**Name of Journal: *World Journal of Immunology***

**ESPS Manuscript NO: 21054**

**Manuscript Type: Review**

**New insights on chitinases immunologic activities**

Di Rosa M *et al*. Chitinases and immunity

**Michelino Di Rosa, Violetta Brundo, Lucia Malaguarnera**

**Michelino Di Rosa, Lucia Malaguarnera,** Department of Biomedical and Biotechnology Sciences, University of Catania, 95124 Catania, Italy

**Violetta Brundo,** Department of Biological, Geological and environmental Sciences, University of Catania, 95124 Catania, Italy

**Auhtor contributions:** di Rosa M analyzed and interpreted the data; Brundo V collected the data; Malaguarnera L wrote the paper.

**Conflict-of-interest statement:** The authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to: Lucia Malaguarnera MD, PhD, Professor,** Department of Biomedical Science and Biotechnology, University of Catania, 95124 Catania, Italy. lucmal@unict.it

**Telephone:** +39-095-313429

**Fax:** +39-095-320267

**Received:** June 28, 2015

**Peer-review started:** July 5, 2015

**First decision:** September 17, 2015

**Revised:** March 15, 2016

**Accepted:** April 7, 2016

**Article in press:**

**Published online:**

**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

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Di Rosa M, Brundo V, Malaguarnera L. New insights on chitinases immunologic activities. *World J Immunol* 2016; In press

**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*i*n macrophages[14], strongly confirmsthe 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 CHIT-1 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 (NAFLD) 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 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 (MAPK) 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 (AMCASE) 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 AMCase contain a C-terminal chitinase binding domain (CBM)[5]. The presence of AMCase in the gastrointestinal tract and lung indicates that it plays a crucial role as afood 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 actsas chemotactic agents and synergistically with otherchemokines attracting eosinophils and T cells to sites of parasiticinfection, appears to modulate tissueinﬂammation, immunity, and therefore plays activeroles in anti-infective defense and repairresponses[8]. Recently it has been demonstrated that AMCaseand CHIT1 play different rule in the immune response[8]. Comparing the modulation of both AMCaseand CHIT1 expression during monocyte/macrophagesdifferentiation 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[39-41], 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 interleukin-25 (IL-25), IL-33 and thymic stromal lymphopoitin 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 (CHI3L1) AND IMMUNITY**

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 interleukin (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, CHI3L1is 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 inflammosome 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 colonand 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].

**CHITINASE 3-LIKE 2 (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) versus 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 auto-antigens 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.

# REFERENCES

1. **Bussink AP**, Speijer D, Aerts JM, Boot RG. Evolution of mammalian chitinase(-like) members of family 18 glycosyl hydrolases. *Genetics* 2007; **177**: 959-970 [PMID: 17720922 DOI: 10.1534/genetics.107.075846]
2. **Boot RG**, Blommaart EF, Swart E, Ghauharali-van der Vlugt K, Bijl N, Moe C, Place A, Aerts JM. Identification of a novel acidic mammalian chitinase distinct from chitotriosidase. *J Biol Chem* 2001; **276**: 6770-6778 [PMID: 11085997 DOI: 10.1074/jbc.M009886200]
3. **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 U S A* 2001; **98**: 8979-8984 [PMID: 11481469 DOI: 10.1073/pnas.151103798]
4. **Malaguarnera L**. Chitotriosidase: the yin and yang. *Cell Mol Life Sci* 2006; **63**: 3018-3029 [PMID: 17075695 DOI: [10.1007/s00018-006-6269-2](http://dx.doi.org/10.1007/s00018-006-6269-2%22%20%5Ct%20%22_blank)]
5. **Kzhyshkowska J**, Gratchev A, Goerdt S. Human chitinases and chitinase-like proteins as indicators for inflammation and cancer. *Biomark Insights* 2007; **2**: 128-146 [PMID: 19662198]
6. **Di Rosa M**, Malaguarnera G, De Gregorio C, D'Amico F, Mazzarino MC, Malaguarnera L. Modulation of chitotriosidase during macrophage differentiation. *Cell Biochem Biophys* 2013; **66**: 239-247 [PMID: 23152091 DOI: 10.1007/s12013-012-9471-x]
7. **Di Rosa M**, Malaguarnera G, De Gregorio C, Drago F, Malaguarnera L. Evaluation of CHI3L-1 and CHIT-1 expression in differentiated and polarized macrophages. *Inflammation* 2013; **36**: 482-492 [PMID: 23149946 DOI: 10.1007/s10753-012-9569-8]
8. **Di Rosa M**, De Gregorio C, Malaguarnera G, Tuttobene M, Biazzo F, Malaguarnera L. Evaluation of AMCase and CHIT-1 expression in monocyte macrophages lineage. *Mol Cell Biochem* 2013; **374**: 73-80 [PMID: 23129258 DOI: 10.1007/s11010-012-1506-5]
9. **Qureshi AM**, Hannigan A, Campbell D, Nixon C, Wilson JB. Chitinase-like proteins are autoantigens in a model of inflammation-promoted incipient neoplasia. *Genes Cancer* 2011; **2**: 74-87 [PMID: 21779482 DOI: 10.1177/1947601911402681]
10. **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**: 1288-1292 [PMID: 8132768 DOI: 10.1172/JCI117084]
11. **Boven LA**, van Meurs M, Boot RG, Mehta A, Boon L, Aerts JM, Laman JD. Gaucher cells demonstrate a distinct macrophage phenotype and resemble alternatively activated macrophages. *Am J Clin Pathol* 2004; **122**: 359-369 [PMID: 15362365 DOI: 10.1309/BG5VA8JRDQH1M7HN]
12. **Boot RG**, Renkema GH, Verhoek M, Strijland A, Bliek J, de Meulemeester TM, Mannens MM, Aerts JM. The human chitotriosidase gene. Nature of inherited enzyme deficiency. *J Biol Chem* 1998; **273**: 25680-25685 [PMID: 9748235 DOI: 10.1074/jbc.273.40.25680]
13. **Wiesner DL**, Specht CA, Lee CK, Smith KD, Mukaremera L, Lee ST, Lee CG, Elias JA, Nielsen JN, Boulware DR, Bohjanen PR, Jenkins MK, Levitz SM, Nielsen K. Chitin recognition via chitotriosidase promotes pathologic type-2 helper T cell responses to cryptococcal infection. *PLoS Pathog* 2015; **11**: e1004701 [PMID: 25764512 DOI: 10.1371/journal.ppat.1004701]
14. **van Eijk M**, Scheij SS, van Roomen CP, Speijer D, Boot RG, Aerts JM. TLR- and NOD2-dependent regulation of human phagocyte-specific chitotriosidase. *FEBS Lett* 2007; **581**: 5389-5395 [PMID: 17976376 DOI: http: //dx.doi.org/10.1016/j.febslet.2007.10.039]
15. **Malaguarnera L**, Simporè J, Prodi DA, Angius A, Sassu A, Persico I, Barone R, Musumeci S. A 24-bp duplication in exon 10 of human chitotriosidase gene from the sub-Saharan to the Mediterranean area: role of parasitic diseases and environmental conditions. *Genes Immun* 2003; **4**: 570-574 [PMID: 14647197 DOI: 10.1038/sj.gene.6364025]
16. **van Eijk M**, van Roomen CP, Renkema GH, Bussink AP, Andrews L, Blommaart EF, Sugar A, Verhoeven AJ, Boot RG, Aerts JM. Characterization of human phagocyte-derived chitotriosidase, a component of innate immunity. *Int Immunol* 2005; **17**: 1505-1512 [PMID: 16214810 DOI: 10.1093/intimm/dxh328]
17. **Malaguarnera L**, Ohazuruike LN, Tsianaka C, Antic T, Di Rosa M, Malaguarnera M. Human chitotriosidase polymorphism is associated with human longevity in Mediterranean nonagenarians and centenarians. *J Hum Genet* 2010; **55**: 8-12 [PMID: 19881466 DOI: 10.1038/jhg.2009.111]
18. **Di Rosa M**, Mangano K, De Gregorio C, Nicoletti F, Malaguarnera L. Association of chitotriosidase genotype with the development of non-alcoholic fatty liver disease. *Hepatol Res* 2013; **43**: 267-275 [PMID: 22971072 DOI: 10.1111/j.1872-034X.2012.01063.x]
19. **Artieda M**, Cenarro A, Gañán A, Lukic A, Moreno E, Puzo J, Pocoví M, Civeira F. Serum chitotriosidase activity, a marker of activated macrophages, predicts new cardiovascular events independently of C-reactive protein. *Cardiology* 2007; **108**: 297-306 [PMID: 17290100 DOI: 10.1159/000099099]
20. [**Kanneganti M**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Kanneganti%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23439988), [Kamba A](http://www.ncbi.nlm.nih.gov/pubmed/?term=Kamba%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23439988), [Mizoguchi E](http://www.ncbi.nlm.nih.gov/pubmed/?term=Mizoguchi%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23439988). Role of chitotriosidase (chitinase 1) under normal and disease conditions. *J Epithel Biol Pharmacol* 2012; **5**: 1-9 [PMID: 23439988]
21. **Bargagli E**, Margollicci M, Nikiforakis N, Luddi A, Perrone A, Grosso S, Rottoli P. Chitotriosidase activity in the serum of patients with sarcoidosis and pulmonary tuberculosis. *Respiration* 2007; **74**: 548-552 [PMID: 17347558 DOI: 10.1159/000100555]
22. **Iyer A**, van Eijk M, Silva E, Hatta M, Faber W, Aerts JM, Das PK. Increased chitotriosidase activity in serum of leprosy patients: association with bacillary leprosy. *Clin Immunol* 2009; **131**: 501-509 [PMID: 19307157 DOI: 10.1016/j.clim.2009.02.003]
23. **Cho SJ**, Weiden MD, Lee CG. Chitotriosidase in the Pathogenesis of Inflammation, Interstitial Lung Diseases and COPD. *Allergy Asthma Immunol Res* 2015; **7**: 14-21 [PMID: 25553258 DOI: 10.4168/aair.2015.7.1.14]
24. **Malaguarnera L**, Musumeci M, Di Rosa M, Scuto A, Musumeci S. Interferon-gamma, tumor necrosis factor-alpha, and lipopolysaccharide promote chitotriosidase gene expression in human macrophages. *J Clin Lab Anal* 2005; **19**: 128-132 [PMID: 15900564]
25. **Stein M**, Keshav S, Harris N, Gordon S. Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. *J Exp Med* 1992; **176**: 287-292 [PMID: 1613462]
26. **Malaguarnera L**, Di Rosa M, Zambito AM, dell'Ombra N, Di Marco R, Malaguarnera M. Potential role of chitotriosidase gene in nonalcoholic fatty liver disease evolution. *Am J Gastroenterol* 2006; **101**: 2060-2069 [PMID: 16848812 DOI: 10.1111/j.1572-0241.2006.00680.x]
27. **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**: 1313-1320 [PMID: 16825325 DOI: 10.1136/gut.2005.075697]
28. **Gavala ML**, Kelly EA, Esnault S, Kukreja S, Evans MD, Bertics PJ, Chupp GL, Jarjour NN. Segmental allergen challenge enhances chitinase activity and levels of CCL18 in mild atopic asthma. *Clin Exp Allergy* 2013; **43**: 187-197 [PMID: 23331560 DOI: 10.1111/cea.12032]
29. **Lee CG**, Herzog EL, Ahangari F, Zhou Y, Gulati M, Lee CM, Peng X, Feghali-Bostwick C, Jimenez SA, Varga J, Elias JA. Chitinase 1 is a biomarker for and therapeutic target in scleroderma-associated interstitial lung disease that augments TGF-β1 signaling. *J Immunol* 2012; **189**: 2635-2644 [PMID: 22826322 DOI: 10.4049/jimmunol.1201115]
30. **Di Rosa M**, Tibullo D, Vecchio M, Nunnari G, Saccone S, Di Raimondo F, Malaguarnera L. Determination of chitinases family during osteoclastogenesis. *Bone* 2014; **61**: 55-63 [PMID: 24440516 DOI: 10.1016/j.bone.2014.01.005]
31. **Di Rosa M**, Szychlinska MA, Tibullo D, Malaguarnera L, Musumeci G. Expression of CHI3L1 and CHIT1 in osteoarthritic rat cartilage model. A morphological study. *Eur J Histochem* 2014; **58**: 2423 [PMID: 25308850 DOI: 10.4081/ejh.2014.2423]
32. **Di Rosa M**, Tibullo D, Cambria D, Distefano G, Saccone S, Di Raimondo F, Malaguarnera L. Chitotriosidase Expression during Monocyte-Derived Dendritic Cells Differentiation and Maturation. *Inflammation* 2015; **38**: 2082-2091 [PMID: 26026464 DOI: 10.1007/s10753-015-0190-5]
33. **Di Rosa M**, Dell'Ombra N, Zambito AM, Malaguarnera M, Nicoletti F, Malaguarnera L. Chitotriosidase and inflammatory mediator levels in Alzheimer's disease and cerebrovascular dementia. *Eur J Neurosci* 2006; **23**: 2648-2656 [PMID: 16817867 DOI: 10.1111/j.1460-9568.2006.04780.x]
34. **Di Rosa M**, Zambito AM, Marsullo AR, Li Volti G, Malaguarnera L. Prolactin induces chitotriosidase expression in human macrophages through PTK, PI3-K, and MAPK pathways. *J Cell Biochem* 2009; **107**: 881-889 [PMID: 19415692 DOI: 10.1002/jcb.22186]
35. **Di Rosa M**, Musumeci M, Scuto A, Musumeci S, Malaguarnera L. Effect of interferon-gamma, interleukin-10, lipopolysaccharide and tumor necrosis factor-alpha on chitotriosidase synthesis in human macrophages. *Clin Chem Lab Med* 2005; **43**: 499-502 [PMID: 15899671 DOI: 10.1515/CCLM.2005.088]
36. **Zhu Z**, Zheng T, Homer RJ, Kim YK, Chen NY, Cohn L, Hamid Q, Elias JA. Acidic mammalian chitinase in asthmatic Th2 inflammation and IL-13 pathway activation. *Science* 2004; **304**: 1678-1682 [PMID: 15192232 DOI: 10.1126/science.1095336]
37. **Chou YT**, Yao S, Czerwinski R, Fleming M, Krykbaev R, Xuan D, Zhou H, Brooks J, Fitz L, Strand J, Presman E, Lin L, Aulabaugh A, Huang X. Kinetic characterization of recombinant human acidic mammalian chitinase. *Biochemistry* 2006; **45**: 4444-4454 [PMID: 16584180 DOI: 10.1021/bi0525977]
38. **Adrangi S**, Faramarzi MA. From bacteria to human: a journey into the world of chitinases. *Biotechnol Adv* 2013; **31**: 1786-1795 [PMID: 24095741 DOI: 10.1016/j.biotechadv.2013.09.012]
39. **Zimmermann N**, Mishra A, King NE, Fulkerson PC, Doepker MP, Nikolaidis NM, Kindinger LE, Moulton EA, Aronow BJ, Rothenberg ME. Transcript signatures in experimental asthma: identification of STAT6-dependent and -independent pathways. *J Immunol* 2004; **172**: 1815-1824 [PMID: 14734765 DOI: 10.4049/jimmunol.172.3.1815]
40. **Bierbaum S**, Nickel R, Koch A, Lau S, Deichmann KA, Wahn U, Superti-Furga A, Heinzmann A. Polymorphisms and haplotypes of acid mammalian chitinase are associated with bronchial asthma. *Am J Respir Crit Care Med* 2005; **172**: 1505-1509 [PMID: 16179638 DOI: 10.1164/rccm.200506-890OC]
41. **Seibold MA**, Reese TA, Choudhry S, Salam MT, Beckman K, Eng C, Atakilit A, Meade K, Lenoir M, Watson HG, Thyne S, Kumar R, Weiss KB, Grammer LC, Avila P, Schleimer RP, Fahy JV, Rodriguez-Santana J, Rodriguez-Cintron W, Boot RG, Sheppard D, Gilliland FD, Locksley RM, Burchard EG. Differential enzymatic activity of common haplotypic versions of the human acidic Mammalian chitinase protein. *J Biol Chem* 2009; **284**: 19650-19658 [PMID: 19435888 DOI: 10.1074/jbc.M109.012443]
42. **Cash HL**, Whitham CV, Behrendt CL, Hooper LV. Symbiotic bacteria direct expression of an intestinal bactericidal lectin. *Science* 2006; **313**: 1126-1130 [PMID: 16931762 DOI: 10.1126/science.1127119]
43. **Chen HC**, Chang CC, Mau WJ, Yen LS. Evaluation of N-acetylchitooligosaccharides as the main carbon sources for the growth of intestinal bacteria. *FEMS Microbiol Lett* 2002; **209**: 53-56 [PMID: 12007653]
44. **Noverr MC**, Falkowski NR, McDonald RA, McKenzie AN, Huffnagle GB. Development of allergic airway disease in mice following antibiotic therapy and fungal microbiota increase: role of host genetics, antigen, and interleukin-13. *Infect Immun* 2005; **73**: 30-38 [PMID: 15618138 DOI: 10.1128/IAI.73.1.30-38.2005]
45. **Hartl D**, He CH, Koller B, Da Silva CA, Kobayashi Y, Lee CG, Flavell RA, Elias JA. Acidic mammalian chitinase regulates epithelial cell apoptosis via a chitinolytic-independent mechanism. *J Immunol* 2009; **182**: 5098-5106 [PMID: 19342690 DOI: 10.4049/jimmunol.0803446]
46. **Roy RM**, Wüthrich M, Klein BS. Chitin elicits CCL2 from airway epithelial cells and induces CCR2-dependent innate allergic inflammation in the lung. *J Immunol* 2012; **189**: 2545-2552 [PMID: 22851704 DOI: 10.4049/jimmunol.1200689]
47. **Van Dyken SJ**, Mohapatra A, Nussbaum JC, Molofsky AB, Thornton EE, Ziegler SF, McKenzie AN, Krummel MF, Liang HE, Locksley RM. Chitin activates parallel immune modules that direct distinct inflammatory responses via innate lymphoid type 2 and γδ T cells. *Immunity* 2014; **40**: 414-424 [PMID: 24631157 DOI: 10.1016/j.immuni.2014.02.003]
48. **Rehli M**, Niller HH, Ammon C, Langmann S, Schwarzfischer L, Andreesen R, Krause SW. Transcriptional regulation of CHI3L1, a marker gene for late stages of macrophage differentiation. *J Biol Chem* 2003; **278**: 44058-44067 [PMID: 12933821 DOI: 10.1074/jbc.M306792200]
49. **Lee JH**, Kim SS, Kim IJ, Song SH, Kim YK, In Kim J, Jeon YK, Kim BH, Kwak IS. Clinical implication of plasma and urine YKL-40, as a proinflammatory biomarker, on early stage of nephropathy in type 2 diabetic patients. *J Diabetes Complications* ; **26**: 308-312 [PMID: 22705282 DOI: 10.1016/j.jdiacomp.2012.04.012]
50. **Di Rosa M**, Tibullo D, Saccone S, Distefano G, Basile MS, Di Raimondo F, Malaguarnera L. CHI3L1 nuclear localization in monocyte derived dendritic cells. *Immunobiology* 2016; **221**: 347-356 [PMID: 26466985 DOI: 10.1016/j.imbio.2015.09.023]
51. **Libreros S**, Garcia-Areas R, Shibata Y, Carrio R, Torroella-Kouri M, Iragavarapu-Charyulu V. Induction of proinflammatory mediators by CHI3L1 is reduced by chitin treatment: decreased tumor metastasis in a breast cancer model. *Int J Cancer* 2012; **131**: 377-386 [PMID: 21866546 DOI: 10.1002/ijc.26379]
52. **Chen CC**, Pekow J, Llado V, Kanneganti M, Lau CW, Mizoguchi A, Mino-Kenudson M, Bissonnette M, Mizoguchi E. Chitinase 3-like-1 expression in colonic epithelial cells as a potentially novel marker for colitis-associated neoplasia. *Am J Pathol* 2011; **179**: 1494-1503 [PMID: 21763261 DOI: 10.1016/j.ajpath.2011.05.038]
53. **Nielsen AR**, Erikstrup C, Johansen JS, Fischer CP, Plomgaard P, Krogh-Madsen R, Taudorf S, Lindegaard B, Pedersen BK. Plasma YKL-40: a BMI-independent marker of type 2 diabetes. *Diabetes* 2008; **57**: 3078-3082 [PMID: 18650368 DOI: 10.2337/db08-0182]
54. **Coffman FD**. Chitinase 3-Like-1 (CHI3L1): a putative disease marker at the interface of proteomics and glycomics. *Crit Rev Clin Lab Sci* 2008; **45**: 531-562 [PMID: 19003601 DOI: [10.1080/10408360802334743](http://dx.doi.org/10.1080/10408360802334743%22%20%5Ct%20%22_blank)]
55. **Johansen JS**, Milman N, Hansen M, Garbarsch C, Price PA, Graudal N. Increased serum YKL-40 in patients with pulmonary sarcoidosis--a potential marker of disease activity? *Respir Med* 2005; **99**: 396-402 [PMID: 15763444 DOI: [10.1016/j.rmed.2004.09.016](http://dx.doi.org/10.1016/j.rmed.2004.09.016%22%20%5Ct%20%22_blank)]
56. **Nordenbaek C**, Johansen JS, Halberg P, Wiik A, Garbarsch C, Ullman S, Price PA, Jacobsen S. High serum levels of YKL-40 in patients with systemic sclerosis are associated with pulmonary involvement. *Scand J Rheumatol* 2005; **34**: 293-297 [PMID: 16195162 DOI: 10.1080/03009740510018598]
57. **Lebensztejn DM**, Skiba E, Werpachowska I, Sobaniec-Łotowska ME, Kaczmarski M. Serum level of YKL-40 does not predict advanced liver fibrosis in children with chronic hepatitis B. *Adv Med Sci* 2007; **52**: 120-124 [PMID: 18217402]
58. **Choi J**, Lee HW, Suk K. Plasma level of chitinase 3-like 1 protein increases in patients with early Alzheimer's disease. *J Neurol* 2011; **258**: 2181-2185 [PMID: 21562723 DOI: 10.1007/s00415-011-6087-9]
59. **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 [PMID: 12825867 DOI: [10.1080/00365520310000537](http://dx.doi.org/10.1080/00365520310000537%22%20%5Ct%20%22_blank)]
60. **Wang Y**, Ripa RS, Johansen JS, Gabrielsen A, Steinbruchel DA, Friis T, Bindslev L, Haack-Sørensen M, Jørgensen E, Kastrup J. YKL-40 a new biomarker in patients with acute coronary syndrome or stable coronary artery disease. *Scand Cardiovasc J* 2008; **42**: 295-302 [PMID: 18615353 DOI: 10.1080/14017430802220567]
61. **Nielsen AR**, Plomgaard P, Krabbe KS, Johansen JS, Pedersen BK. IL-6, but not TNF-α, increases plasma YKL-40 in human subjects. *Cytokine* 2011; **55**: 152-155 [PMID: 21478032 DOI: 10.1016/j.cyto.2011.03.014]
62. **Bara I**, Ozier A, Girodet PO, Carvalho G, Cattiaux J, Begueret H, Thumerel M, Ousova O, Kolbeck R, Coyle AJ, Woods J, Tunon de Lara JM, Marthan R, Berger P. Role of YKL-40 in bronchial smooth muscle remodeling in asthma. *Am J Respir Crit Care Med* 2012; **185**: 715-722 [PMID: 22281830 DOI: 10.1164/rccm.201105-0915OC]
63. **Di Rosa M**, Sanfilippo C, Libra M, Musumeci G, Malaguarnera L. Different pediatric brain tumors are associated with different gene expression profiling. *Acta Histochem* 2015; **117**: 477-485 [PMID: 25792036 DOI: 10.1016/j.acthis.2015.02.010]
64. **Mizoguchi E**. Chitinase 3-like-1 exacerbates intestinal inflammation by enhancing bacterial adhesion and invasion in colonic epithelial cells. *Gastroenterology* 2006; **130**: 398-411 [PMID: 16472595 DOI: [10.1053/j.gastro.2005.12.007](http://dx.doi.org/10.1053/j.gastro.2005.12.007%22%20%5Ct%20%22_blank)]
65. **Ahangari F**, Sood A, Ma B, Takyar S, Schuyler M, Qualls C, Dela Cruz CS, Chupp GL, Lee CG, Elias JA. Chitinase 3-like-1 regulates both visceral fat accumulation and asthma-like Th2 inflammation. *Am J Respir Crit Care Med* 2015; **191**: 746-757 [PMID: 25629580 DOI: 10.1164/rccm.201405-0796OC]
66. **Tran HT**, Lee IA, Low D, Kamba A, Mizoguchi A, Shi HN, Lee CG, Elias JA, Mizoguchi E. Chitinase 3-like 1 synergistically activates IL6-mediated STAT3 phosphorylation in intestinal epithelial cells in murine models of infectious colitis. *Inflamm Bowel Dis* 2014; **20**: 835-846 [PMID: 24694795 DOI: 10.1097/MIB.0000000000000033]
67. **Dela Cruz CS**, Liu W, He CH, Jacoby A, Gornitzky A, Ma B, Flavell R, Lee CG, Elias JA. Chitinase 3-like-1 promotes Streptococcus pneumoniae killing and augments host tolerance to lung antibacterial responses. *Cell Host Microbe* 2012; **12**: 34-46 [PMID: 22817986 DOI: 10.1016/j.chom.2012.05.017]
68. **Rathcke CN**, Vestergaard H. YKL-40--an emerging biomarker in cardiovascular disease and diabetes. *Cardiovasc Diabetol* 2009; **8**: 61 [PMID: 19930630 DOI: 10.1186/1475-2840-8-61]
69. **Kawada M**, Chen CC, Arihiro A, Nagatani K, Watanabe T, Mizoguchi E. Chitinase 3-like-1 enhances bacterial adhesion to colonic epithelial cells through the interaction with bacterial chitin-binding protein. *Lab Invest* 2008; **88**: 883-895 [PMID: 18490894 DOI: 10.1038/labinvest.2008.47]
70. **Lee CG**, Hartl D, Lee GR, Koller B, Matsuura H, Da Silva CA, Sohn MH, Cohn L, Homer RJ, Kozhich AA, Humbles A, Kearley J, Coyle A, Chupp G, Reed J, Flavell RA, Elias JA. Role of breast regression protein 39 (BRP-39)/chitinase 3-like-1 in Th2 and IL-13-induced tissue responses and apoptosis. *J Exp Med* 2009; **206**: 1149-1166 [PMID: 19414556 DOI: 10.1084/jem.20081271]
71. **Ober C**, Tan Z, Sun Y, Possick JD, Pan L, Nicolae R, Radford S, Parry RR, Heinzmann A, Deichmann KA, Lester LA, Gern JE, Lemanske RF, Nicolae DL, Elias JA, Chupp GL. Effect of variation in CHI3L1 on serum YKL-40 level, risk of asthma, and lung function. *N Engl J Med* 2008; **358**: 1682-1691 [PMID: 18403759 DOI: 10.1056/NEJMoa0708801]
72. **Létuvé S**, Kozhich A, Arouche N, Grandsaigne M, Reed J, Dombret MC, Kiener PA, Aubier M, Coyle AJ, Pretolani M. YKL-40 is elevated in patients with chronic obstructive pulmonary disease and activates alveolar macrophages. *J Immunol* 2008; **181**: 5167-5173 [PMID: 18802121 DOI: 10.4049/jimmunol.181.7.5167]
73. **Kim SH**, Choi H, Yoon MG, Ye YM, Park HS. Dipeptidyl-peptidase 10 as a genetic biomarker for the aspirin-exacerbated respiratory disease phenotype. *Ann Allergy Asthma Immunol* 2015; **114**: 208-213 [PMID: 25592153 DOI: 10.1016/j.anai.2014.12.003]
74. **Ling H**, Recklies AD. The chitinase 3-like protein human cartilage glycoprotein 39 inhibits cellular responses to the inflammatory cytokines interleukin-1 and tumour necrosis factor-alpha. *Biochem J* 2004; **380**: 651-659 [PMID: 15015934 DOI: 10.1042/BJ20040099]
75. **van Bilsen JH**, van Dongen H, Lard LR, van der Voort EI, Elferink DG, Bakker AM, Miltenburg AM, Huizinga TW, de Vries RR, Toes RE. Functional regulatory immune responses against human cartilage glycoprotein-39 in health vs. proinflammatory responses in rheumatoid arthritis. *Proc Natl Acad Sci USA* 2004; **101**: 17180-17185 [PMID: 15569925 DOI: 10.1073/pnas.0407704101]
76. **Matsumoto T**, Tsurumoto T. Serum YKL-40 levels in rheumatoid arthritis: correlations between clinical and laborarory parameters. *Clin Exp Rheumatol* 2001; **19**: 655-660 [PMID: 11791636]
77. **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**: 1685-1688 [PMID: 14500601 DOI: 10.1373/49.10.1685]
78. **Cintin C**, Johansen JS, Skov F, Price PA, Nielsen HJ. Accumulation of the neutrophil-derived protein YKL-40 during storage of various blood components. *Inflamm Res* 2001; **50**: 107-111 [PMID: 11289654 DOI: [10.1007/s000110050732](http://dx.doi.org/10.1007/s000110050732%22%20%5Ct%20%22_blank)]
79. **Recklies AD**, White C, Ling H. The chitinase 3-like protein human cartilage glycoprotein 39 (HC-gp39) stimulates proliferation of human connective-tissue cells and activates both extracellular signal-regulated kinase- and protein kinase B-mediated signalling pathways. *Biochem J* 2002; **365**: 119-126 [PMID: 12071845 DOI: 10.1042/BJ20020075]
80. **Boot RG**, van Achterberg TA, van Aken BE, Renkema GH, Jacobs MJ, Aerts JM, de Vries CJ. Strong induction of members of the chitinase family of proteins in atherosclerosis: chitotriosidase and human cartilage gp-39 expressed in lesion macrophages. *Arterioscler Thromb Vasc Biol* 1999; **19**: 687-694 [PMID: 10073974 DOI: 10.1161/01.ATV.19.3.687]
81. **Nagy ZS**, Czimmerer Z, Szanto A, Nagy L. Pro-inflammatory cytokines negatively regulate PPARγ mediated gene expression in both human and murine macrophages via multiple mechanisms. *Immunobiology* 2013; **218**: 1336-1344 [PMID: 23870825 DOI: 10.1016/j.imbio.2013.06.011]
82. **Steck E**, Breit S, Breusch SJ, Axt M, Richter W. Enhanced expression of the human chitinase 3-like 2 gene (YKL-39) but not chitinase 3-like 1 gene (YKL-40) in osteoarthritic cartilage. *Biochem Biophys Res Commun* 2002; **299**: 109-115 [PMID: 12435396 DOI: 10.1016/S0006-291X(02)02585-8]
83. **De Ceuninck F**, Marcheteau E, Berger S, Caliez A, Dumont V, Raes M, Anract P, Leclerc G, Boutin JA, Ferry G. Assessment of some tools for the characterization of the human osteoarthritic cartilage proteome. *J Biomol Tech* 2005; **16**: 256-265 [PMID: 16461950]
84. **Du H**, Masuko-Hongo K, Nakamura H, Xiang Y, Bao CD, Wang XD, Chen SL, Nishioka K, Kato T. The prevalence of autoantibodies against cartilage intermediate layer protein, YKL-39, osteopontin, and cyclic citrullinated peptide in patients with early-stage knee osteoarthritis: evidence of a variety of autoimmune processes. *Rheumatol Int* 2005; **26**: 35-41 [PMID: 15378262 DOI: 10.1007/S00296-004-04972]
85. **Ishii H**, Tanaka H, Katoh K, Nakamura H, Nagashima M, Yoshino S. Characterization of infiltrating T cells and Th1/Th2-type cytokines in the synovium of patients with osteoarthritis. *Osteoarthritis Cartilage* 2002; **10**: 277-281 [PMID: 11950250 DOI: 10.1053/joca.2001.0509]
86. **Di Rosa M**, Tibullo D, Malaguarnera M, Tuttobene M, Malaguarnera L. Comparison of CHI3L2 and CHIT-1 expression during macrophages differentiation and polarization. *Modern Res Inflamm* 2013; **2**: 82-89 [DOI: 10.4236/mri.2013.24011]
87. **Tsuruha J**, Masuko-Hongo K, Kato T, Sakata M, Nakamura H, Sekine T, Takigawa M, Nishioka K. Autoimmunity against YKL-39, a human cartilage derived protein, in patients with osteoarthritis. *J Rheumatol* 2002; **29**: 1459-1466 [PMID: 12136906]
88. **Gratchev A**, Schmuttermaier C, Mamidi S, Gooi L, [Goerdt S](http://www.ncbi.nlm.nih.gov/pubmed/?term=Goerdt%20S%5BAuthor%5D&cauthor=true&cauthor_uid=19578492), Kzhyshkowska J. Expression of Osteoarthritis Marker YKL-39 is Stimulated by Transforming Growth Factor Beta (TGF-beta) and IL-4 in Differentiating Macrophages. *Biomark Insights* 2008; **3**: 39-44 [PMID: 19578492]

**P-Reviewer:** Ferrante A, Nagata T **S-Editor:** Kong JX **L-Editor: E-Editor:**