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REVIEW

New insights on chitinases immunologic activities

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Abstract

Mammalian chitinases and the related chilectins (ChiLs) belong to the GH18 family, which hydrolyse the glycosidic bond of chitin by a substrate-assisted mechanism. Chitin the fundamental component in the coating of numerous living species is the most abundant natural biopolymer. Mounting evidence suggest that the function of the majority of the mammalian chitinases is not exclusive to catalyze the hydrolysis of chitin producing pathogens, but include crucial role specific in the immunologic activities. The chitinases and chitinase-like proteins are expressed in response to different proinflammatory cues in various tissues by activated macrophages, neutrophils and in different monocyte-derived cell lines. The mechanism and molecular interaction of chitinases in relation to immune regulation embrace bacterial infection, inflammation, dismetabolic and degenerative disease. The aim of this review is to update the reader with regard to the role of chitinases proposed in the recent innate and adaptive immunity literature. The deep scrutiny of this family of enzymes could be a useful base for further studies addressed to the development of potential procedure directing these molecules as diagnostic and prognostic markers for numerous immune and inflammatory diseases.

Key words: Chitinases; Chitinase like proteins; Chronic inflammation; Immune regulation; Autoimmunity

Core tip: The chitinases and chitinase-like proteins are expressed in response to different pro-inflammatory signals by activated macrophages and in different monocyte-derived cell lines. The mechanism and molecular interaction of chitinases in the immune regulation embrace bacterial infection, inflammation, dismetabolic and degenerative disease. The concept of the chitinases involvement in human diseases discussed herein may stimulate the development of new studies leading to a deeper understanding on the biochemical mechanisms inducing chitinases regulation and on the consequences that the increases in chitinases levels impact with immunity and autoimmunity in different conditions. The future understanding on chitinase functions will lead to the opportunity to develop selective and specific chitinase inhibitors.

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INTRODUCTION

Mammalian chitinases and the related chilectins (ChiL) belong to the GH18 family[1]. Chitinases embraces members both with and without glycohydrolase enzymatic activity against chitin. Chitotriosidase (CHIT1) and acidic mammalian chitinase (CHIA) are recognized as true chitinase because are the only two chitinases demonstrating chitinolytic (glycohydrolase) activity[2]. In contrast none of the other mammalian chitinases, encompassing chitinase 3-like-1 (CHI3L1), chitinase 3-like-2 (CHI3L2), chitinase domain–containing 1 (CHID1), display enzymatic activity in the face of the retention and conservation of the substrate-binding cleft of the chitinases[3] and for this reason they are called chitinase-like-lectins (Chi-lectins) or chitinase-like proteins (C/CLPs). Mammalian chitinases with enzymatic activity have a chitin binding domain containing six cysteine residues predisposed for the binding of chitin[4]. Instead, CLPs do not contain such typical chitin-binding domains, but still can bind to chitin with high affinity[5]. A number of evidence reports that the expression of the majority of the mammalian chitinases is differentially regulated during specific immunologic activities and has important biological roles in chronic inflammatory diseases[6-8]. Additionally chitinases have been widely shown to have an antipathogen function, through their capability to degrade both colloidal chitin and chitin in the cell wall of the fungal pathogen. Similarly, mammalian ChiLs may play a role in immunomodulation. The majority of chitinase families are produced by monocyte/macrophages lineage. In addition, macrophages induce inflammatory responses by producing cytokines, chemokines, and lipid mediators. Interestingly, chitinase play a role in modulating the local and/or circulating concentration of chitins in the body and, therefore, in regulating the immune response to this polysaccharide. Hypothetically, when exogenous chitin from sources such as fungi or dust mites are present in the tissues, chitinases act by cleaving chitin which consequently prevent chitin from stimulating immune responses. Hence, it is possible that without active chitinases, chitin accumulate in tissues triggering an excessive inflammatory response. Therefore is clear that induction of chitinase and CLPs is associated with inflammatory disease, including allergy, asthma, dismetabolic and degenerative diseases and several types of cancer[9].

In the last decade various investigations have brought new insights on the immune properties of chitinases and their functions in inflammatory pathologies. Both chitinases and CLPs can activate specific receptors and signaling pathways stimulating immune mediators' generation and amplification of inflammation. New studies are helping to understand the beneficial as well the detrimental properties of chitinases. Characterizing the role of induced chitinases activity promises interesting perspectives. As well, understanding the molecular signalling pathways involved in the immune function influenced by chitinases might be a valuable approach to investigate new therapeutic alternatives for pathological conditions in which the increased immune response and inflammation are involved.

CHITOTRIOSIDASE AND IMMUNITY

CHIT1 was the first mammalian chitinase measured in disease states[4]. CHIT1 has been encompassed as one of the secreted biomarkers for Gaucher's disease[10]. The elevation of CHIT1 in these patients may reflect a particular state of activation of macrophages[11]. CHIT1 is a very critical enzyme to regulate the susceptibility to infection of organisms containing chitin as structural components[2].

The *CHIT1* gene is localized in chromosome 1q31-q32[12] and consists of 12 exons and spans approximately 20 kb of genomic DNA[12]. Recombinant CHIT1 inhibits hyphal growth of fungi, suggesting a physiological role in the host defense mechanism against the invasion/attack of chitin-containing pathogens[13] which to act as adjuvants by stimulating the production of cytokines and chemokines[6]. Further evidence indicates that the enzymatic role of CHIT1 extends to bacteria[4,13]. Usually, CHIT1 activity is very low and originates in the circulating polymorphonuclear cells[12]. CHIT1 rises significantly in response to various pro-inflammatory signals in a complementary fashion in neutrophils and macrophages[4]. The evidence that TLR signaling is a potent inducer in neutrophils, while NOD-2 signaling induces *CHIT1* in macrophages[14], strongly confirms the importance of this enzyme in the immune response. A defect in *CHIT1* gene consisting of 24-bp duplication in exon 10 that activates a cryptic 39 splice site in the same exon generates an abnormally spliced mRNA with an in-frame deletion of 87 nucleotides. This spliced mRNA encodes an enzymatically inactive protein that lacks an internal stretch of 29 amino acids[12]. CHIT1 deficiency appears as an autosomal incompletely dominant disorder, with no activity in homozygous subjects for the defective allele and approximately half-normal activities in heterozygous subjects. *CHIT1* gene mutation has been encountered with high incidence in different Caucasian populations[12], instead, in African peoples living in malaria parasite endemic areas CHIT1 mutation shows a low prevalence. The absence of homozygosis for CHIT1 deficiency in malaria endemics area suggests the hypothesis that susceptibility to parasitic disease influences the CHIT1 allele composition. In sub-Saharan regions the maintenance of the wild-type *CHIT1* gene confirms that CHIT1 provides innate protection from malaria infection[15]. As well the studies reporting that

individuals bearing the mutant allele exhibit an increased susceptibility to chitin-containing pathogens including *Wuchereria bancrofti* filarial, *Plasmodium falciparum* malaria, *Cryptococcus neoformans* and *Candida albicans*[16] confirmed the CHIT1 allele arrangement hypothesis. Nevertheless, in others studies have been reported that a functional polymorphism produces protective effect in human longevity[17] and protects from nonalcoholic fatty liver disease progression[18]. CHIT1 may have organ- as well as cell-specific effects in the setting of infectious diseases and inflammatory disorders. In fact, CHIT1 overexpression in Kupffer cells is involved in the modulation of the tissue remodeling processes in fibroblastic hepatic tissue[18]. Furthermore, the CHIT1 produced by macrophages enhances atherosclerotic plaques formation and subsequent thrombosis[19]. Therefore this enzyme produced by differentiated macrophages can also be damaging to host tissues and are implicated in the progression of a number of chronic inflammatory diseases[20]. In this context, it is important to note that CHIT1 displays different role in the specialized macrophages. CHIT1 modulation changed during the diverse stages of macrophages maturation and in polarized M1 and M2 macrophages[6]. This data could explain why the expression of CHIT-1 is particularly elevated in the later inflamed stages of infection-induced diseases such as tuberculosis and leprosy[21,22]. Remarkably, was also reported that in monocytes interleukin-4 (IL-4) treatment induced a significant increase on CHIT-1 expression[6]. Since IL-4 promotes immune responses to parasites, this finding set straight why CHIT-1 increased secretion is closely associated with pathophysiological conditions dominated by T-helper type 2 (Th2) cells including infections with fungal pathogens and malaria parasites, fibrosis, allergy, and asthma[23-25]. Macrophages are involved in both generation of fibrosis and its resolution. Conversely M2 polarization generates a positive feedback loop during resolution of inflammation, therefore it is unclear what are the events influencing M2 differentiation and interrupting tissue repair/remodeling as well fibrotic outcomes. The finding reporting that CHIT1 increases in M2 subset suggest that CHIT1 could be involved in the modulation of the extracellular matrix affecting cell adhesion and migration during the tissue remodeling processes that take place in fibrogenesis[26,27]. CHIT1 is also involved in human airway hyper-responsiveness and asthma[28], as well as being active to IL-13-driven alveolar fibrosis by augmenting transforming growth factor beta (TGFβ) and mitogen-activated protein kinase signaling in mice[29]. Therefore, it is conceivable that chitinase inhibition might have beneficial effects on the expression of genes associated with tissues remodeling. Additionally, the recent findings demonstrating that CHIT1 is not exclusively produced by macrophages but is expressed in other cells involved in the immune response such as osteoclasts[30,31] and monocyte-derived DCs[32] confirm the active role of CHIT-1 in the immune response and in disease states where inflammatory responses prevail[21,22,28,33-35].

ACIDIC MAMMALIAN CHITINASE AND IMMUNITY

The second true chitinase called AMCase or CHIA has a 30-kDa N-terminal catalytic domain that hydrolyze chitin, and it expressed mainly in the gastrointestinal tract and lung of both mouse and human[36]. Similarly to CHIT1, is located on chromosome 1q13.1e 21.3, and in addition to the N-terminal catalytic domain acidic mammalian chitinase (AMCase) contain a C-terminal chitinase binding domain[5]. The presence of AMCase in the gastrointestinal tract and lung indicates that it plays a crucial role as a food processor in stomach and its involvement in lung inflammation[5,37]. As well, the expression of AMCase in the lung suggests that the enzyme may have a dual function in digestion of chitinous substrates and host defense[38]. This enzyme plays protective role against parasites. AMCase acts as chemotactic agents and synergistically with other chemokines attracting eosinophils and T cells to sites of parasitic infection, appears to modulate tissue inflammation, immunity, and therefore plays active roles in anti-infective defense and repair responses[8]. Recently it has been demonstrated that AMCase and CHIT1 play different rule in the immune response[8]. Comparing the modulation of both AMCase and CHIT1 expression during monocyte/macrophages differentiation and polarization was found that AMCase was not selectively expressed and highly regulated in activated macrophages. The slight increases of AMCase in M1 stage following treatment with pro-inflammatory stimuli indicated AMCase is ineffective against infections and therefore may be involved only in innate immunity[8]. It has been reported that AMCase is specifically upregulated in response to Th2 inflammation in the lung, and is strictly related to pathophysiological conditions dominated by Th2 type cells such as allergy and asthma[39-41]. The early up regulation of AMCase expression in undifferentiated monocytes treated with IL-4 suggested that an inhibition of AMCase prevents this immune response[8]. In addition, genetic studies of the AMCase gene have indicated that certain polymorphisms and haplotypes of AMCase are associated with bronchial asthma in humans[40]. In contrast, other studies revealed that a haplotype encoding an AMCase isoform displaying a significant enzymatic activity was associated with protection from asthma in several United States ethnic populations[41]. These data indicated that an increased AMCase enzymatic activity could be protective against the development of human asthma, possibly through cleavage of inflammatory chitin polymers[41]. This protective isoform of AMCase may reproduce an improved activity in the stomach, where the degradation of ingested polymeric environmental chitin or chitin-containing microorganisms could induce changes of the bowel commensal flora or to alterations in immune

responses to ingested allergens[42,43]. Ingested polymeric chitin has been observed to disrupt interactions with host proteins involved in regulating bacterial adherence to the gastrointestinal epithelium, such as RegⅢ, and to be used as the preferred energy source by certain gut bacteria[44,45]. Alterations in intestinal microflora alter the subsequent immune response to allergens in the lung in experimental models[46]. It has been reported that inhibition with the transition-state analog allosamidin, an inhibitor of chitinase, enhanced the Th2 driven, IL-13-dependent inflammation, endorsing that its chitinase activity play a role in asthma, even in the absence of chitin[47]. The enzymatic activity of AMCase was found critical in the regulation of pulmonary Th2 inflammation in both murine models exposed and unexposed to polymeric chitin. Since AMCase expression is regulated by active Th2 inflammation it is possible that the active isoform predominates in severe asthmatics and/or during asthma exacerbations. Furthermore, expression of the active isoform could be up-regulated by environmental chitin exposures. Chitin microparticles induce alternative macrophage activation through CCL2 signaling in response to binding of chitin by airway epithelial cells[45]. Moreover, chitin induces the release of IL-25, IL-33 and thymic stromal lymphopoietin that are able to activate the production of the type 2 cytokines such as IL-5 and IL-13 in innate lymphoid type 2 cells. This induction also led to both eosinophilia and alternative activation of macrophages[48]. It has been reported that chitin itself is a pattern recognition molecule stimulating the tissue accumulation of innate immune cells associated with asthma, such as eosinophils and basophils[43]. In addition, AMCase preserves airway epithelial cells from undergoing apoptosis by stimulating phosphoinositide 3-kinase (PI3K) and AKT signaling, through a mechanism associated to its chitin-binding site[45].

CHITINASE-3-LIKE-1 AND IMMUNITY

Chitinase-3-like-1 (CHI3L1) protein or YLK-40 binds chitin polymers in the absence of the active site residues necessary for cleavage. CHI3L1 is produced by neutrophils, monocytes/macrophages, monocyte derived dendritic cells and osteoclasts[32,49,50]. CHI3L1 is a pro-inflammatory biomarke[51] and is capable of inducing inflammatory mediators including chemokines (CCL2, CXCL2) and metalloproteases (MMP-9)[51]. Local inflamed tissues including intestinal mucosa in inflammatory bowel disease (IBD)[52] and adipose tissues in type 2 diabetes produce CHI3L1[53]. Induction of CHI3L1 has been reported in autoimmune disorders, in pulmonary sarcoidosis, systemic sclerosis, liver fibrosis, rheumatoid arthritis, bronchial asthma, coronary artery disease, Alzheimer's disease and inflammatory-related illnesses in humans[54-62]. CHI3L1 secretion is induced by interferon (IFN)-γ[5] and IL-6[61] and is an acute phase reactant associated with disease severity and mortality in numerous infectious diseases. The expression of CHI3L1 has been reported to be significantly associated with migration of human macrophages[52] bronchial smooth muscle cells[62] and glioma cells[63]. In inflammation activated macrophages are the major CHI3L1 producers[50]. Substantial evidence supports a role of CHI3L1 in endothelial dysfunction and atherosclerosis[52,60]. CHI3L1 expression was found variably modulated during macrophages activation and polarization supporting that CHI3L1 plays a crucial role during the initial innate immune responses at the site of pathogen invasion[64]. The modulation of CHI3L1 following treatment with pro-inflammatory stimuli in monocytes and its strong increases in M1 polarized macrophages indicates that the antimicrobial pathway in human macrophages involves also a vigorous activation of CHI3L1. Additionally the higher expression in M2 polarized macrophages highlight that CHI3L1 is a mediator of innate and acquired immunity[7]. Remarkably, some evidence indicated that CHI3L1 may play a role in type 2 helper cell-mediated inflammation[65]. Additionally, CHI3L1 is involved in intestinal inflammation and diverse pathologies concerning the mucosal barriers of the stomach and gastrointestinal tract integrity such as inflammatory bowel disorders. Specifically, *CHI3L1* is upregulated in inflammatory conditions of the gut. Moreover, infection studies have suggested a function in both development and resolution of intestinal inflammation as well as bacterial removal[66]. The infection stimulating effects have been found to arise from enhanced adhesion of bacteria to intestinal epithelial cells (IECs)[66], precisely through bacterial interaction with N-glycosylation patterns on *CHI3L1* expressed by IECs[66]. *CHI3L1* also stimulates clearance and resolution of bacterial infections and inflammation in colitis *via* Stat3 signaling[66]. Moreover, elevated serum levels of *CHI3L1* promote a marked protection against *Streptococcus pneumoniae* infection, improving the aptitude of macrophages to kill bacteria and simultaneously protecting the immune cells from pyroptosis by inhibiting IL-1β-driven inflammasome activation[66]. Serum levels of *CHI3L1* are elevated in patients with pathogen-induced inflammation, including purulent meningitis, and endotoxaemia caused by endotoxin of *Escherichia coli*[66]. In both meningitis and pneumonia, CHI3L1 is secreted by locally activated macrophages[66] and neutrophils[67], and thus, has been proposed as a specific supplementary serological marker for the activation of granulocytes and macrophages in inflamed tissues[68]. These evidences confirm that CHI3L1 may have a particular affinity with some pathogenic bacteria. Though chitin is not expressed in bacteria, the majority of chitinase-producing pathogenic microorganisms enclose a gene encoding for the chitin binding protein, which possibly interacts with the binding ability between chitinase producing bacteria and chitin[69]. In a knock-out model of the murine CHI3L1 analogue, CHI3L1 is important in establishing Th2 polarized immune responses and enhance the

recruitment of macrophages, dendritic cells and T-cells by inhibiting apoptosis[70].

Genetic variants of CHI3L1 are associated with reduced lung function in asthmatics[71]. The increase of this protein in the lung has been found also in patients with COPD and pulmonary sarcoidosis[72]. Both macrophages and giant cells in pulmonary sarcoid granuloma express CHI3L1, and serum levels of CHI3L1 are indicative for sarcoid disease activity and ongoing fibrosis[73]. In addition, CHI3L1 promotes the proliferation and antagonizes catabolic or degradative processes during the inflammatory response of connective tissues[74]. Increased concentrations of CHI3L1 have been detected also in serum of patients with rheumatoid arthritis (RA). The ability of CHI3L1 to regulate cell proliferation, adhesion, migration, and activation, as well as to regulate extracellular matrix assembly, correlates well with elevated level of CHI3L1 in the sites of chronic inflammation and active connective tissue turnover. Local release of CHI3L1 in the arthritic joint is followed by a secondary increase of CHI3L1 concentration in serum. Neutrophil-released CHI3L1 acts as an autoantigen in RA. In contrast to healthy individuals, who show strong bias to regulatory response to CHI3L1, patients with RA exhibit polarization towards Th1 phenotype[73]. At the same time CHI3L1 is able to suppress the TNFα and IL-1-induced secretion of matrix metalloproteases and IL-8 in both human skin fibroblasts and articular chondrocytes[74]. In contrast, in RA the serum levels of CHI3L1 positively correlated with serum levels of IL-6 and CRP[75]. Increased levels of CHI3L1 in serum reflect the degree of the synovial inflammation and joint destruction in patients with RA and OA[76]. Moreover, elevated level of CHI3L1 is a marker for joint involvement in IBD[77] and for the activity of the disease[59]. Rheumatic symptoms are also common for extra-intestinal manifestations of IBD, which is an autoimmune inflammatory disorder of the colon and small intestine. CHI3L1 also colocalises with lactoferrin, but not with gelatinase in both stimulated and non-stimulated neutrophils. Moreover, release of CHI3L1 from specific neutrophil granules was suggested to lead to the post-transfusional complications, which were avoided depleting leukocytes by filtration of whole blood in order to inhibit extracellular CHI3L1 accumulation during storage of erythrocyte components[78]. CHI3L1 promotes proliferation of human synovial cells, skin and fetal lung fibroblasts, an effect that occurs in synergy with the insulin-like growth factor[79]. CHI3L1 is upregulated in distinct subsets of macrophages, particularly, in early atherosclerotic lesions and in macrophages which infiltrated deep in the lesion[80]. Later proteomics study identified elevated levels of CHI3L1 in supernatants of macrophage cell line THP-1 treated with oxidized LDL[81], proving that CHI3L1 expression is indicative for the differentiation of macrophages during formation of atherosclerotic plaque[79].

CHI3L2 AND IMMUNITY

CHI3L2 was originally isolated from the cultured medium of primary human articular cartilage chondrocytes[82]. CHI3L2 is homologous to the family 18 chitinases in the human genome, it lacks of chitinase activity but possesses a chitinase-like fold and putative lectin properties[83]. CHI3L2 is recognized as a biochemical marker for the activation of chondrocytes and the progress of the osteoarthritis in human. CHI3L2 mRNA is significantly up-regulated in cartilage of patients with osteoarthritis (OA) *vs* normal subjects, while no significant up-regulation was detected for CHI3L2 mRNA in OA cartilage[82]. Particularly CHI3L2 expression is upregulated both in early degenerative and late stage of osteoarthritis. Proteomic analysis established that CHI3L2 is secreted by human osteoarthritic cartilage in culture[5]. The contribution of CHI3L2 to the OA progression is suggested by the induction of autoimmune response[84] and by its involvement in tissue remodeling. However these finding suggested that synovial fibroblasts do not represent the exclusive producers of CHI3L2 in OA. Recently, CHI3L2 has been found slightly expressed in macrophages differentiated in the presence of IFN-γ or IL-4[85]. Only classically activated or M1 macrophages are able to produce CHI3L2, whereas in response to IFN-γ and LPS stimulation undifferentiated monocytes were unable to produce CHI3L2[85]. Thus, IFN-γ which is one of the main cytokines in OA tissues that is able to induce the production of CHI3L2 by monocyte-derived macrophages. In patients with OA, the amount of autoantibodies to CHI3L2 and other autoantigens on early phases of disease indicates that the autoimmune response occurs during the initial phase of cartilage degeneration[86]. It has been demonstrated that Th1 cells prevail in the synovium of patients with OA[87]. In addition the co-treatment of IL-4 and TGF-β promotes stimulatory effect on the expression of CHI3L2 in macrophage cultures[88]. So far, the studies on biological activity of CHI3L2 are limited, therefore further studies are necessary to elucidate the role of CHI3L2 in immunopathology and inflammatory diseases.

CONCLUSION

Chitinases synthesis occurs in most innate immune responses against fungi, bacteria and other non-viral pathogens. In the context of infectious diseases, it is likely that chitinases activity can be both detrimental and beneficial for the host organism. In addition, it cannot be excluded that chitinases augmentations have negative consequences in those conditions in which they are regarded as biochemical markers of macrophage activation. Although we do not yet fully understand the implications of chitinases production in response to chitinous pathogens, the concept of their function as "more than just antipathogens and antifungicidals" seems reasonable. In support to this opinion, the

aforesaid investigations confirming that CHIT-1, CHI3L1 and CHI3L2 can be regarded as mediators of the immune and inflammatory responses and are involved in the progression of degenerative and dismetabolic disorders. The general concept of the chitinases involvement in human diseases discussed in this review may stimulate the development of new planning and experiments leading to a deeper understanding, not only on the biochemical mechanisms inducing chitinases regulation, but also on the consequences that the increases in chitinases levels impact with immunity and autoimmunity in different conditions. The future understanding will lead to the opportunity to develop selective and specific chitinase inhibitors.

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