 rs946263 polymorphism is correlated with susceptibility to both insulin resistance and atherosclerosis in type 2 diabetic populations [3].

Recent mechanistic insights demonstrate that within the diabetic vascular calcification microenvironment, lactylation modification at histone H3 lysine 18 in vascular smooth muscle cells (VSMCs) upregulates CHI3L1 expression, which subsequently activates the IL-13–IL-13Rα2–JAK1–STAT3 signaling cascade, thereby promoting the progression of arterial calcification [48].

In the context of obesity, CHI3L1 demonstrates distinctive metabolic regulatory characteristics, exhibiting a significant inverse correlation with high-density lipoprotein cholesterol (HDL-C) levels and a positive association with serum triglyceride concentrations [20]. Investigations of thyroid disorders reveal that CHI3L1 expression levels correlate significantly with clinical severity in Graves' disease. Notably, fine-needle aspiration specimens from patients with thyroid carcinoma display substantially

elevated CHI3L1 mRNA expression compared to those from benign nodules, with this elevation independently associated with an increased risk of disease recurrence [49]. Functional experiments confirm that specific silencing of CHI3L1 reverses the pro-tumorigenic effects induced by miR-6867-5p suppression [50].

8. Research Advances on CHI3L1 in Immune-Mediated Diseases

In rheumatoid arthritis (RA), CHI3L1 is predominantly secreted by synovial cells, chondrocytes, and infiltrating neutrophils within affected joints, resulting in serum concentrations that are significantly elevated compared to healthy controls. Clinical investigations confirm that serum CHI3L1 levels in RA patients correlate closely with multiple disease activity parameters, including rheumatoid factor titers, inflammatory markers (C-reactive protein and erythrocyte sedimentation rate), proinflammatory cytokines (such as IL-6 and TNF-α), and immune biomarkers associated with joint destruction[3]. Mechanistic studies demonstrate that CHI3L1 promotes T-cell proliferation and activates the FAK/PI3K/Akt signaling pathway, thereby stimulating osteoblasts to produce IL-18 while suppressing miR-590-3p expression. This cascade enhances endothelial progenitor cell-mediated pathological angiogenesis and exacerbates articular inflammation. Notably, CHI3L1 levels are significantly associated with the development and progression of RA-associated interstitial lung disease (ILD), achieving 76.67% sensitivity as a predictive biomarker for this complication [51].

Psoriasis, an immune-mediated chronic inflammatory disorder, manifests clinically as well-demarcated erythematous plaques with silvery scales. Multiple clinical studies have demonstrated significantly elevated serum CHI3L1 levels in psoriatic patients, with particularly pronounced increases observed in generalized pustular psoriasis, suggesting its potential utility as a novel biomarker for assessing disease severity [52]. In patients with systemic lupus erythematosus (SLE) and Behçet's disease, while no direct correlation has been established between serum CHI3L1 levels and disease activity, SLE patients exhibit significantly attenuated T-cell immune responses to CHI3L1 stimulation [52].

Kawasaki disease, a systemic vasculitis predominantly affecting children, is characterized by significantly elevated serum CHI3L1 levels during the acute phase, with the magnitude of increase demonstrating a positive linear correlation with disease incidence. Notably, CHI3L1 tertile levels exhibit exceptional predictive value across all Kawasaki disease subtypes (sensitivity: 0.938), establishing this protein as a novel serological indicator for clinical diagnosis [53].

9. Research Advances on CHI3L1 in Musculoskeletal Disorders

Osteoporosis, a metabolic bone disorder characterized by reduced bone mineral density and deterioration of bone microarchitecture, substantially increases fracture risk. Investigations reveal significantly elevated serum CHI3L1 levels in osteoporotic patients, with underlying molecular mechanisms potentially involving METTL3-mediated transcriptional regulation of early growth response 1 (EGR1), which promotes osteoclast differentiation through the METTL3/m6A/CHI3L1 signaling axis [3]. Furthermore, CHI3L1 interacts with bone morphogenetic protein receptor type 1a (BMPRIa), upregulating its membrane expression and thereby potentiating bone morphogenetic protein 2 (BMP2) signaling to stimulate osteoblast differentiation [54]. Notably, CHI3L1 also increases osteoprotegerin (OPG) expression via non-canonical BMP2 signaling in osteoblasts, consequently inhibiting osteoclastogenesis [3]. Recent research elucidates that IL-13 receptor α2 (IL13Rα2), which functions as a key receptor for CHI3L1, enhances RANKL-induced MAPK/AKT signaling pathway activation to facilitate osteoclast differentiation [55].

In inflammatory musculoskeletal disorders, CHI3L1 fulfills a significant pathological role. Clinical investigations identify CHI3L1 as a valuable biomarker for the early diagnosis of spondyloarthritis; notably, TNF-α inhibitor treatment

substantially reduces serum CHI3L1 levels, confirming its regulatory function in disease progression [3]. In osteomyelitis, a condition primarily caused by Staphylococcus aureus infection, CHI3L1 mediates disease exacerbation through activation of the p38/MAPK and Smad signaling pathways, which drive abnormal osteoblast proliferation and differentiation. Inhibition of CHI3L1 expression effectively attenuates the pathogenicity of S. aureus [3]. Multiple studies suggest CHI3L1 as a potential biomarker for osteoarthritis severity, with diagnostic accuracy enhanced when combined with ultrasonographic and other imaging modalities [3]. Regarding osteoarthritis pathogenesis, CHI3L1 is predominantly secreted by chondrocytes under the regulation of proinflammatory cytokines such as IL-6. Animal studies confirm that in post-traumatic osteoarthritis murine models, Nrf2 alleviates inflammatory responses and ameliorates disease progression through the negative regulation of CHI3L1 expression [3].

10. Research Advances on CHI3L1 in Reproductive System Disorders

In female reproductive malignancies, CHI3L1 contributes to the pathogenesis and progression of endometrial, breast, ovarian, and cervical cancers, whereas in male reproductive tumors its expression is significantly associated solely with prostate cancer. Molecular mechanistic investigations confirm that RNA interference-mediated silencing of the CHI3L1 gene in THP-1 cells substantially suppresses inflammatory cytokine expression, impairs endometrial cancer cell invasion and migration capabilities, and inhibits in vitro angiogenesis [1][3]. In high-grade serous ovarian carcinoma, genetic knockout experiments reveal that ablation of the CHI3L1 receptor integrin β4 effectively blocks CHI3L1-induced cancer cell proliferation, migration, and invasion. Clinicopathological analyses further establish that co-overexpression of CHI3L1 and integrin β4 constitutes an independent risk factor for unfavorable prognosis in serous ovarian cancer patients [3]. Recent immunological research demonstrates that CHI3L1 is aberrantly overexpressed in triple-negative breast cancer, where it upregulates cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression via MAF transcription factors, consequently impairing CD8+ T-cell function and facilitating tumor immune evasion [3][56]. Genetic association studies indicate that CHI3L1 single nucleotide polymorphisms (rs6691378 and rs10399805) are significantly correlated with the clinicopathological progression of prostate cancer in Taiwanese populations [57].(Figure2)

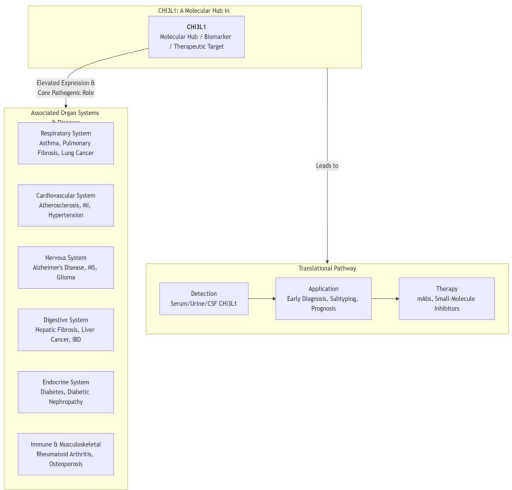

Figure 2：CHI3L1 as a Molecular Hub in Multisystem Diseases

11. Discussion and Summary

Chitinase-3-like protein 1 (CHI3L1) has emerged as a pivotal regulatory molecule across multiple pathological systems, with its core functions centered on the modulation of inflammatory responses, oncogenesis, cardiovascular pathologies, and

neurodegenerative processes. Within tumor biology, CHI3L1 exerts dual roles in therapeutic response and immune evasion through its regulation of the tumor microenvironment. Recent investigations integrating single-cell transcriptomics, genomic profiling, and clinical data have established a novel classification system for glioma vascular phenotypes: Type A (highly vascularized with activated stroma but limited lymphocyte infiltration), Type B (moderate vascularization with high lymphocyte density), and Type C (low vascularization with sparse immune cell infiltration) [58]. This taxonomy provides a crucial framework for developing personalized therapeutic strategies.

Substantial advancements in detection methodologies have markedly improved the sensitivity and specificity of CHI3L1 measurements, thereby solidifying its promise as a biomarker for early disease screening and dynamic monitoring. The delineation of CHI3L1-involved signal transduction pathways—notably the IL-13Rα2/STAT3 and NF-κB networks—will further clarify its molecular mechanisms and uncover novel avenues for targeted therapeutic development. The integration of multi-omics data, spanning genomics, proteomics, and metabolomics, will facilitate a deeper exploration of CHI3L1's collaborative regulatory networks with other biomolecules. This integrated approach is critical for constructing more precise disease risk prediction models and treatment response evaluation systems. Collectively, the existing evidence underscores the significant translational value of CHI3L1 in precision medicine, and continued mechanistic investigation is poised to yield transformative advances in diagnostics and therapeutics across a spectrum of diseases.

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