Review

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The chitinases as biomarkers in immune-mediate diseases

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Abstract: The role of chitinases has been focused as potential biomarkers in a wide number of inflammatory diseases, in monitoring active disease state, and predicting prognosis and response to therapies. The main chitinases, CHIT1 and YKL-40, are derived from 18 glycosyl hydrolases macrophage activation and play important roles in defense against chitin-containing pathogens and in food processing. Moreover, chitinases may have organ- as well as cell-specific effects in the context of infectious diseases and inflammatory disorders and able to induce tissue remodelling. The CHIT1 measurement is an easy, reproducible, reliable, and cost-effective affordable assay. The clinical use of CHIT1 for the screening of lysosomal storage disorders is quite practical, when proper cut-off values are determined for each laboratory. The potential of CHIT1 and chitinases has not been fully explored yet and future studies will produce many surprising discoveries in the immunology and allergology fields of research. However, since the presence of a *null CHIT1* gene in a subpopulation would be responsible of false-negative values, the assay should be completed with the other markers such ACE and, if necessary, by genetic analysis when CHIT1 is unexpected low.

Keywords: biomarker; chitin; chitinases; macrophage activation.

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Functions and role of chitinases

This review has been developed by searching in the PubMed database literature from 2000 until July 2022 using the search terms “chitinase” or “chitotriosidase” and/or “immune-mediate and/or biomarker”. Only articles published in English were reviewed. Both articles dealing with chitinases in crops/plants or showing human population studies with low statistical power were excluded. The final reference list was obtained mainly based on originality and relevance to the topic of the review.

Chitinases are omnipresent throughout nature and are produced by a wide range of organisms from bacteria to higher plants and animals in which they play important roles [1–3] (Figure 1). These enzymes are responsible for the biological degradation of chitin, an essential structural component of different fungi, nematodes, arthropods, insects, and crustaceans. Chitin is composed of linear β-1,4-linked *N*-acetylglucosamine (NAG) units forming chains that are packed into crystals with intervening amorphous regions. Chitinases participate in nutrition, parasitism, morphogenesis and immunity. Many organisms, produce also inactive chitinase-like lectins lacking enzymatic activity and involved in several regulatory functions [4].

Chitinases appear to be key regulators of medium-size chitin fragments production responsible for immunomodulation switching on the same chitinases; they would also help to limit local injury by fostering the more complete degradation of chitin.

Based on sequence homologies, chitinases fall into two groups: families 18 and 19 of glycosyl hydrolases [5]. Members of family 18 employ a substrate-assisted reaction mechanism [6, 7], whereas those of family 19 adopt a lysozyme-like fold-and-reaction mechanism [8], suggesting an independent evolution of these families.

18 Glycosyl hydroxylases are a class of ancient, conserved evolutionary enzymes [5] whose size range from 20 kDa to about 90 kDa [9]. They were isolated from the stomachs of certain mammals, including humans [10] but

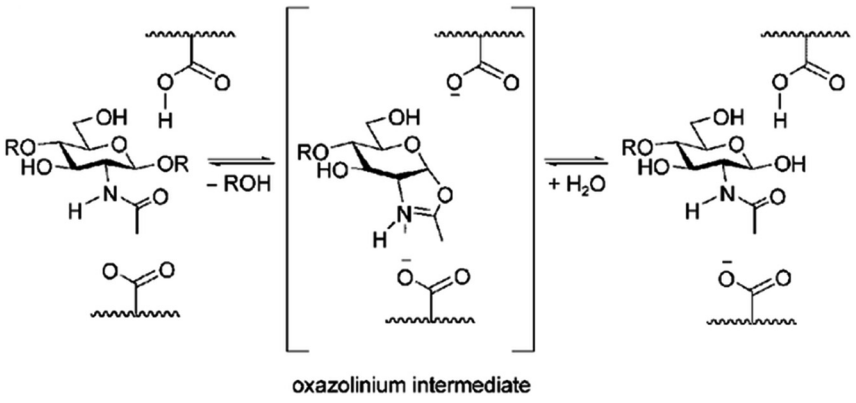

Figure 1: Mechanism of chitin hydrolysis by family 18 glycosyl hydrolases. Figure reprinted from MacDonald et al. [13], with permission from Wiley. Copyright © 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

enzyme activity can be detected in human blood [11] and cartilage [12].

The generally accepted mechanism of action of family 18 involves neighboring group participation (substrate-assisted reaction mechanism [6, 7]) with the formation of an oxazolinium intermediate within the one subsite (Figure 1, from MacDonald et al. [13]). Inhibitors of chitinases mimicking the oxazolinium intermediate moiety [7, 14], have several potential applications, including use as insecticides and fungicides [15], the prevention of human malaria-parasite transmission [16], and the treatment of human asthma [17] as well as the sexually transmitted disease human trichomoniasis [18].

As the main component of the fungal cell wall and insect shell playing an important role in resisting crop diseases and insect pests, chitin is the ideal target of chitinase when the latter is used as an antifungal agent [19].

Human chitotriosidases

Although humans do not synthesize chitin of their own, their genome expresses certain chitinases whose physiological role has been attracting the interest of researchers [20, 21] even in the biotechnology area of research [22] (Figure 2).

Human chitotriosidase (CHIT1) is a glycosyl hydrolase belonging to the family of chitinases. It is expressed in macrophages at very low levels in healthy persons [23] but is highly expressed in activated macrophages and different monocyte-derived cell lines such as Kupffer cells and osteoclasts. A striking increase of plasma CHIT1 activity is observed in serum from Gaucher's disease (GD) type I patients, and in many other inherited and acquired conditions, sharing macrophage activation [24, 25].

CHIT1 and acidic mammalian chitinase (AMCase) [25, 26] along with several chitinase-like proteins (CLPs) have been described. While bacteria degrade chitin for energy supply, human chitinases play a protective role against chitin-containing pathogens through their capability to degrade chitin present in the cell wall of pathogens; therefore, human chitinases are considered parts of the innate immune system possibly through activation of signaling pathways involved in inflammation [27, 28].

The recombinant CHIT1 inhibits the hyphal growth of fungi [29]. Elevated CHIT1 is associated with several potent growth factors able to induce tissue remodeling [reviewed in 30]. Furthermore, atherosclerotic plaque formation and subsequent thrombosis were enhanced by CHIT1 produced by macrophages [31, 32]. All together these lines of evidence suggest that CHIT1 may have organ- as well as cell-specific effects in the context of infectious diseases and inflammatory disorders.

An ancient gene duplication event likely occurred very early in tetrapod evolution and led to the specialization of two active chitinases, CHIT1 and AMCase (Figure 3). Then, more recent duplications followed by loss-of-enzymatic-function mutations, led to the subsequent evolution of chi-lectins (ChiLs) [33, 34] and CLPs molecules which lack enzymatic activity but can bind to chitin or chitooligosaccharides (e.g. the structurally related chitinase-like protein YKL-40) [4, 35]. Both these hydrolases, the "true-chitinases" CHIT1/AMCase [36, 37] and the "chitinase like protein" YKL-40 [38], are being evaluated as chemical mediators or biomarkers involved in inflammation-mediated diseases.

Chitin and the immune system

The immune system is a complex machinery involving many cells and cytokines able to produce an orchestrated response of the organism to non-self-antigens [39] (Figure 4).

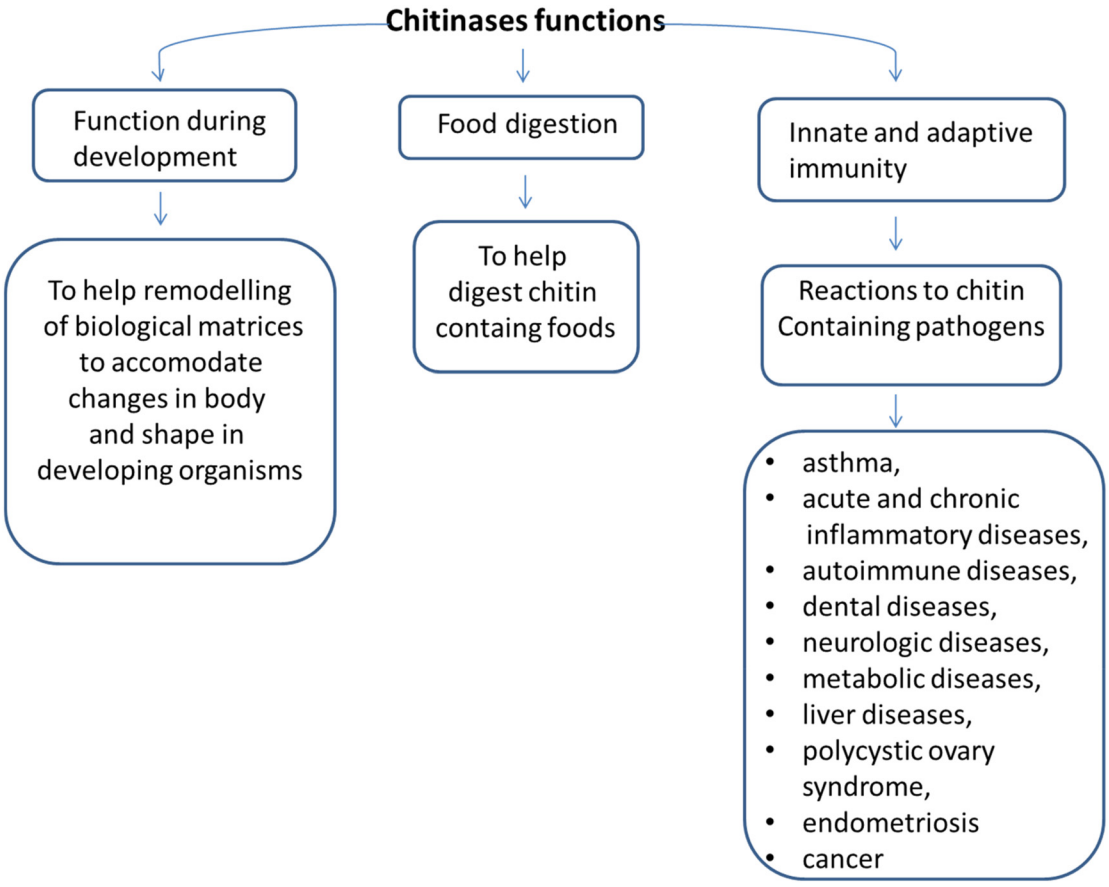

Figure 2: Chitinases proposed functions in organisms.

On the other side, the immune response needs to be finely controlled as it is an energy costly process that results also in damage to the host tissue. Therefore, a complete and rapid resolution of the immune response is an important part of its global efficacy. There is a range of immune cells including Tregs, express anti-inflammatory actions by IL-10 expression to suppress inflammatory process [40].

Amongst the substances with immunomodulatory effects, there is chitin, first identified in 1811 by the French scientist Henri Braconnot, who discovered an alkali resistant fraction during his studies of fungi. It is the polysaccharide most abundant in nature after cellulose, and it represents a structural component in the cell walls of fungi, in the exoskeleton of crustaceans [41], insects [42], and eggshells of nematodes [43]. Interestingly, chitin is also a common component of allergy-triggering antigens including those in shrimp, crab, cockroaches, and house dust mites [44–46]. Chitin and chitosan (a chitin deacetylated derivative) are potential targets for recognition by the mammalian immune system since mammalians lack such biopolymers naturally. Chitin is sensed primarily in the lungs or gut where it activates a variety of innate (eosinophils, macrophages) and adaptive immune cells (IL-4/IL-13 expressing T helper type-2 lymphocytes) [47]. Chitin induces cytokine production, leukocyte recruitment, and alternative macrophage activation [48]. The chitin-mediated response is size-dependent: only small chitin fragments of 40- to 70-μm size – but not large size chitin polymers such as those of chitin-containing pathogens that are biologically inert – can be sensed as "non-self" by the innate immune system. These chitin fragments have immunomodulatory effects, including the ability to recruit and activate innate immune cells and induce cytokine and chemokine production via a variety of cell surface receptors including macrophage mannose receptor, toll-like receptor 2 (TLR-2), and Dectin-1 [reviewed in 27].

Lee et al. [49] hypothesize that when chitin-containing pathogens (with inert large chitin polymers) enter a host, they trigger the innate anti-pathogen response mediated by oxidants and chitinases that in turn generate additional chitin proinflammatory 40–70 μm-size fragments. The latter serve as an "alarm signal" to induce and amplify

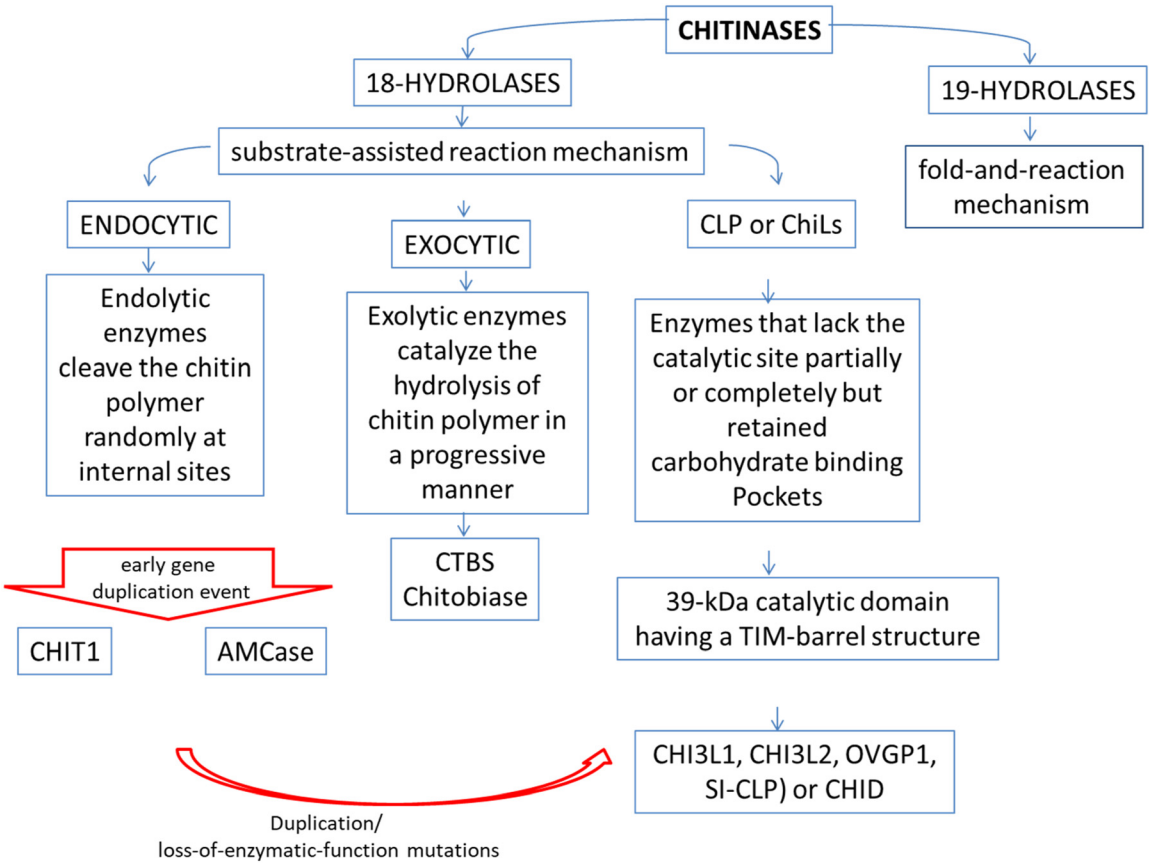

Figure 3: Chitinase classification. CLP, chitinase-like proteins; ChiLs, chi-lectins; CHI3L1, CHI3L2, chitinase-3-like 1, like 2; OVGP1, oviductin; SI-CLP, stabilin-1 interacting chitinase-like protein or CHID; AMCase, acidic mammalian chitinase (red arrows indicate proposed evolutionary events in the chitinase protein family).

local inflammation by activating pattern recognition receptors and pathways like NF-κB. These medium-size chitin fragments also regulate the intensity and chronicity of local inflammation by regulating local inflammatory cell apoptosis. The immune response machinery would be in motion to deal with the pathogen until smaller chitin fragments (<40 μm) would be generated by chitinases; these smaller chitin fragments appear able to induce molecules such as IL-10, able to control the local inflammatory response as a feedback mechanism.

In this hypothesis chitin degradation to different fragments size would initially maintain switched on immunomodulation and then triggers the end of it (Figure 5).

The chitinase activity assays

The chitinase CHIT1 activity assay in biological samples is relatively simple. A non-fluorescent substrate is cleaved by enzymatically active chitinase to produce a fluorescent product, which is then measured as an indirect marker of chitinase activity. The chitinases within the samples break down the substrate 4-methylumbelliferyl-D-*N*,*N*′-diacetylchitobiose present in the 1× McIlvain buffer. A fluorescent molecule 4-methylumbelliferyl is released. By measuring the total fluorescence of each well, an accurate measurement of the active chitinase in each sample can be obtained. Because the breakdown of chitin by CHIT1 is a hydrolytic reaction, the stop buffer, a mixture of 0.3 M glycine and NaOH (12.0 g/L at pH 10.6), ends the breakdown of chitin by creating an environment that is too basic for the enzyme to function [50].

Plasma analysis of YKL-40 is performed on EDTA-blood samples left on the blood cells at room temperature for less than 8 h because it is known that in EDTA plasma YKL-40 is only stable when samples are processed within this time. Then, the samples can be separated by centrifugation at 2000*g* for 10 min at room temperature and plasma EDTA samples stored in aliquots at −80 °C until analysis. Plasma levels of YKL-40 are determined in duplicates by a commercial two-site, sandwich-type enzyme-linked

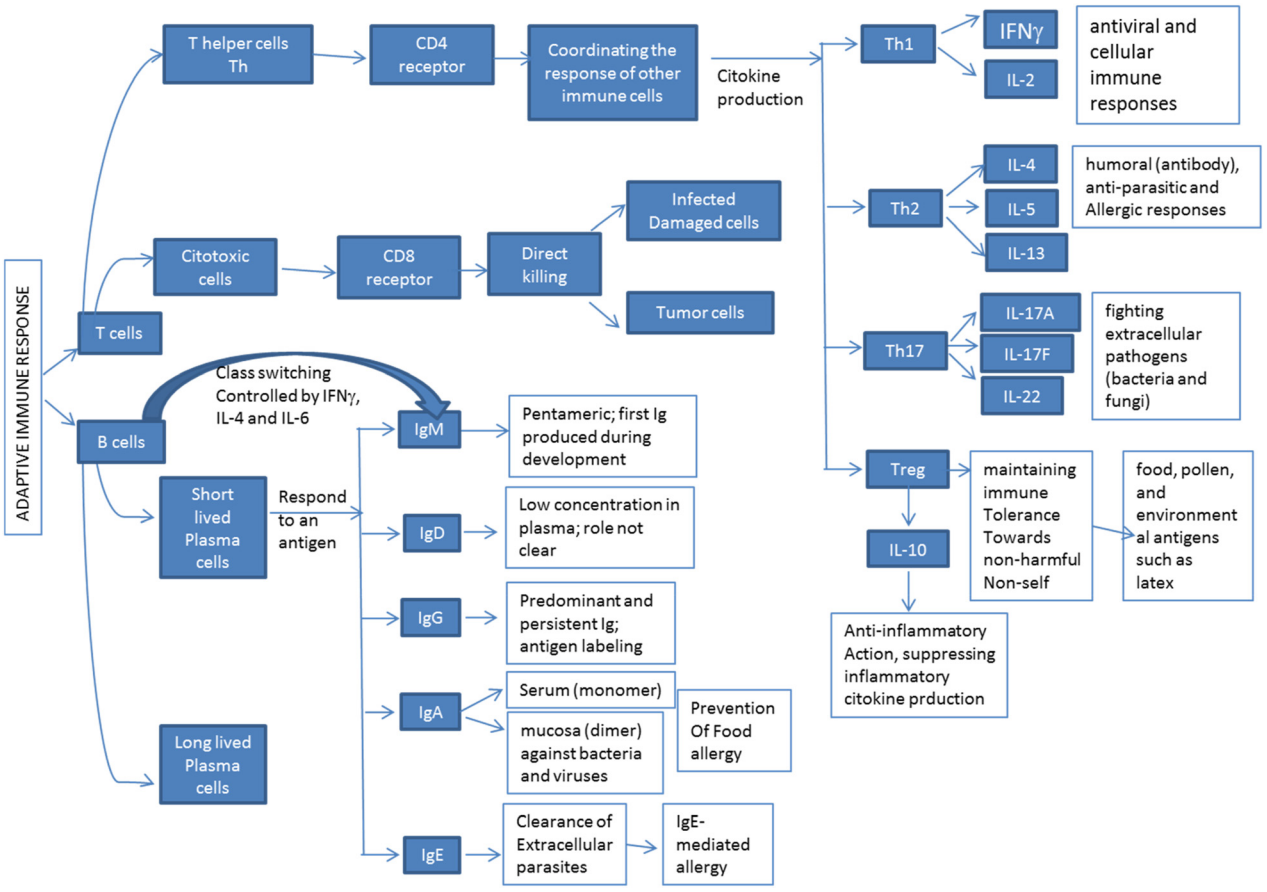

Figure 4: A simplified overview of the main cells mediated pathways set in motion in the adaptive immune response.

immunosorbent assay (Quidel, Santa Clara, CA, USA) using streptavidin coated microplate wells, a biotinylated- Fab monoclonal capture antibody, and an alkaline phosphatase-labeled polyclonal detection antibody. The detection limit is 20 µg/L. The intra-assay coefficient of variation (CV) is ≤ 5.0% and inter-assay CVs ≤ 10.2%. The samples are analyzed blinded to clinical parameters and study endpoint [51].

The chitinases as a potential markers of inflammation-mediated diseases

CHIT1 and YKL-40, are significantly higher in patients with certain bioimplants and these markers of monocyte/macrophage activation rose progressively as adverse reactions progress [52].

CHIT1 usability as a screening marker is limited by the evidence that the enzyme is a nonspecific marker of macrophage activation and is deficient in about 6–21% of Caucasians due to homozygosity of 24-bp duplication mutation at exon 10 of the *CHIT1* gene [53]. However, in non-deficient patients with an established diagnosis, CHIT1 has shown to be of great utility to monitor compliance and response to treatment especially when there is the involvement of inflammatory pathways [54, 55].

YKL-40 has a substantial role in acute and chronic infections and in cancer, where it is associated with a poor prognosis. Indeed, YKL-40 plays a role in relation to cell migration, reorganization and tissue remodelling during atherogenesis and seems to play a pivotal role in the differentiation of monocytes to activated macrophages in tissues characterized by inflammation. Together these data imply a significant role of YKL-40 in endothelial dysfunction and in the process of atherosclerosis [56].

Modic vertebral endplate changes (MC) represent an intense inflammatory status where CHI3L2 is found as marker of activation of host defense response and immunological pathways [57].

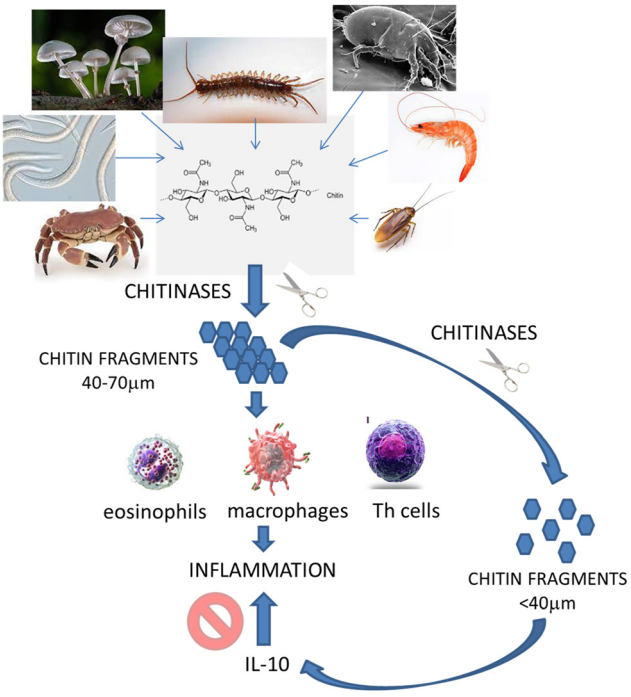

Figure 5: Roles of chitinases in response to chitin-bearing organisms (fungi, nematodes, crabs, cockroaches, shrimps, dermatophagoides) indicating that an efficacious complete immune response should involve control of the possible cellular and tissue damage caused by a maintained inflammatory process. Chitin degradation to different fragments size (blue hexagons: chitin monomers) would initially maintain switched on immunomodulation and then triggers the end of it through IL-10 release (see the text).

The chitinases in lysosomal storage diseases

CHIT1 has been demonstrated as an established or a candidate screening marker, severity marker, and/or therapeutic monitor for lysosomal storage diseases (LSDs) which are a group of 70 monogenic disorders caused by mutations in genes encoding lysosomal proteins, such as glycosidases, proteases, integral membrane proteins, transporters, enzyme modifiers, or activators. The consequence is a progressive accumulation of metabolic products inside lysosomes that ultimately leads to cell dysfunction and death [58] (Table 1).

CHIT1 is of clinical utility for both screening and monitoring the efficacy of therapy and severity in Gaucher Disease (GD) or β-glucocerebrosidase deficiency [59] and insphingolipidoses, such as Niemann Pick [60], GM1-gangliosidosis, and Krabbe's disease [61–63]. The use by CHIT1 as biomarker could investigate the progression of disease from GD to monoclonal gammopathy and to multiple myeloma [64, 65].

Fabry disease is an important an X-linked LSD caused by the deficiency of the lysosomal enzyme α-galactosidase A (AGA), resulting in glycosphingolipids accumulation in lysosomes of several cell types, as endothelial cells and podocytes [66]. Unlike of GD where CHIT1 has proven an extremely useful biomarker of pathophysiological processes in this disorder [67], in Fabry disease patients, lipid-laden macrophages seem to play a far less prominent role in the pathogenesis of the disease and consequently the value of plasma CHIT1 appears more limited for this condition [68].

CHIT1 represents a promising clinical biomarker and therapeutic monitor also for nephropathic cystinosis (NC). There are many lines of evidence that macrophages are activated by different types of crystals; cystine crystals have been observed in tissue macrophages of cystinotic patients [69]. Plasma CHIT1 activity was significantly elevated in cystinotic patients at diagnosis over age; it matched normal and renal controls and correlated with white blood cells (WBC) cystine assay [70] for treated patients above 2 years of age. Moreover, bone marrow cell transplantation [71] and hematopoietic stem cell gene therapy [72], are both lines of intervention proven successful in human NC patients. CHIT1 activity measurements represent a rapid and non-invasive method for routine follow-up of patient's response post-transplantation compared to the invasive estimation of cystine accumulation in tissue biopsies and cystine measuring in the donor's WBCs.

Plasma CHIT1 activity was increased in Krabbe disease patients where it ranged from 1.4 to 10.4 times the upper normal limit [73]. Krabbe disease is caused by the deficiency of β-galactocerebrosidase (GALC, E.C. 3.2.146) which impairs the degradation of galactocerebroside, a major myelin lipid, and of galactosylsphingosine or psychosine [74, 75], resulting in the formation of the characteristic multinucleated macrophages known as globoid cells. CHIT1 increased activity observed in Krabbe disease patients could reflect the psychosine-induced activation of peripheral immune cells [76, 77], strongly suggesting that assaying this enzyme activity is in the diagnosis/monitoring of Krabbe disease [61, 78].

CHIT1 activity was proposed as an useful biomarker in the screening of other LSDs such as Farber disease (FD), GM1 gangliosidosis, and Sialidosis type II [79]. Acid ceramidase deficiency in FD produces accumulation of ceramide resulting in the clinical manifestations. However, it could not be ruled out that elevation of CHIT1 in a FD patient could be secondary to intercurrent infection rather than a direct expression of the disease itself [80].

The genetic deficiency of the lysosomal enzyme β-galactosidase involved in the degradation of glycoproteins,

Table 1: Simplified list of the main LSD, the enzyme deficiency causing them, the accumulated material and the main clinical features observed.

Disease	Accumulated material	Enzyme deficiency	Heredity	Special features
Gaucher	Glucorebroside	Glucorebrosidase	RA[a]	Adult form: increased phosphatase acid, pathological fractures.
Niemann-Pick	Sphingomyelin	Sphingomyelinase	RA[a]	Pulmonary infiltrations, skin brownish, neuropathic form of childhood, blue-sea histocytes.
Metachromatic leukodystrophy	Galactocerebroside	Galactocerebrosidase	RA[a]	Increase in protein, early anomalies of the limb in walking childhood; peripheral neuropathy.
Fabry	Globotriaosylceramide	Alpha-galactosidase A	X-linked	Angiokeratoma, thrombosis, hypohidrosis
Fucosidosis	Fucose-containing glyolipids	Alpha-fucosidase	RA[a]	Coarse facies, increase in electrolytes of sweat, angiokeratoma in young people.
Farber	Ceramide	Ceramidase	RA[a]	Arthropathy, subcutaneous periarticular and visceral nodules (lipogranulomatosis)
Gangliosidosis Generalized	Ganglioside GM1	Beta-galactosidase	RA[a]	Coarse facies, macroglossia mucopolysaccharidurial; blindness in infancy
Tay-Sachs	Ganglioside GM2	Hexosaminidase A	RA[a]	Macrocephaly, hyperacusis in infancy
Sandhoff	Ganglioside GM2	Hexosaminidase A/B	RA[a]	Macrocephaly, hyperacusis, visceral histiocytosis

[a]RA, recessive autosomal; LSD, lysosomal storage disease.

glycolipids, and keratan sulfate cause the GM1 gangliosidosis, a neurodegenerative disorder where CHIT1 shows a tenfold greater enzyme activity in the infantile form compared to the late-infantile form [81].

Eventually, the deficiency of alpha-N-acetyl neuraminidase-1 (NEU1) is the cause of sialidosis. Increased plasma CHIT1 was observed only in the infantile form of the disease but not in the congenital form, suggesting that enzyme activity could be a supplementary biochemical marker that might be worth investigating in such patients [81].

The chitinases in infectious and parasitic diseases

There are many lines of evidence that CHIT1 or YKL-40 are useful markers for prognosis and therapeutic monitoring in different infectious diseases such as systemic fungal infections, tuberculosis, leprosy [34, 82] and malaria [83] (Table 2).

Mammalian chitinases are linked to airway infections, particularly fungal, where they are considered a key innate immune defense mechanism to pulmonary infection with *Cryptococcus*, *Aspergillus*, and *Candida* [84, 85].

In bronchiectasis patients, monitoring CHIT1 activity may improve risk stratification in appropriate bronchiectasis cohorts and allow better identification of those at high risk for fungal-associated consequences, which include disease exacerbations [86].

In Leprosy (Hansen's disease), CHIT1 activity was potentially useful in distinguishing multibacillary from paucibacillary leprosy and in monitoring response to corticosteroid therapy in erythema nodosum leprosum patients. CHIT1 activity correlated with levels of neopterin, another macrophage activation marker [87].

In Crimean-Congo hemorrhagic fever (CCHF) patients, relatively low CHIT1 enzyme activities may be a poor prognostic marker [88].

In lymphatic filariasis, CHIT1 was proposed to represent a marker in the screening of this disease. A polymorphism in the human *CHIT1* gene, which is highly expressed in phagocytic cells, was associated with susceptibility to filarial infection in a filarial-endemic region of South India. The evidence that the microfilarial sheath of filarial parasite contains chitin may explain the role of CHIT1 in modulating the immune response against complex pathogens, such as the filarial parasite [89].

In brucellosis serum neopterin and CHIT1 appeared high and decreased with therapy; further, of the two markers analyzed, CHIT1 seemed to be more valuable in reflecting the response of brucellosis patients to treatment [90].

Scrub typhus is characterized by elevated levels of monocyte/macrophage and endothelial related inflammatory markers among which YKL-40 may contribute to disease severity and clinical outcome [91].

In *Schistosoma haematobium* infected children, serum YKL-40 levels differed between infected and uninfected people before and after anti-helminthic treatment. The greatest difference occurred in the youngest age group, in keeping with the period when schistosome-related pathological processes were initiated [92].

Table 2: Chitinases and infectious and parasitic diseases. COPD, chronic obstructive pulmonary bronchitis disease.

Disease	Aetiology	Clinical features	Prognosis	References
Necrotizing soft-tissue infection	Fast Bacterial infection	Necrosis of soft tissues	YKL-40 predictor of 30-day mortality	[82]
Fungal	*C. Albicans*	Cystic fibrosis (CF)-associated lung disease	CHIT1 raises efficient antifungal defence against systemic candidiasis	[84, 85]
Fungal	*Aspergillus*	Bronchiectasis COPD	Systemic CHIT1 activity related to disease exacerbation phenotype in South-East Asian patients	[86]
Leprosy (Hansen's disease)	*Mycobacterium leprae*	Nerves, skin, eyes, and lining of the nose involvement	CHIT1 activity correlated with levels of neopterin; CHIT1 distinguishes multibacillary from paucibacillary leprosy	[87]
Crimean-Congo fever (CCHF)	Virus of the genus Nairovirus that is endemic in Africa, Asia (particularly in the Middle East), and southeast Europe	Hemorrhagic fever	Low CHIT1 activity may be a poor prognostic marker : median CHIT1 activity was higher in the non-fatal CCHF group compared with the fatal CCHF group	[88]
Filariasis (elephantiasis)	Mosquitoes which carry on *filarial parasites*	Obstruction of the lymphatic system	A polymorphism in the human *CHIT1* gene was associated with susceptibility to filarial infection in a filarial-endemic region of South India	[89]
Brucellosis	*Brucella abortus*	Zoonotic infection with musculoskeletal involvement	Neopterin and are high and decrease with therapy	[90]
Scrub typhus	*Rickettsia genus*	Systemic endothelitis	High YKL-40 correlates with disease severity	[91]
Schistosomiasis	*Schistosoma haematobium*	Chronic bladder and lung inflammation	Serum YKL-40 levels differed between infected and uninfected people before and after treatment	[92]
Toxoplasmosis	*Toxoplasma gondii*	Systemic inflammation	YKL-40 correlates with disease stage ($p<0.001$)	[93]

In toxoplasmosis YKL-40 is unique and sophisticated biomarker able to detect the stage of the disease, whether acute or chronic ($p<0.001$), besides its ability to detect the infection [93].

The chitinases in respiratory diseases

Allergen exposure leads to asthma through the development of IgE-mediated airways inflammation, bronchial hyperresponsiveness, and reversible airflow obstruction [94], whereas COPD is a debilitating respiratory condition characterized by chronic airway inflammation and emphysematous alveolar destruction, with an abnormal inflammatory response able to produce lung injury.

CHIT1 and YKL-40, were higher in subjects with chronic obstructive pulmonary disease (COPD) than in patients with mild to moderate asthma or those with severe asthma [95, 96]. In allergic nasal polyps, the increased chitinolytic activities of AMCase and CHIT1 confirms the pathogenesis of the disease, suggesting inhibition of chitinolytic activity as a potential novel therapeutic strategy [97].

The increased chitinases levels correlated with reduced lung function and were relatively steroid-refractory biomarkers [98].

Therefore, CHIT1 can assess severe, chronic inflammation rather than acute lung inflammation.

Strategies aimed at specifically neutralizing chitinolytic activity or at limiting CHIT1 synthesis can be of therapeutic value to improve COPD management [96]. Chitinases can be monitored as biomarkers of decline in lung function in patients with asthma, COPD, fibrosis, infections, or pediatric conditions such as bronchopulmonary dysplasia [98]. There is a relationship between serum level of both YKL-40 and CHIT1 and age in patients with obstructive airway diseases (asthma and COPD) and healthy individuals [99].

CHIT1 may represent a potential biomarker for resistance to obstructive, COPD-like lung injury, as shown in a case-control study involving firefighters from the 9/11 World Trade Center disaster. The enzyme levels were also associated with recovery of lung function, whereas the elevated IgE was the risk factor for airflow obstruction and progressive lung function decline [100, 101].

In lung autoimmune diseases as interstitial lung disease (ILD), scleroderma, or systemic sclerosis (SSc) CHIT1 is a potential biomarker for lung fibrosis [102]. Patients with ILD showed high levels of circulating CHIT1 activity that correlates with disease severity; furthermore, CHIT1 plays a critical role in the pathogenesis of SSc-relevant tissue fibrotic responses or to have modulating capacity of TGF-β1

signalling, acting as a biomarker and therapeutic target of scleroderma-associated pulmonary fibrosis [103, 104].

The chitinases in endocrinological diseases

Serum CHIT1 activity increases in patients with newly diagnosed, untreated, and uncomplicated type-2 diabetes mellitus (T2DM), a major cause of accelerated atherosclerosis [105].

Extracts of atherosclerotic tissue showed an increase in CHIT1 activity up to 55-fold, demonstrating a clear association between CHIT1 expression and lipid-laden macrophages in the atherosclerotic vessel wall [106].

In diabetic complications, CHIT1 enzyme activity correlated positively with the progression of nephropathy [107]. Other studies showed that in both type 1 and 2 diabetes mellitus, CHIT1 activity was correlated with age, glomerular filtration rate, and urine albumin to creatinine ratio [106–108]. In a recent study, the enzymatic activity of CHIT1 correlated with neuropathy and retinopathy in type 1 diabetes mellitus. Moreover, CHIT1 activity was higher than those of the controls and related to glycosylated hemoglobin HbA1c levels [109].

An interesting difference was reported between non-smokers and smokers, the latter showing higher enzyme activity likely due to the persistent inflammatory response generated by smoking [110].

The chitinases in cardiovascular diseases

CHIT1 level represents a marker of macrophage activity in atherosclerotic plaque [32] and related to the width and severity of atherosclerotic lesions [111] and pre-stroke infections [112]. Furthermore, plasma CHIT1 activity significantly correlated with intima-media thickness (IMT) [113] and was higher in patients with stroke and ischemic heart disease compared to healthy controls [114]. Kologlu et al. [115] reported that CHIT1 level was more effective in predicting atherosclerosis in dyslipidemic children compared to hs-CRP, IL-6, and TNF-α. Further, serum CHIT1 activity was a strong marker of coronary artery disease [116]. CHIT1 level was increased in a heterogeneous group of atherothrombotic patients with atherothrombotic stroke or with unstable angina pectoris; moreover, CHIT1 predicts the risk of new cardiovascular events in the following four years, independently from CRP [114]. Güçlü et al. [117] reported a correlation between serum CHIT1 level and carotid IMT in hemodialysis patients, hypothesizing a possible role for CHIT1 in the development of atherosclerosis during uremia.

An increased risk of atherosclerosis is observed in sarcoidosis patients, irrespective of exposure to steroids [118].

The role played by CHIT1 as a marker of prognosis in stroke patients is likely due to the evidence that its activity represents a sensitive parameter of activated macrophage proliferation and therefore reflects the innate inflammatory response that occurs after brain ischemia [119].

Among initially healthy U.S. women, plasma levels of the proinflammatory CLPs, YKL-40, were influenced by environmental as well as genetic factors and predicted incident thromboembolic stroke; YKL-40 levels were higher in women with hypertension, diabetes, and obesity and was significantly associated with incident thromboembolic stroke (p=0.006) [120].

The chitinases in neurological diseases

Amyotrophic lateral sclerosis (ALS) is determined by the loss of spinal, bulbar, and cortical motor neurons, which leads to paralysis of voluntary muscles involving also respiratory muscles. There are different reports of substantially elevated CHIT1 expression and activity in the cerebrospinal, motor cortex, and spinal cord of ALS patients in comparison to healthy controls, independently of genotype and other factors (e.g. gender and age) suggesting that disease status determines the extent of dysregulation [121].

A recent multicenter study reported increased levels of CHIT1 in cerebrospinal fluid of both early and late symptomatic ALS patients, reflecting microglial activation; therefore, CHIT1 may be recommended as a potential differential marker for ALS for diagnosis and immune-modulatory therapeutic interventions [122–124].

Neuromyelitis optica (NMO) is a severe demyelinating autoimmune inflammatory process of the eye nerves (optic neuritis) and the spinal cord (myelitis) [125]. Increased CSF (but not serum) chitinase levels were reported in patients with NMO and relapsing-remitting multiple sclerosis compared with healthy controls and patients with secondary progressive multiple sclerosis and other inflammatory neurological diseases. YKL-40 is a biomarker for NMO spectrum disorders severity and a potential target for its treatment [126].

Multiple sclerosis (MS) is a disease that include axonal injury and loss in the central nervous system, where useful markers are neurofilaments (light and heavy chains), CLPs,

soluble surface markers of innate immunity, and oligoclonal immunoglobulin M antibodies [127,128]. The YKL-40 levels were higher at the beginning of the disease and in the clinically isolated syndrome (CIS) group than in the MS group, although they were not involved in the progression to clinically definite MS [129].

CSF levels of YKL-40 and the transcription factor involved in immune cell activity, HoxB3, appear to predict CIS to MS conversion [130]. Dysregulation of TNF and TNF-receptors 1/2 pathways with their associated patterns encompassing high levels of YKL-40, associates with specific clinical/MRI profiles and can be identified at a very early stage in MS patients, at the time of diagnosis, contributing to the prediction of the disease outcome [131]. A potential role of YKL-40 as therapeutic target in MS patients was suggested by an early work showing its neurotoxic effect *in vitro* [132].

Indeed, chitin accumulates in a lot of tissues and may be particularly toxic to neurons as in with Alzheimer's disease (AD) [133] a severe neurodegenerative disease. In particular, CSF CHIT1 and YKL-40 levels are increased in individuals with frontotemporal dementia (FTD) syndromes, due to AD pathology [134]. There is growing evidence that chronic neuroinflammation plays a role in FTD. Late-onset AD patients showed significantly higher expression levels of CHIT1 in comparison with healthy subjects suggesting that an immuno-activation of microglia in amyloid plaque pathology [135]. The putative microglial marker CSF CHIT1 might be useful for the identification of distinct subgroups of patients, and for the development and implementation of drugs targeting microglial pathology [136]. It has been shown that among asymptomatic AD individuals, neuroinflammation (expressed by higher CSF YKL-40) is associated with neural damage [137].

Dementia with Lewy bodies (DLB) is a neurodegenerative dementia, where YKL-40 demonstrated significantly higher protein levels compared to aged individuals with an absence of neurological features [138].

Huntington's disease (HD) is a progressive decline in cognitive, motor and behaviour functions as a consequence of neuronal dysfunction and death. IL-6, CHIT1 and YKL-40 showed disease-related elevations in CSF in HD patients, supporting the role of microglial activation and the innate immune system in the disease [139].

In inflammatory neurological disorders CSF YKL-40 was significantly elevated in pediatric patients compared to controls, [140]. CHIT1 elevation in treatment-naïve spinal muscular atrophy patients indicated the involvement of (neuro)inflammation also in this disease [141].

The chitinases in gynecological and obstetrical diseases

Polycystic ovary syndrome (PCOS) represents a state of low-grade chronic inflammation where the macrophages could play a role due to obesity, insulin resistance, and other metabolic disorders associated with PCOS itself [142]. Indeed, CHIT1 was elevated in PCOS women compared to controls, independent of obesity [143].

Chitinases activity was also statistically higher in severe endometriosis patients compared to control subjects [144] and in ovaric cancer [145]. A panel of noninvasive inflammatory markers for the diagnosis and severity including YKL-40 indicated a significant correlation between CA 125 (a marker of advanced endometriosis) concentrations and IL-6 and prolactin levels, providing valuable information not only for determining the advanced stage of endometriosis but also for the diagnosis of this disease [146].

CHIT1 can play a role as a biomarker of fetal compromise [147]. In this study umbilical cord CHIT1 levels correlated with umbilical artery flow velocity waveform measured just before delivery and both parameters were high in the pre-eclamptic group; indeed, high CHIT1 reflects the severity of fetoplacental blood flow resistance in pregnancies complicated by preeclampsia [147]. Further, high CHIT1 levels were reported in mild preeclampsia women suggesting a role played by activated macrophages in the pathogenesis of this complication of pregnancy [144].

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The chitinases in miscellaneous diseases

Non-alcoholic fatty liver disease

Kupffer cells of non-alcoholic fatty liver disease (NAFLD) patients showed an increased *CHIT1* gene expression [148]. CHIT1 expression differed markedly in livers of normal controls compared to those of patients with NAFLD or non-alcoholic steatohepatitis (NASH). A significant correlation between mRNA CHIT1 and O_2, lipid peroxidation, TNF-α, and ferritin levels was observed in both NASH and NAFLD. CHIT1 may play a role in increasing the risk for a poor outcome in NASH. Moreover,

CHI3L1 is a biomarker for HBV- and HCV-induced liver fibrosis and cirrhosis [149, 150].

Familial Mediterranean fever

In one study, CHIT1 level has been found elevated in Familial Mediterranean fever (FMF) patients with correlation with other inflammation markers during fever attack compared to the silent period of the disease [151]. Furthermore, colchicine reduces the expression and activity of CHIT1 by preventing neutrophil leucocytes chemotaxis and macrophage activity [152].

β-Thalassemia

Highest levels of plasma CHIT1 were observed in patients with β-thalassemia major, with the highest degree of iron overload, suggesting that this factor could trigger CHIT1 overproduction [153].

Sarcoidosis

Sarcoidosis is an inflammatory disease characterized by granuloma formation. It preferentially involves the lungs but may affect any other organ and it is often a diagnosis of exclusion, but several biomarkers as lymphocyte subsets and levels of signaling molecules can also be used to improve the accuracy of diagnosis, disease progression, prognosis, and make treatment decisions [154].

Increased CHIT1 is a sensitive biomarker of active sarcoidosis [155] where it can have prognostic value [200] and it may be used in Fever of Unknown Origin to detect sarcoidosis [156]. CHIT1 sensitivity is about 90% exceeding the sensitivity (about 60%) of the commonly used biomarker ACE [157]. CHIT1 in serum and BAL correlated with radiological stages of sarcoidosis [158], whereas corticosteroids reduce the activity of CHIT1 [156, 157]. Similarly, CHIT1, as ACE, reflects the granulomatous burden of the disease [157].

An infectious trigger has long been suspected in sarcoidosis [154, 159]. The candidates are tuberculous and nontuberculous *Mycobacterium* spp. and *Cutibacterium acnes* (formerly *Propionibacterium acnes*), which is the only microorganism to be isolated from sarcoid lesions in 78% of patients with sarcoidosis [160]. Negi et al. [161] developed a monoclonal antibody (anti-P acnes antibody, PAB) that recognizes the cell membrane-bound lipoteichoic acid of C. acnes in sarcoid granulomas. As for CHIT1, ACE has the same genotypic variability problem that produces false negatives, therefore, the combination of ACE and CHIT1 activity assays can improve the predictability of these tests in sarcoidosis [53].

Sarcoidosis shares with hypersensitivity pneumonitis the possibility of fibrotic evolution; YKL-40 distinguishes patients with hypersensitivity pneumonitis from healthy individuals and from patients with idiopathic pulmonary fibrosis. Their sensitivity and specificity confirm their potential role as biomarkers [162].

Juvenile idiopathic arthritis

CHIT1 level measured in synovial fluid patients with Juvenile idiopathic arthritis (JIA) was up to approximately 1,000 nmol/(h mL) at disease onset representing the activity of macrophages in the synovial fluid, whereas the level in the sera was below 600 nmol/(h mL). Positive correlation has been found between the frequency of Th17 and Th17-derived cell subsets and YKL-40 levels in synovial fluid of JIA patients [163].

Cancer

Chitinases levels were significantly higher in patients with high Gleason scores compared to the control group ($p<0.001$), indicating that it may have a role in the immune reaction to malignant diseases [164, 165], as in patients with primary breast cancer [165].

Glioblastoma multiforme patients with a high expression of CD163 and CHI3L2 had a poor overall survival, prognosis-free survival, and disease-specific survival [166]. The differential expression of the immunomodulatory molecule YKL-40 may affect the treatment efficacy of PI3K/AKT-based pathway inhibitors in glioblastoma [166].

In primary and metastatic tumors, CHI3L2 and the $EOMES^+$ eomesodermin homolog Tr1-like subset correlates with disease progression but is also associated with response to programmed cell death protein 1-targeted immunotherapy; collectively, these findings highlight the heterogeneity of T_{reg} cells that accumulate in primary tumors and metastases and identify a new prospective target for cancer immunotherapy [167].

Autoimmune diseases

This topic has been widely reviewed by Tizaoui et al. [168] who collected the literature about the role of YKL-40; the results are conflicting due the fact the papers regard different phases and complication of these diseases.

Indeed, in rheumatoid arthtritis (RA) the chitinase and N-acetyl-glucosaminidase have been identified as indices

of telomere dysfunction and are greater in RA patients than those in healthy controls [169] and elevated oxidant stress markers correlate with disease activity, but efficacy as a diagnostic and prognostic marker of this disease, requires further studies (reviewed in [168]).

In psoriasis, YKL-40 level is correlated only to complications as carotid intima-media thickness and defective aortic elasticity [170] and arthritis, often in association with severe disease and response to treatment [171].

In systemic lupus erythematosus (SLE) the average plasma levels of YKL-40 is about twice higher in the SLE group than in controls [172] as in active Behcet's disease (BD) an elevation in serum YKL-40 levels has been found [173].

In Crohn's disease, sYKL-40 level was shown higher in patients with intestinal strictures than in those without intestinal strictures [174]. Vind et al. [175] found that sYKL-40 level is increased in 40–50% of ulcerative colitis and Crohn's disease patients with active disease, and the level was also increased in 30% of patients with clinically inactive Crohn's disease. Ytting et al. [176] reported a case where s YKL-40 level is increased as an appearance of Sweet's syndrome in a patient previously diagnosed with ulcerative colitis, sYKL-40 level acted as a marker of disease activity of Sweet's syndrome. Increased sYKL-40 level was also discovered as the marker of articular involvement in IBD [177].

Overall, all this research can be interpreted as a whole, assuming that chitinases in autoimmune diseases are an expression of acute or disease complications, while are not significantly elevated in chronic forms. These results are expected because chitinases correlate with macrophage activation that occurs in the early stages of autoimmune diseases, when autoantigen is presented.

Other diseases

YLK-40 plays a role in the pathogenic process of Lichen planus where it can help in the treatment strategies [178].

Pyoderma gangrenosum (PG) is a rare, neutrophilic autoinflammatory dermatosis where YKL-40 can be considered a valuable biomarker of inflammation correlated with and IL-6 and C-reactive protein [179].

This chitinase level is increased in hemodialyzed patients, especially in those with cardiovascular disease, and it is independently associated with neopterin – a biomarker of monocyte/macrophage activation; anti-HCV seropositivity enhances plasma YKL-40 levels in these patients [180].

Arthroscopic partial meniscectomy and total knee arthroplasty cartilage expresses distinct sets of osteoarthritis transcripts amongst which CHI3L2 [181].

Interestingly, the serum YKL-40 is a prognostic and sensitive biomarker of all-cause mortality in octogenarians [182].

Take home messages and limitations of this review

In this review, the role of the macrophage activation enzymes chitinases, as potential biomarkers of diagnosis, prognosis, severity, and therapy monitoring has been focused (Table 3). The role of chitinases in the immune system and in many inflammatory-based diseases supports the growing interest in this area of research, aimed to unveil the still uncovered functions of CHIT1 and chitinases in human diseases. The use of chitinases assay has been

Table 3: Take home messages: proposed biomarker roles for chitinases in different human diseases.

Chitinase biomarker	Disease group	Disease	Biological sample	References
Screening	LSD	GD; Niemann Pick; Krabbe; Farber; GM1; Sialidosis type II	Plasma/serum	[54, 55, 59–62, 67, 73, 78–81]
	Infectious diseases	Filariasis, CF	Plasma/serum	[84, 89]
	Respiratory diseases	Interstitial diseases, COPD, Bronchiectasis.	Plasma/serum	[86]
	Neurological diseases	ALS, NMO, MS	CSF	[123]
	Miscellaneous	FMF; acute appendicitis; JIA; sarcoidosis.	Plasma/serum/BAL	[156, 162]
Therapeutic monitoring	LSD	Cystinosis, Fabry	Plasma/serum	[55, 68, 69]
	Infectious diseases	Systemic fungal infections; tuberculosis; brucellosis; leprosy.	Plasma/serum	[87, 90]
	Miscellaneous	β-thalassemia; Sarcoidosis; Lichen planus; Psoriasis	Plasma/serum	[153, 154, 171, 178]
Marker of severity	LSD	Krabbe	Plasma/serum	[61, 62]
	Respiratory diseases	Asthma; COPD	Plasma/serum BAL (in COPD)	[95, 96]

Table 3: (continued)

Chitinase biomarker	Disease group	Disease	Biological sample	References
	Cardiovascular diseases	Atherosclerosis; Erectile disfunction	Plasma/serum	[91, 92, 107]
	Neurological diseases	ALS	Plasma/serum; CSF	[122, 123]
	Miscellaneous	NAFLD; FMF; β-thalassemia; JIA; endometriosis; preeclampsia; Sweet's syndrome	Plasma/serum	[106, 116, 151, 153, 176]
Prognosis	Infectious diseases	Systemic fungal infections; malaria; tuberculosis; Leprosy; CCHF.	Plasma/serum	[87–89]
	Cardiovascular diseases	Stroke; Coronary artery disease	Plasma/serum	[103, 119]
	Neurological diseases	MS	CSF	[125]
	Gynecological and obstetrical diseases	PCOS	Plasma/serum	[143]
	Miscellaneous	Prostate cancer; Sarcoidosis	Plasma/serum/BAL	[55, 164]
Marker of endothelial damage/nephropathy progression	Endocrinological diseases	Diabetes	Plasma/serum	[92, 106]

AML, amyotrophic lateral sclerosis; COPD, chronic obstructive pulmonary bronchitis disease; LSD, lysosomal storage diseases; FMF, familial mediterranean fever; GD, gaucher disease; MS, multiple sclerosis; NAFLD, non-alcoholic fatty liver disease; NMO, neuromyelitis optica; JIA, juvenile idiopathic arthritis; PCOS, polycystic ovary syndrome.

extended in Italy to third level centres specialised for the diagnosis and staging of sarcoidosis and in the diagnosis of fever of unknown origin [156]. The use in the clinics has spread in other countries, as China, where chronic hepatitis HBV and HCV in fibrotic evolution is a common problem, and therefore this assay is widespread. Multiple developments are expected in this field of research and will expand current knowledge.

However, as the bias of these data is the presence of a *null CHIT1* gene subpopulation [53] which is responsible of false-negative values, the assay should be completed with the other markers of macrophagic activity such as ACE and, if necessary, by genetic analysis in low CHIT1 activity patients. Furthermore, the clinical use of blood spot CHIT1 for the screening of lysosomal storage disorders can be quite practical, provided proper cut-off values are determined for each lab [183].

About appropriateness of these tests in the different diseases, the quality specifications of these assays are so good to provide reliable results; but the proportion of false-negative and false-positive results need to be investigated in every specific disease, consistently with the disease stadiation and factors interfering with the development of the disease.

The potential of CHIT1 and chitinases has not been fully explored yet and future studies will produce many surprising discoveries in the immunology and allergology fields of research.

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References

1. Bussink AP, van Eijk M, Renkema GH, Aerts JM, Boot RG. The biology of the Gaucher cell: the cradle of human chitinases. Int Rev Cytol 2006;252:71–128.
2. Kesari P, Patil DN, Kumar P, Tomar S, Sharma AK, Kumar P. Structural and functional evolution of chitinase-like proteins from plants. Proteomics 2015;15:1693–705.
3. Ober C, Chupp GL. The chitinase and chitinase-like proteins: a review of genetic and functional studies in asthma and immune-mediated diseases. Curr Opin Allergy Clin Immunol 2009;9:401–8.
4. Adrangi S, Faramarzi MA. From bacteria to human: a journey into the world of chitinases. Biotechnol Adv 2013;31:1786–95.
5. Henrissat B, Bairoch A. New families in the classification of glycosyl hydrolases based on amino acid sequence similarities. Biochem J 1993;293:781–8.

6. Terwisscha van Scheltinga AC, Armand S, Kalk KH, Isogai A, Henrissat B, Dijkstra BW. Stereochemistry of chitin hydrolysis by a plant chitinase/lysozyme and X-ray structure of a complex with allosamidin: evidence for substrate assisted catalysis. Biochemistry 1995;34:15619–23.
7. van Aalten DM, Komander D, Synstad B, Gåseidnes S, Peter MG, Eijsink VG. Structural insights into the catalytic mechanism of a family 18 exo-chitinase. Proc Natl Acad Sci USA 2001;98: 8979–84.
8. Huet J, Rucktooa P, Clantin B, Azarkan M, Looze Y, Villeret V, et al. X-ray structure of papaya chitinase reveals the substrate binding mode of glycosyl hydrolase family 19 chitinases. Biochemistry 2008;47:8283–91.
9. Hamid R, Khan MA, Ahmad M, Ahmad MM, Abdin MZ, Musarrat J, et al. Chitinases: an update. J Pharm BioAllied Sci 2013;5:21–9.
10. Paoletti MG, Norberto L, Damini R, Musumeci S. Human gastric juice contains chitinase that can degrade chitin. Ann Nutr Metab 2007;51:244–51.
11. Renkema GH, Boot RG, Muijsers AO, Donker-Koopman WE, Aerts JM. Purification and characterization of human chitotriosidase, a novel member of the chitinase family of proteins. J Biol Chem 1995;270:2198–202.
12. Hakala BE, White C, Recklies AD. Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. J Biol Chem 1993;268:25803–10.
13. MacDonald JM, Tarling CA, Taylor EJ, Dennis RJ, Myers DS, Knapp S, et al. Chitinase inhibition by chitobiose and chitotriose thiazolines. Angew Chem Int Ed Engl 2010;49:2599–602.
14. Whitworth GE, Macauley MS, Stubbs KA, Dennis RJ, Taylor EJ, Davies GJ, et al. Analysis of PUGNAc and NAG-thiazoline as transition state analogues for human O-GlcNAcase: mechanistic and structural insights into inhibitor selectivity and transition state poise. J Am Chem Soc 2007;129:635–44.
15. Andersen OA, Dixon MJ, Eggleston IM, van Aalten DM. Natural product family 18 chitinase inhibitors. Nat Prod Rep 2005;22: 563–79.
16. Vinetz JM, Valenzuela JG, Specht CA, Aravind L, Langer RC, Ribeiro JM, et al. Chitinases of the avian malaria parasite Plasmodium gallinaceum, a class of enzymes necessary for parasite invasion of the mosquito midgut. J Biol Chem 2000;275: 10331–41.
17. Zhu Z, Zheng T, Homer RJ, Kim YK, Chen NY, Cohn L, et al. Acidic mammalian chitinase in asthmatic Th2 inflammation and IL-13 pathway activation. Science 2004;304:1678–82.
18. Loiseau PM, Bories C, Sanon A. The chitinase system from Trichomonas vaginalis as a potential target for antimicrobial therapy of urogenital trichomoniasis. Biomed Pharmacother 2002;56:503–10.
19. Le B, Yang SH. Characterization of a chitinase from Salinivibrio sp. BAO-1801 as an antifungal activity and a biocatalyst for producing chitobiose. J Basic Microbiol 2018;58:848–56.
20. Di Rosa M, Malaguarnera L. Chitotriosidase: a new inflammatory marker in diabetic complications. Pathobiology 2016;83:211–9.
21. Tang WJ, Fernandez J, Sohn JJ, Amemiya CT. Chitin is endogenously produced in vertebrates. Curr Biol 2015;25:897–900.
22. Pereira JL, Noronha EF, Miller RN, Franco OL. Novel insights in the use of hydrolytic enzymes secreted by fungi with biotechnological potential. Lett Appl Microbiol 2007;44:573–81.
23. Boot RG, Renkema GH, Strijland A, van Zonneveld AJ, Aerts JM. Cloning of a cDNA encoding chitotriosidase, a human chitinase produced by macrophages. J Biol Chem 1995;270:26252–6.
24. Barone R, Sotgiu S, Musumeci S. Plasma chitotriosidase in health and pathology. Clin Lab 2007;53:321–33.
25. Kanneganti M, Kamba A, Mizoguchi E. Role of chitotriosidase (chitinase 1) under normal and disease conditions. J Epithelial Biol Pharmacol 2012;5:1–9.
26. Ohno M, Kimura M, Miyazaki H, Okawa K, Onuki R, Nemoto C, et al. Acidic mammalian chitinase is a proteases-resistant glycosidase in mouse digestive system. Sci Rep 2016;6: 37756.
27. Elieh Ali Komi D, Sharma L, Dela Cruz CS. Chitin and its effects on inflammatory and immune responses. Clin Rev Allergy Immunol 2018;54:213–23.
28. Korolenko TA, Bgatova NP, Ovsyukova MV, Shintyapina A, Vetvicka V. Hypolipidemic effects of β-glucans, mannans, and fucoidans: mechanism of action and their prospects for clinical application. Molecules 2020;25:1819.
29. Elias JA, Homer RJ, Hamid Q, Lee CG. Chitinases and chitinase-like proteins in T(H)2 inflammation and asthma. J Allergy Clin Immunol 2005;116:497–500.
30. Lee CG. Chitin, chitinases, and chitinase-like proteins in allergic inflammation and tissue remodeling. Yonsei Med J 2009;50: 22–30.
31. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med 1999;340:115–26.
32. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 1994;90:775–8.
33. Bussink AP, Speijer D, Aerts JM, Boot RG. Evolution of mammalian chitinase(-like) members of family 18 glycosyl hydrolases. Genetics 2007;177:959–70.
34. Vega K, Kalkum M. Chitin, chitinase responses, and invasive fungal infections. Internet J Microbiol 2012;2012:920459.
35. Bleau G, Massicotte F, Merlen Y, Boisvert C. Mammalian chitinase-like proteins. EXS 1999;87:211–21.
36. Kidibule PE, Santos-Moriano P, Jiménez-Ortega E, Ramírez-Escudero M, Limón MC, Remacha M, et al. Use of chitin and chitosan to produce new chitooligosaccharides by chitinase Chit42: enzymatic activity and structural basis of protein specificity. Microb Cell Factories 2018;17:47.
37. Synstad B, Gåseidnes S, Van Aalten DM, Vriend G, Nielsen JE, Eijsink VG. Mutational and computational analysis of the role of conserved residues in the active site of a family 18 chitinase. Eur J Biochem 2004;271:253–62.
38. Oyeleye A, Normi YM. Chitinase: diversity, limitations, and trends in engineering for suitable applications. Biosci Rep 2018; 38:1–19.
39. Parkin J, Cohen B. An overview of the immune system. Lancet 2001;357:1777–89.
40. Saraiva M, O'Garra A. The regulation of IL-10 production by immune cells. Nat Rev Immunol 2010;10:170–81.
41. Nagasawa H. The crustacean cuticle: structure, composition and mineralization. Front Biosci (Elite Ed) 2012;4:711–20.
42. Henriques BS, Garcia ES, Azambuja P, Genta FA. Determination of chitin content in insects: an alternate method based on calcofluor staining. Front Physiol 2020;11:117.
43. Chen Q, Chen W, Kumar A, Jiang X, Janezic M, Zhang KYJ, et al. Crystal structure and structure-based discovery of inhibitors of

the nematode chitinase CeCht1. J Agric Food Chem 2021;69:3519–26.
44. Arlian LG, Platts-Mills TA. The biology of dust mites and the remediation of mite allergens in allergic disease. J Allergy Clin Immunol 2001;107:S406–13.
45. Chew GL, Perzanowski MS, Canfield SM, Goldstein IF, Mellins RB, Hoepner LA, et al. Cockroach allergen levels and associations with cockroach-specific IgE. J Allergy Clin Immunol 2008;121:240–5.
46. Zhang Y, Matsuo H, Morita E. Cross-reactivity among shrimp, crab and scallops in a patient with a seafood allergy. J Dermatol 2006;33:174–7.
47. O'Dea EM, Amarsaikhan N, Li H, Downey J, Steele E, Van Dyken SJ, et al. Eosinophils are recruited in response to chitin exposure and enhance Th2-mediated immune pathology in aspergillus fumigatus infection. Infect Immun 2014;82:3199–205.
48. Di Rosa M, Distefano G, Zorena K, Malaguarnera L. Chitinases and immunity: ancestral molecules with new functions. Immunobiology 2016;221:399–411.
49. Lee CG, Da Silva CA, Lee JY, Hartl D, Elias JA. Chitin regulation of immune responses: an old molecule with new roles. Curr Opin Immunol 2008;20:684–9.
50. Amick AK, Liu Q, Gautam S, Chupp G, Dela Cruz CS, Sharma L. Measurement of chitinase activity in biological samples. J Vis Exp 2019;1–6.
51. Høgdall EV, Ringsholt M, Høgdall CK, Christensen IJ, Johansen JS, Kjaer SK, et al. YKL-40 tissue expression and plasma levels in patients with ovarian cancer. BMC Cancer 2009;9:1–10.
52. Sánchez O, Rodríguez-Sureda V, Domínguez C, Fernández-Figueras T, Vilches A, Llurba E, et al. Study of biomaterial-induced macrophage activation, cell-mediated immune response and molecular oxidative damage in patients with dermal bioimplants. Immunobiology 2012;217:44–53.
53. Csongrádi A, Altorjay IT, Fülöp GÁ, Enyedi A, Enyedi EE, Hajnal P, et al. Chitotriosidase gene polymorphisms and mutations limit the determination of chitotriosidase expression in sarcoidosis. Clin Chim Acta 2021;513:50–6.
54. Shemesh E, Deroma L, Bembi B, Deegan P, Hollak C, Weinreb NJ, et al. Enzyme replacement and substrate reduction therapy for Gaucher disease. Cochrane Database Syst Rev 2015;9:1–45.
55. Elmonem MA, Makar SH, van den Heuvel L, Abdelaziz H, Abdelrahman SM, Bossuyt X, et al. Clinical utility of chitotriosidase enzyme activity in nephropathic cystinosis. Orphanet J Rare Dis 2014;9:155.
56. Rathcke CN, Vestergaard H. YKL-40, a new inflammatory marker with relation to insulin resistance and with a role in endothelial dysfunction and atherosclerosis. Inflamm Res 2006;55:221–7.
57. Rajasekaran S, Soundararajan DCR, Nayagam SM, Tangavel C, Raveendran M, Thippeswamy PB, et al. Modic changes are associated with activation of intense inflammatory and host defense response pathways – molecular insights from proteomic analysis of human intervertebral discs. Spine J 2022;22:19–38.
58. Sun A. Lysosomal storage disease overview. Ann Transl Med 2018;6:476.
59. Hollak CE, van Weely S, van Oers MH, Aerts JM. Marked elevation of plasma chitotriosidase activity. A novel hallmark of Gaucher disease. J Clin Invest 1994;93:1288–92.
60. Brinkman J, Wijburg FA, Hollak CE, Groener JE, Verhoek M, Scheij S, et al. Plasma chitotriosidase and CCL18: early biochemical surrogate markers in type B Niemann-Pick disease. J Inherit Metab Dis 2005;28:13–20.
61. Michelakakis H, Dimitriou E, Labadaridis I. The expanding spectrum of disorders with elevated plasma chitotriosidase activity: an update. J Inherit Metab Dis 2004;27:705–6.
62. Guo Y, He W, Boer AM, Wevers RA, de Bruijn AM, Groener JE, et al. Elevated plasma chitotriosidase activity in various lysosomal storage disorders. J Inherit Metab Dis 1995;18:717–22.
63. Bondar C, Mucci J, Crivaro A, Ormazabal M, Ceci R, Oliveri B, et al. In vitro osteoclastogenesis from Gaucher patients' cells correlates with bone mineral density but not with Chitotriosidase. Bone 2017;103:262–9.
64. Nair S, Branagan AR, Liu J, Boddupalli CS, Mistry PK, Dhodapkar MV. Clonal immunoglobulin against lysolipids in the origin of myeloma. N Engl J Med 2016;374:555–61.
65. Balreira A, Cavallari M, Sá Miranda MC, Arosa FA. Uncoupling between CD1d upregulation induced by retinoic acid and conduritol-B-epoxide and iNKT cell responsiveness. Immunobiology 2010;215:505–13.
66. Desnick RJ, Ioannou YA, Eng ME. α-galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease, 8th ed. New York: McGraw-Hill; 2001, vol 3:3733–74.
67. Hollak CE, Maas M, Aerts JM. Clinically relevant therapeutic endpoints in type I Gaucher disease. J Inherit Metab Dis 2001;24:97–105.
68. Vedder AC, Cox-Brinkman J, Hollak CE, Linthorst GE, Groener JE, Helmond MT, et al. Plasma chitotriosidase in male Fabry patients: a marker for monitoring lipid-laden macrophages and their correction by enzyme replacement therapy. Mol Genet Metabol 2006;89:239–44.
69. Veys KRP, Elmonem MA, Van Dyck M, Janssen MC, Cornelissen EAM, Hohenfellner K, et al. Chitotriosidase as a novel biomarker for therapeutic monitoring of nephropathic cystinosis. J Am Soc Nephrol 2020;31:1092–106.
70. Oshima RG, Willis RC, Furlong CE, Schneider JA. Binding assays for amino acids. The utilization of a cystine binding protein from Escherichia coli for the determination of acid-soluble cystine in small physiological samples. J Biol Chem 1974;249:6033–9.
71. Syres K, Harrison F, Tadlock M, Jester JV, Simpson J, Roy S, et al. Successful treatment of the murine model of cystinosis using bone marrow cell transplantation. Blood 2009;114:2542–52.
72. Harrison F, Yeagy BA, Rocca CJ, Kohn DB, Salomon DR, Cherqui S. Hematopoietic stem cell gene therapy for the multisystemic lysosomal storage disorder cystinosis. Mol Ther 2013;21:433–44.
73. Dimitriou E, Cozar M, Mavridou I, Grinberg D, Vilageliu L, Michelakakis H. The spectrum of Krabbe disease in Greece: biochemical and molecular findings. JIMD Rep 2016;25:57–64.
74. Suzuki K. Twenty-five years of the "psychosine hypothesis": a personal perspective of its history and present status. Neurochem Res 1998;23:251–9.
75. Wenger DA, Escolar MI, Luzi P, Rafi MA. Krabbe disease (globoid cell leukodystrophy). In: Valle D, Beaudet AL, Vogelstein D, Kinzler KW, Antonarakis SE, Ballabio A, editors. The online metabolic and molecular bases of inherited disease. New York: McGraw Hill; 2013.

76. Pasqui AL, Di Renzo M, Auteri A, Federico G, Puccetti L. Increased TNF-alpha production by peripheral blood mononuclear cells in patients with Krabbe's disease: effect of psychosine. Eur J Clin Invest 2007;37:742–5.
77. Formichi P, Radi E, Battisti C, Pasqui A, Pompella G, Lazzerini PE, et al. Psychosine-induced apoptosis and cytokine activation in immune peripheral cells of Krabbe patients. J Cell Physiol 2007; 212:737–43.
78. Wajner A, Michelin K, Burin MG, Pires RF, Pereira ML, Giugliani R, et al. Comparison between the biochemical properties of plasma chitotriosidase from normal individuals and from patients with Gaucher disease, GM1-gangliosidosis, Krabbe disease and heterozygotes for Gaucher disease. Clin Biochem 2007;40: 365–9.
79. Caciotti A, Di Rocco M, Filocamo M, Grossi S, Traverso F, d'Azzo A, et al. Type II sialidosis: review of the clinical spectrum and identification of a new splicing defect with chitotriosidase assessment in two patients. J Neurol 2009;256:1911–5.
80. Muranjan M, Agarwal S, Lahiri K, Bashyam M. Novel biochemical abnormalities and genotype in Farber disease. Indian Pediatr 2012;49:320–2.
81. Arash-Kaps L, Komlosi K, Seegräber M, Diederich S, Paschke E, Amraoui Y, et al. The clinical and molecular spectrum of GM1 gangliosidosis. J Pediatr 2019;215:152–7.
82. Labadaridis I, Dimitriou E, Theodorakis M, Kafalidis G, Velegraki A, Michelakakis H. Chitotriosidase in neonates with fungal and bacterial infections. Arch Dis Child Fetal Neonatal 2005;90:F531–2.
83. Erdman LK, Petes C, Lu Z, Dhabangi A, Musoke C, Cserti-Gazdewich CM, et al. Chitinase 3-like 1 is induced by Plasmodium falciparum malaria and predicts outcome of cerebral malaria and severe malarial anaemia in a case-control study of African children. Malar J 2014;13:279.
84. Hector A, Chotirmall SH, Lavelle GM, Mirković B, Horan D, Eichler L, et al. Chitinase activation in patients with fungus-associated cystic fibrosis lung disease. J Allergy Clin Immunol 2016;138:1183–9. Erratum in: J Allergy Clin Immunol 2021;148: 908.
85. Wiesner DL, Specht CA, Lee CK, Smith KD, Mukaremera L, Lee ST, et al. Chitin recognition via chitotriosidase promotes pathologic type-2 helper T cell responses to cryptococcal infection. PLoS Pathog 2015;11:e1004701.
86. Poh TY, Tiew PY, Lim AYH, Thng KX, Mohamed Ali BinteNA, Narayana JK, et al. Increased chitotriosidase is associated with Aspergillus and frequent exacerbations in south-east asian patients with bronchiectasis. Chest 2020;158:512–22.
87. Iyer A, van Eijk M, Silva E, Hatta M, Faber W, Aerts JM, et al. Increased chitotriosidase activity in serum of leprosy patients: association with bacillary leprosy. Clin Immunol 2009;131:501–9.
88. Kurt YG, Cayci T, Onguru P, Akgul EO, Yaman H, Aydin I, et al. Serum chitotriosidase enzyme activity in patients with Crimean-Congo hemorrhagic fever. Clin Chem Lab Med 2009;47:1543–7.
89. Choi EH, Zimmerman PA, Foster CB, Zhu S, Kumaraswami V, Nutman TB, et al. Genetic polymorphisms in molecules of innate immunity and susceptibility to infection with Wuchereria bancrofti in South India. Gene Immun 2001;2:248–53.
90. Coskun O, Oter S, Yaman H, Kilic S, Kurt I. Eyigun CP Evaluating the validity of serum neopterin and chitotriosidase levels in follow-up brucellosis patients. Intern Med 2010;49:1111–8.
91. Otterdal K, Janardhanan J, Astrup E, Ueland T, Prakash JA, Lekva T, et al. Increased endothelial and macrophage markers are associated with disease severity and mortality in scrub typhus. J Infect 2014;69:462–9.
92. Appleby LJ, Nausch N, Bourke CD, Rujeni N, Midzi N, Mduluza T, et al. Chitinase 3-like 1 protein levels are elevated in Schistosoma haematobium infected children. PLoS Neglected Trop Dis 2012;6:e1898.
93. Shahad FAA, Mohammed AA, Jasim GA. YKL-40 as a novel diagnostic biomarker in Toxoplasmosis. J Popul Ther Clin Pharmacol 2022;29:e61–e70.
94. Khan DA. Allergic rhinitis and asthma: epidemiology and common pathophysiology. Allergy Asthma Proc 2014;35: 357–61.
95. Bargagli E, Olivieri C, Margollicci M, Bennett D, Luddi A, Perrone M, et al. Serum chitotriosidase levels in patients with allergic and non-allergic asthma. Respiration 2010;79:437–8.
96. Létuvé S, Kozhich A, Humbles A, Brewah Y, Dombret MC, Grandsaigne M, et al. Lung chitinolytic activity and chitotriosidase are elevated in chronic obstructive pulmonary disease and contribute to lung inflammation. Am J Pathol 2010; 176:638–49.
97. Park SK, Heo KW, Hur DY. Yang YI Chitinolytic activity in nasal polyps. Am J Rhinol Allergy 2011;25:12–4.
98. James AJ, Reinius LE, Verhoek M, Gomes A, Kupczyk M, Hammar U, et al. Increased YKL-40 and chitotriosidase in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2016;193:131–42.
99. Przysucha N, Górska K, Krenke R. Chitinases and chitinase-like proteins in obstructive lung diseases – current concepts and potential applications. Int J Chronic Obstr Pulm Dis 2020;15: 885–99.
100. Cho SJ, Nolan A, Echevarria GC, Kwon S, Naveed B, Schenck E, et al. Chitotriosidase is a biomarker for the resistance to World Trade Center lung injury in New York City firefighters. J Clin Immunol 2013;33:1134–42.
101. Byers DE, Wu K, Dang-Vu G, Jin X, Agapov E, Zhang X, et al. Triggering receptor expressed on myeloid cells-2 expression tracks with M2-like macrophage activity and disease severity in COPD. Chest 2018;153:77–86.
102. Furue M, Mitoma C, Mitoma H, Tsuji G, Chiba T, Nakahara T, et al. Pathogenesis of systemic sclerosis-current concept and emerging treatments. Immunol Res 2017;65:790–7.
103. Lee CG, Herzog EL, Ahangari F, Zhou Y, Gulati M, Lee CM, et al. Chitinase 1 is a biomarker for and therapeutic target in scleroderma-associated interstitial lung disease that augments TGF-β1 signaling. J Immunol 2012;189:2635–44.
104. Hübner K, Karwelat D, Pietsch E, Beinborn I, Winterberg S, Bedenbender K, et al. NF-κB-mediated inhibition of microRNA-149-5p regulates Chitinase-3-like 1 expression in human airway epithelial cells. Cell Signal 2020;67:109498.
105. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 2002; 287:2570–81.
106. Sonmez A, Haymana C, Tapan S, Safer U, Celebi G, Ozturk O, et al. Chitotriosidase activity predicts endothelial dysfunction in type-2 diabetes mellitus. Endocrine 2010;37:455–9.
107. Elmonem MA, Amin HS, El-Essawy RA, Mehaney DA, Nabil M, Kamel LN, et al. Association of chitotriosidase 1 enzyme activity

and genotype with the risk of nephropathy in type 2 diabetes. Clin Biochem 2016;49:444–8.
108. Zurawska-Plaksej E, Knapik-Kordecka M, Rorbach-Dolata A, Piwowar A. Increased chitotriosidase activity in plasma of patients with type 2 diabetes. Arch Med Sci 2016;12:977–84.
109. Turan E, Sozmen B, Eltutan M, Sozmen EY. Serum chitotriosidase enzyme activity is closely related to HbA1c levels and the complications in patients with diabetes mellitus type 2. Diabetes Metabol Syndr 2017;11:S503–6.
110. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun 2010; 34:J258–65.
111. Boot RG, van Achterberg TA, van Aken BE, Renkema GH, Jacobs MJ, Aerts JM, et al. Strong induction of members of the chitinase family of proteins in atherosclerosis: chitotriosidase and human cartilage gp-39 expressed in lesion macrophages. Arterioscler Thromb Vasc Biol 1999;19:687–94.
112. Sotgiu S, Barone R, Zanda B, Arru G, Fois ML, Arru A, et al. Chitotriosidase in patients with acute ischemic stroke. Eur Neurol 2005;54:149–53.
113. Rastogi T, Girerd N, Lamiral Z, Bresso E, Bozec E, Boivin JM, et al. Impact of smoking on cardiovascular risk and premature ageing: findings from the STANISLAS cohort. Atherosclerosis 2022;346: 1–9. 35247627.
114. Artieda M, Cenarro A, Gañán A, Jericó I, Gonzalvo C, Casado JM, et al. Serum chitotriosidase activity is increased in subjects with atherosclerosis disease. Arterioscler Thromb Vasc Biol 2003;23: 1645–52.
115. Kologlu T, Ucar SK, Levent E, Akcay YD, Coker M, Sozmen EY. Chitotriosidase as a possible marker of clinically evidenced atherosclerosis in dyslipidemic children. J Pediatr Endocrinol Metab 2014;27:701–8.
116. Karadag B, Kucur M, Isman FK, Hacibekiroglu M, Vural VA. Serum chitotriosidase activity in patients with coronary artery disease. Circ J 2008;72:71–5.
117. Güçlü A, Yilmaz MI, Tokmak TT, Unal HU, Karaman M, Gezer M, et al. Chitotriosidase as a novel biomarker of early atherosclerosis in hemodialysis patients. Hemodial Int 2017;21:41–6.
118. Bargagli E, Rosi E, Pistolesi M, Lavorini F, Voltolini L, Rottoli P. Increased risk of atherosclerosis in patients with sarcoidosis. Pathobiology 2017;84:258–63.
119. Bustamante A, Dominguez C, Rodriguez-Sureda V, Vilches A, Penalba A, Giralt D, et al. Prognostic value of plasma chitotriosidase activity in acute stroke patients. Int J Stroke 2014;9:910–6.
120. Ridker PM, Chasman DI, Rose L, Loscalzo J, Elias JA. Plasma levels of the proinflammatory chitin-binding glycoprotein YKL-40, variation in the chitinase 3-like 1 gene (CHI3L1), and incident cardiovascular events. J Am Heart Assoc 2014;3: e000897.
121. Oeckl P, Weydt P, Steinacker P, Anderl-Straub S, Nordin F, Volk AE, et al. Different neuroinflammatory profile in amyotrophic lateral sclerosis and frontotemporal dementia is linked to the clinical phase. J Neurol Neurosurg Psychiatry 2019; 90:4–10.
122. Steinacker P, Feneberg E, Halbgebauer S, Witzel S, Verde F, Oeckl P, et al. Chitotriosidase as biomarker for early stage amyotrophic lateral sclerosis: a multicenter study. Amyotroph Lateral Scler Frontotemporal Degener 2021;22:276–86.
123. Yang X, Ji Y, Wang W, Zhang L, Chen Z, Yu M, et al. Amyotrophic lateral sclerosis: molecular mechanisms, biomarkers, and therapeutic strategies. Antioxidants (Basel) 2021;10:1012.
124. Gray E, Thompson AG, Wuu J, Pelt J, Talbot K, Benatar M, et al. CSF chitinases before and after symptom onset in amyotrophic lateral sclerosis. Ann Clin Transl Neurol 2020;7:1296–306.
125. Correale J, Fiol M. Chitinase effects on immune cell response in neuromyelitis optica and multiple sclerosis. Mult Scler 2011;17: 521–31.
126. Qi Y, Chou LS, Zhang LJ, Liu MQ, Yi M, Zhang QX, et al. Increased cerebrospinal fluid YKL-40 levels are associated with disease severity of neuromyelitis optica spectrum disorders. Mult Scler Relat Disord 2020;45:102395.
127. Harris VK, Tuddenham JF, Sadiq SA. Biomarkers of multiple sclerosis: current findings. Degener Neurol Neuromuscul Dis 2017;7:19–29.
128. De Fino C, Lucchini M, Lucchetti D, Nociti V, Losavio FA, Bianco A, et al. The predictive value of CSF multiple assay in multiple sclerosis: a single center experience. Mult Scler Relat Disord 2019;35:176–81.
129. Dönder A, Özdemir HH. Serum YKL-40 levels in patients with multiple sclerosis. Arq Neuropsiquiatr 2021;79:795–8.
130. Tamam Y, Gunes B, Akbayir E, Kizilay T, Karaaslan Z, Koral G, et al. CSF levels of HoxB3 and YKL-40 may predict conversion from clinically isolated syndrome to relapsing remitting multiple sclerosis. Mult Scler Relat Disord 2021;48:102697.
131. Magliozzi R, Pezzini F, Pucci M, Rossi S, Facchiano F, Marastoni D, et al. Changes in cerebrospinal fluid balance of TNF and TNF receptors in naïve multiple sclerosis patients: early involvement in compartmentalised intrathecal inflammation. Cells 2021;10:1712.
132. Matute-Blanch C, Calvo-Barreiro L, Carballo-Carbajal I, Gonzalo R, Sanchez A, Vila M, et al. Chitinase 3-like 1 is neurotoxic in primary cultured neurons. Sci Rep 2020;10:7118.
133. Stern R. Go fly a chitin: the mystery of chitin and chitinases in vertebrate tissues. Front Biosci (Landmark Ed) 2017;22:580–95.
134. Muszyński P, Groblewska M, Kulczyńska-Przybik A, Kułakowska A, Mroczko B. YKL-40 as a potential biomarker and a possible target in therapeutic strategies of Alzheimer's disease. Curr Neuropharmacol 2017;15:906–17.
135. Sanfilippo C, Malaguarnera L, Di Rosa M. Chitinase expression in Alzheimer's disease and non-demented brains regions. J Neurol Sci 2016;369:242–9.
136. Mattsson N, Tabatabaei S, Johansson P, Hansson O, Andreasson U, Månsson JE, et al. Cerebrospinal fluid microglial markers in Alzheimer's disease: elevated chitotriosidase activity but lack of diagnostic utility. Neuromol Med 2011;13: 151–9.
137. Melah KE, Lu SY, Hoscheidt SM, Alexander AL, Adluru N, Destiche DJ, et al. Cerebrospinal fluid markers of Alzheimer's disease pathology and microglial activation are associated with altered white matter microstructure in asymptomatic adults at risk for Alzheimer's disease. J Alzheimers Dis 2016;50:873–86.
138. Erskine D, Ding J, Thomas AJ, Kaganovich A, Khundakar AA, Hanson PS, et al. Molecular changes in the absence of severe pathology in the pulvinar in dementia with Lewy bodies. Mov Disord 2018;33:982–91.
139. Rodrigues FB, Byrne LM, McColgan P, Robertson N, Tabrizi SJ, Zetterberg H, et al. Cerebrospinal fluid inflammatory biomarkers

reflect clinical severity in Huntington's disease. PLoS One 2016; 11:e0163479.
140. Pranzatelli MR, Tate ED, McGee NR. Microglial/macrophage markers CHI3L1, sCD14, and sCD163 in CSF and serum of pediatric inflammatory and non-inflammatory neurological disorders: a case-control study and reference ranges. J Neurol Sci 2017;381:285–90.
141. Freigang M, Steinacker P, Wurster CD, Schreiber-Katz O, Osmanovic A, Petri S, et al. Increased chitotriosidase 1 concentration following nusinersen treatment in spinal muscular atrophy. Orphanet J Rare Dis 2021;16:330.
142. Repaci A, Gambineri A, Pasquali R. The role of low-grade inflammation in the polycystic ovary syndrome. Mol Cell Endocrinol 2011;335:30–41.
143. Alanbay I, Ercan CM, Sakinci M, Coksuer H, Ozturk M, Tapan S. A macrophage activation marker chitotriosidase in women with PCOS: does low-grade chronic inflammation in PCOS relate to PCOS itself or obesity? Arch Gynecol Obstet 2012; 286:1065–71.
144. Alanbay İ, Coksuer H, Ercan CM, Sakinci M, Karaşahin E, Ceyhan ST, et al. Chitotriosidase levels in patients with severe endometriosis. Gynecol Endocrinol 2012;28:220–3.
145. Kahramanoğlu İ, Tokgözoğlu N, Turan H, Şal V, Şimşek G, Gelişgen R, et al. YKL-40 in the diagnosis, prediction of prognosis, and platinum sensitivity in serous epithelial ovarian cancer. Turk J Obstet Gynecol 2018;15:177–81.
146. Kokot I, Piwowar A, Jędryka M, Sołkiewicz K, Kratz EM. Diagnostic significance of selected serum inflammatory markers in women with advanced endometriosis. Int J Mol Sci 2021;22: 2295.
147. Aksoy Ü, Aksoy H, Açmaz G, Babayiğit M, Kandemir Ö. Umbilical artery serum chitotriosidase concentration in pregnancies complicated by preeclampsia and relationship between chitotriosidase levels and fetal blood flow velocity. Hypertens Pregnancy 2013;32:401–9.
148. Malaguarnera L, Di Rosa M, Zambito AM, dell'Ombra N, Nicoletti F, Malaguarnera M. Chitotriosidase gene expression in Kupffer cells from patients with non-alcoholic fatty liver disease. Gut 2006;55:1313–20.
149. Huang H, Wu T, Mao J, Fang Y, Zhang J, Wu L, et al. CHI3L1 is a liver-enriched, noninvasive biomarker that can be used to stage and diagnose substantial hepatic fibrosis. OMICS 2015;19:339–45.
150. Johansen JS, Christoffersen P, Møller S, Price PA, Henriksen JH, Garbarsch C, et al. Serum YKL-40 is increased in patients with hepatic fibrosis. J Hepatol 2000;32:911–20.
151. Taylan A, Gurler O, Toprak B, Sisman AR, Yalcin H, Colak A, et al. Chitotriosidase, and resolvin D1 as potential biomarkers of familial mediterranean fever. J Kor Med Sci 2015;30:1241–5.
152. Doğan HO, Omma A, Turhan T, Boğdaycıoğlu N, Karaaslan Y, Yavuz H, et al. Decreased chitotriosidase activity and levels in familial mediterranean fever. J Kor Med Sci 2016;31:1902–6.
153. Barone R, Bertrand G, Simporè J, Malaguarnera M, Musumeci S. Plasma chitotriosidase activity in beta-thalassemia major: a comparative study between Sicilian and Sardinian patients. Clin Chim Acta 2001;306:91–6.
154. Zhou ER, Arce S. Key players and biomarkers of the adaptive immune system in the pathogenesis of sarcoidosis. Int J Mol Sci 2020;21:7398.
155. Bargagli E, Bennett D, Maggiorelli C, Di Sipio P, Margollicci M, Bianchi N, et al. Human chitotriosidase: a sensitive biomarker of sarcoidosis. J Clin Immunol 2013;33:264–70.
156. Di Francesco AM, Verrecchia E, Sicignano LL, Massaro MG, Antuzzi D, Covino M, et al. The use of chitotriosidase as a marker of active sarcoidosis and in the diagnosis of fever of unknown origin (FUO). J Clin Med 2021;10:5283.
157. Harlander M, Salobir B, Zupančič M, Dolenšek M, Bavčar Vodovnik T. Serial chitotriosidase measurements in sarcoidosis—two to five year follow-up study. Respir Med 2014; 108:775–82.
158. Sellarés J, Francesqui J, Llabres M, Hernandez-Gonzalez F, Baughman RP. Current treatment of sarcoidosis. Curr Opin Pulm Med 2020;26:591–7.
159. Tarasidis A, Arce S. Immune response biomarkers as indicators of sarcoidosis presence, prognosis, and possible treatment: an immunopathogenic perspective. Autoimmun Rev 2020;19: 102462.
160. Abe C, Iwai K, Mikami R, Hosoda Y. Frequent isolation of Propionibacterium acnes from sarcoidosis lymph nodes. Zentralbl Bakteriol Mikrobiol Hyg 1984;256:541–7.
161. Negi M, Takemura T, Guzman J, Uchida K, Furukawa A, Suzuki Y, et al. Localization of propionibacterium acnes in granulomas supports a possible etiologic link between sarcoidosis and the bacterium. Mod Pathol 2012;25:1284–97.
162. Sánchez-Díez S, Munoz X, Ojanguren I, Romero-Mesones C, Espejo D, Villar A, et al. YKL-40 and KL-6 levels in serum and sputum of patients diagnosed with hypersensitivity pneumonitis. J Allergy Clin Immunol Pract 2022;10:2414–23.
163. Brunner JK, Scholl-Bürgi S, Hössinger D, Wondrak P, Prelog M, Zimmerhackl LB. Chitotriosidase activity in juvenile idiopathic arthritis. Rheumatol Int 2008;28:949–50.
164. Özdemir E, Çiçek T, Kaya MO. Association of serum YKL-40 level with tumor burden and metastatic stage of prostate cancer. Urol J 2012;9:568–73.
165. Thein MS, Kohli A, Ram R, Ingaramo MC, Jain A, Fedarko NS. Chitotriosidase, a marker of innate immunity, is elevated in patients with primary breast cancer. Cancer Biomark 2017;19: 383–91.
166. Li H, Wang D, Yi B, Cai H, Xi Z, Lou X, et al. Comprehensive analysis of CD163 as a prognostic biomarker and associated with immune infiltration in glioblastoma Multiforme. BioMed Res Int 2021;2021:8357585.
167. Bonnal RJP, Rossetti G, Lugli E, De Simone M, Gruarin P, Brummelman J, et al. Clonally expanded EOMES^{+} Tr1-like cells in primary and metastatic tumors are associated with disease progression. Nat Immunol 2021;22:735–45.
168. Tizaoui K, Yang JW, Lee KH, Kim JH, Kim M, Yoon S, et al. The role of YKL-40 in the pathogenesis of autoimmune diseases: a comprehensive review. Int J Biol Sci 2022;18:3731–46.
169. Gamal RM, Hammam N, Zakary MM, Abdelaziz MM, Razek MRA, Mohamed MSE, et al. Telomere dysfunction-related serological markers and oxidative stress markers in rheumatoid arthritis patients: correlation with diseases activity. Clin Rheumatol 2018;37:3239–46.
170. Alpsoy S, Akyuz A, Erfan G, Akkoyun DC, Topcu B, Guzel S, et al. Atherosclerosis, some serum inflammatory markers in psoriasis. G Ital Dermatol Venereol 2014;149:167–75.

171. Jensen P, Wiell C, Milting K, Poggenborg RP, Østergaard M, Johansen JS, et al. Plasma YKL-40: a potential biomarker for psoriatic arthritis? J Eur Acad Dermatol Venereol 2013;27:815–9.
172. Wcisło-Dziadecka D, Kotulska A, Brzezińska-Wcisło L, Kucharz EJ, Lis-Swiety A, Kamińska-Wiciorek G. Serum human cartilage glycoprotein-39 levels in patients with systemic lupus erythematosus. Pol Arch Med Wewn 2009;119:777–84.
173. Seo J, Ahn Y, Zheng Z, Kim BO, Choi MJ, Bang D, et al. Clinical significance of serum YKL-40 in Behçet disease. Br J Dermatol 2016;174:1337–44.
174. Erzin Y, Uzun H, Karatas A, Celik AF. Serum YKL-40 as a marker of disease activity and stricture formation in patients with Crohn's disease. J Gastroenterol Hepatol 2008;23:e357–62.
175. Vind I, Johansen JS, Price PA, Munkholm P. Serum YKL-40, a potential new marker of disease activity in patients with inflammatory bowel disease. Scand J Gastroenterol 2003;38: 599–605.
176. Ytting H, Vind I, Bang D, Munkholm P. Sweet's syndrome—an extraintestinal manifestation in inflammatory bowel disease. Digestion 2005;72:195–200.
177. Bernardi D, Podswiadek M, Zaninotto M, Punzi L, Plebani M. YKL-40 as a marker of joint involvement in inflammatory bowel disease. Clin Chem 2003;49:1685–8.
178. Khattab FM, Said NM. Chitinase-3-like protein 1 (YKL-40): novel biomarker of lichen planus. Int J Dermatol 2019;58: 993–6.
179. Jankowska-Konsur A, Łyko M, Rubas K, Nowicka-Suszko D, Maj J, Szepietowski JC. Chitinase-3-like protein 1 (YKL-40): a new biomarker of inflammation in pyoderma gangrenosum. Acta Derm Venereol 2022;102:adv00646.
180. Pawlak K, Rozkiewicz D, Mysliwiec M, Pawlak D. YKL-40 in hemodialyzed patients with and without cardiovascular complications – the enhancement by the coexistence of the seropositivity against hepatitis C virus infection. Cytokine 2013; 62:75–80.
181. Rai MF, Tycksen ED, Cai L, Yu J, Wright RW, Brophy RH. Distinct degenerative phenotype of articular cartilage from knees with meniscus tear compared to knees with osteoarthritis. Osteoarthritis Cartilage 2019;27:945–55.
182. Johansen JS, Pedersen AN, Schroll M, Jørgensen T, Pedersen BK, Bruunsgaard H. High serum YKL-40 level in a cohort of octogenarians is associated with increased risk of all-cause mortality. Clin Exp Immunol 2008;151:260–6.
183. Elmonem MA, Ramadan DI, Issac MS, Selim LA, Elkateb SM. Blood spot versus plasma chitotriosidase: a systematic clinical comparison. Clin Biochem 2014;47:38–43.