International Journal of Pharmaceutical and Bio-Medical Science

ISSN(print): 2767-827X, ISSN(online): 2767-830X

Volume 04 Issue 03 March 2024

Page No: 182-187

DOI: https://doi.org/10.47191/ijpbms/v4-i3-10, Impact Factor: 7.792

Biological Roles of Chitinase 1 in Pathogenic Conditions

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ABSTRACT

Chitin is a prevalent biopolymer found in arthropods such as mollusks, crustaceans, nematodes, worms, and insects. Chitin do not consider as a structural component in mammals. Chitinase enzymes are a group of proteins that have a special ability to attach to and break down chitin, and they are widely preserved throughout evolution. Chitinase in humans was first identified by its ability to break down chitotrioside which is considered as its substrates and for that reason it named chitotriosidase which is also known as CHIT1 or chitinase-1. It is primarily secreted from macrophages during their activated phase in both typical and inflammatory circumstances. Individuals with Gaucher's disease (GD) have a notable rise in CHIT1 activity in both plasma and tissues compared to those without the condition. GD is a hereditary ailment characterized by lipid buildup in certain organs' macrophages such as the lungs, spleen, liver, kidneys, bone marrow, and brain. Serum CHIT1 levels are commonly utilized as a robust diagnostic biomarker to assess the effectiveness of therapy for several diseases that we reviewed in this review.

KEYWORDS: Chitinase, Chitotriosidase, Gaucher's disease, Niemann-Pick Disease, Diabetes Mellitus, Sarcoidosis, Atherosclerosis.

ARTICLE DETAILS

Published On:
14 March 2024

Available on:
https://ijpbms.com/

CHITINASES (GLYCOHYDROLASE 18 FAMILY)

Chitin is a prevalent biopolymer found in arthropods such as mollusks, crustaceans, nematodes, worms, and insects. Chitin do not consider as a structural component in mammals. It is a polymer composed of N-acetyl-D-glucosamine units linked together in a linear β (1 → 4) fashion. Chitinase enzymes are a group of proteins that have a special ability to attach to and break down chitin, and they are widely preserved throughout evolution. Mammalian chitinases are part of the glycoside hydrolase 18 family, which includes chitinases that are not enzymatically active (Vandevenne et al., 2011).

Mammalian chitinases can break down chitin to oligosaccharides of different sizes through endochitinase activity that cause a fragmentation of Chitin into smaller parts which is also subjected to exochitinase enzyme that cause a release of a monomer of glucosamine from chitin's end. Chitinases have a role in immunity either adaptive and innate and are essential for three distinct functions: Chitinases are produced in specific organisms throughout growth to help modify their biological structures to adapt to alterations in body size and form. Chitinases aid certain species in digesting food that contains chitin (Kanneganti et al., 2012).

Chitinases are found in mammals such as humans and mice, which can react with pathogens containing chitin such parasites, fungus, and house dust mites, to break down the protective layer of these microbes that cause infection which contain chitin in their outer layer. Chitinases can destroy the inner core of chitin, causing expulsion of the pathogen's body which lead to death of these organisms (Park et al., 2009).

Mammalian Chitinases and Chitinase-Like Proteins (CLPs)

Chitinases are produced to safeguard mammalian cells from external infections that have chitin in their composition. Mammalian chitinases are categorized based on their enzymatic activity into chitinases and chitinase-like proteins. The genuine chitinase enzymes are chitotriosidases (CHIT1) and the acidic mammalian chitinases (AMCase), CHIT1 are recognized as the initial mammalian chitinases that identified and subjected to researches. Chitinase 3-like 1 (YKL40) and chitinase 3-like 2 (YKL39) which are

considered as Chitinase-like proteins are mentioned in the study of Eurich et al. (2009). Chitinases have a structure where the N-terminal catalytic domain of proteins from the glycohydrolase 18 family adopts the triose-phosphate isomerase fold, known for its (β/α) γ barrel structure. The 4th strand in this barrel features a conserved motif sequence (DXXDXDXE), with D representing aspartic acid, E representing glutamic acid, and X representing any amino acid. This constitutes the active region of the enzyme, where glutamic acid is the crucial residue that provides the proton necessary for breaking down the β (1→4) glycosidic link in chitin (Kanneganti et al., 2012).

Conversely, the essential glutamic acid was replaced in CHI3L1by leucine, in CHI3L2 or eosinophil chemotactic factor by isoleucine, or glutamine, resulting in the absence of chitinolytic action. Nevertheless, these proteins can still effectively bind chitin even in the absence of enzymatic activity due to the preserved chitin-binding aromatic residues on the triose-phosphate isomerase barrel (Kanneganti et al., 2012). Members of chitinase family in Human are situated on the chromosome near the genes of major histocompatibility complex paralogue, suggesting that there is a possible role for chitinases in the immunity whether adaptive or innate, as mentioned before. Enzymatically active chitinases such AMCase and CHIT1 break down chitin to eliminate pathogens, while CLPs play a crucial biological role by strongly attaching to chitin (Shuhui et al., 2009). They may play a role in detecting pathogen-associated molecular patterns found in chitin, which then triggers the immunity system of the host to launch a targeted attack against the pathogen. Moreover, CHI3L1 cause significant increases the in invasiveness and the adhesion ability of pathogenic bacteria onto epithelial cells in the colon through the interaction with the chitin/chitin-binding protein complex which is expressed on the bacteria (Frederiksen et al., 2013; Kawada et al., 2008).

Chitotriosidase 1 (CHIT1) is mostly produced in neutrophils and macrophages, whereas AMCase is predominantly synthesized in both macrophages and epithelial cells, primarily in tissues of lungs. Chitinases and CLPs are elevated in Th2-related inflammation, such as allergen-induced inflammation, rhinitis, and bronchial asthma. CHIT1 is a diagnostic marker for several illnesses such as Gaucher's disease (GD), nonalcoholic fatty liver disease, atherosclerosis, and juvenile idiopathic arthritis. CHI3L1 is mainly elevated in rheumatoid arthritis, liver fibrosis, inflammatory bowel disease, and various cancers. Chitinases and CLPs show a notable rise in expression levels in acute and/or chronic inflammatory conditions, as indicated by Kanneganti et al. (2012).

THE CHIT1 ROLE IN NORMAL AND DISEASE CONDITIONS

Chitinase in humans was first identified by its ability to break down chitotrioside which is considered as its substrates and for that reason it named chitotriosidase which is also known as CHIT1 or chitinase-1. It is primarily secreted from macrophages during their activated phase in both typical and inflammatory circumstances. Individuals with Gaucher's disease have a notable rise in CHIT1 activity in both plasma and tissues compared to those without the condition. Gaucher's disease is a hereditary ailment characterized by lipid buildup in certain organs' macrophages such as the lungs, spleen, liver, kidneys, bone marrow, and brain. Serum CHIT1 levels are commonly utilized as a robust diagnostic biomarker to assess the effectiveness of therapy for Gaucher's disease or β-glucocerebrosidase deficiency (Kanneganti et al., 2012).

Individuals with a deficiency in CHIT1 due to a mutation in the CHIT1 gene, are more susceptible to infections caused by pathogens containing chitin in their body such as Plasmodium falciparum malaria, Candida albicans, Wuchereria bancrofti filaria, and Cryptococcus neoformans. The results of previous studies reveled that CHIT1 has a crucial role in regulating susceptibility to infection by organisms that include chitin as structural components. In fibroblastic hepatic tissue CHIT1 has been demonstrated to participate in modulating tissue remodelling processes (Kanneganti et al., 2012). Kupffer cells in their activated status have the responsibility of CHIT1 is synthesis. Kupffer cells are considered as a kind of resident liver macrophages. These cells trigger hepatic stellate cells to make collagen, leading to excessive collagen production, which in turn causes hepatic fibrosis and liver cirrhosis (Eurich et al., 2009).

Moreover, CHIT1 secreted by macrophages enhances the likelihood of atherosclerotic plaque formation and that can cause thrombosis. Other researchers observed that the colonic epithelial cells synthesis of CHIT1 is significantly reduced during the inflammatory bowel disease's active phase of, such as ulcerative colitis. CHIT1 could have unique impacts on organs and cells during viral infections and inflammatory conditions (Kanneganti et al., 2012).

The CHIT1 Roles in Normal Biological Status

CHIT1 is considered as the first known chitinase that identified and studied profoundly in mammals. It exhibits transglycosylation activity on chitin and it is recognized as an enzymatically active chitinase. It is the primary chitinase that detected in healthy or/and diseased conditions. neutrophils and macrophages are the cells that responsible for the synthesize, storage and release of CHIT1, which are key players in innate immune responses, indicating a significant function in regulating homeostasis in the innate immune system. Nevertheless, the precise operational mechanism has not been completely elucidated. The chitotriosidase enzyme is a highly abundant protein released by differentiated and activated macrophages which is strongly correlated with the macrophage lineage's activation status of (Larsen et al., 2014). CHIT1 enzymatic activity is elevated in abnormal

situations due to the heightened activity of peripheral macrophages in acute/chronic inflammatory states. Recombinant CHIT1 hinders the formation of fungal hyphae, playing a role in the host's defence mechanism against diseases that have chitin in their structure (Larsen et al., 2014).

New research indicates that chitotriosidase's enzymatic activity extends to bacteria as well. Studies show that people with low chitotriosidase activity are more prone to infection by microfilarial due to the decreased in the chitinolytic activity, allowing for pathogen inside the host to reproduce properly. Studies demonstrated that CHIT1 is a protein which has a molecular weight of 50 kilodaltons. The structure comprises a C-terminal chitin-binding domain and 39 kD N-terminal triose phosphate isomerase (TIM) barrel containing the catalytic groove and connected by a brief hinge region (Hamid et al., 2013).

The catalytic region of CHIT1 which is of a molecular mass of 39 kD looks similar to that of chitinases in less evolved organisms. The primarily form of enzyme that secreted is that with a molecular mass of 50 kD which is subjected to cleavage and the subunit with a molecular mass of 39 kD which is considered as the catalytic region will be accumulated in the lysosomes of neutrophils and macrophages, this catalytic subunit were located mainly in the tissues whereas the holoenzyme (50 kD) released into the bloodstream (Hamid et al., 2013).

Chitotriosidase Roles in Pathogenic Conditions

1. Gaucher's Disease (GD)

It is defined by macrophages filled with glucocerebroside, which are referred to as Gaucher cells. The cells were also shown to be surrounded by inflammatory phagocytes. Accumulation of glucocerebroside leads to inflammation in macrophages, causing them to swell, reduce their ability to engulf particles, and damage various organs such as the liver, bone, spleen, kidneys, lungs, and bone marrow (Kanneganti et al., 2012). Some biomarkers were released from Gaucher cells into the bloodstream which are useful for GD diagnosis, assessment of the clinical severity, and for the evaluation of the effectiveness of the enzyme replacement therapy (ERT), one of these biomarkers is CHIT1 which is recognized as a secreted GD biomarker. Abnormal increased CHIT1 levels in patients with GD may indicate that the macrophages are in a specific activation status, resulting in an overproduction of CHIT1. CHIT1 activity is minimal in a healthy population and comes from the circulating polymorphonuclear cells (Irún et al., 2013).

Patients with Gaucher's disease have a 10 to 1000-fold increase in the activity of this enzyme in their blood. This measure is useful for ERT monitoring patients with GD, as stated by Hizarcioglu-Gulsen et al. (2014). Enzyme replacement therapy may lead to a decrease in chitotriosidase activity, which could affect the activation of tissue macrophage rather than reducing Gaucher cells in the disease. The activity of CHIT1 has the most significant decrease in the initial year of enzyme replacement therapy (ERT). ERT shown the greatest effectiveness in the initial six months and after one year, which is indicated by the significant decrease in the activity of CHIT1 as chitinolytic which indicates that the quick initial decrease in CHIT1 activity after ERT can result from the changes in the macrophages and their progenitors' differentiation or activation, rather than a reduction in Gaucher cell load. Serum chitotriosidase activity levels typically stabilize around two years after initiating enzyme replacement therapy (ERT). Despite 5 years of ERT, serum CHIT1 levels remained elevated at 10 folds the normal levels (Shawky and Elsayed, 2016).

Elevated chitotriosidase activity levels suggest that enzyme replacement therapy (ERT) may not completely eliminate Gaucher cells in certain affected areas. Following the discontinuation of enzyme replacement therapy (ERT), macrophages accumulated glucocerebrosides once more, suggesting elevated CHIT1 production and a relapse of Gaucher's illness. The specific relationship between the elevated chitotriosidase activity levels and the molecular processes of macrophage activation/infiltration and it effect on the progression of GD remains uncertain (Shawky and Elsayed, 2016).

The role of Chitotriosidase variants in the diagnosis and therapeutic monitoring patients with Gaucher disease

Various biomarkers such as CD163, tartrate-resistant acid phosphatase (TRAP), ferritin or angiotensin-converting enzyme (ACE), are used to monitor Gaucher disease (GD). Nevertheless, these symptoms are not exclusive to this particular illness. The highly efficient biomarker for GD is now chitotriosidase (ChT; EC 3.2.1.14) which is an enzyme that released into the bloodstream by activated macrophages. It is valuable in the medical treatment of several lysosomal and other disorders (Irún et al., 2013).

The chromosome 1q31-32 is the chromosome in which a CHIT1 gene locates that comprises 12 exons. Gaucher storage cells secrete the enzyme, which is elevated by an average of 600 times in GD patients' plasma. The levels of CHIT1 significantly fall after receiving the treatment with enzyme replacement therapy (ERT) and rise again after stopping the treatment, serving as a reliable indicator of the success of ERT and substrate reduction therapy (Irún et al., 2013). Yet, two constraints have been identified in utilizing CHIT1 activity as a biomarker. Conventional substrates such as 4-methylumbelliferyl-β-D-N,N′, N″triacetylchitotrioside (4MU-chitotrioside) cannot be employed at maximum concentrations due to substrate blockage from transglycosidase activity. Thus, these settings do not precisely represent CHIT1 protein levels (Irún et al., 2013).

A new substrate, 4MU-deoxychitobiose, has been created to address this constraint and enable a more precise and sensitive assessment. Nevertheless, 4MU-deoxychitobioside is more expensive than 4MU-chitotrioside, leading to its limited use in laboratories. Furthermore, the majority of CHIT1activity data provided is

analysed using conventional substrates (Irún et al., 2013). Polymorphisms in the CHIT1 gene can lead to a decrease in CHIT1activity, causing another potential issue. c.1049_1072dup24 is a prevalent 24-base pair duplication in exon 10 that results in the removal of 87 nucleotides in-frame and causes a total absence of CHIT1activity. This genetic variation is present in a homozygous state in around 6% of individuals with European heritage. Another prevalent genetic variation, p.G102S, hinders CHIT1enzyme activity when utilising 4MU-chitotrioside substrate, resulting in underestimated CHIT1levels and subsequent misunderstanding (Irún et al., 2013).

An increase in the CHIT1 activity which is considered as an endo-β-glucosaminidase, was seen in the plasma of patients with GD as reported firstly by Hollak and his co-workers in 1994. Aerts and his colleagues in 1995 demonstrated that the activity of the enzyme in the sample of 491 patients with GD type 1 4 patients with GD type 2, and 11 patients with GD type 3 were 1033-fold, 199-fold, and 650-fold, respectively, higher than the median value of the healthy participants (Aerts et al, 1995a). In asymptomatic patients with GD, the increase was reported to be just 4.5-9.7 times higher. No significant correlation was found between the mild increase in the levels of CHIT1 in asymptomatic GD patients and the clinical manifestations severity or the patients' genotype, as evaluated using Zimran's severity score index (SSI) (Hollak et al, 1994).

About 6% of the population lacks CHIT1 activity due to a hereditary defect produced by a gene duplication in the chitotriosidase gene (Irún et al., 2013). CHIT1 activity is unlikely to play a role in the GD's clinical signs in people who lack it, as per Hollak et al's study in 1994. Recent studies have shown a 12-fold rise in Chitotriosidase activity in the brain and a 50-time increase in the spleen of a GD patient type 1 compared to healthy people (Aerts et al, 1995b). Two primary isoforms of chitotriosidase were isolated from the spleen, one of them with an isoelectric point of 7.2 with a molecular weight of 50 KDa whereas another isoform have an isoelectric point of 8.0 with molecular weights of 39 KDa. The amino acid sequence at the N-terminal of the two forms were shown to be the same (Renkema et al, 1995a).

The CHIT1 internal and N-terminal region sequence were similar to the sequences of proteins belonging to the chitinase family as demonstrated by Hakala and his colleagues in 1993 (Hakala et al., 1993). These proteins are from different organisms and share significant similarity in multiple domains, particularly in the area responsible for catalyzing chitin and the synthetic substrate 4-MU-chitotrioside (Watanabe et al, 1993). The human enzyme CHIT1 exhibits chitin-degrading activity towards both artificial substrates and chitin itself. It can be classified as a chitinase due to its similarity to chitinases found in non-mammalian organisms such as the nematode Brugia malayi or the fungus Aphanocladium album.

The discovery that chitotriosidase functions as a chitinase is significant because it was previously thought that the human body does not contain chitin (Raghavan et al, 1994). In the spleen of GD patients, CHIT1 showed distinct differences comparing with chitinase proteins obtained from other mammalian in that it dose not have a chitinolytic activity. Instead, CHIT1 in the spleen of GD patients seemed more similar to non-mammalian chitinases. This human chitotriosidase is believed to have a role in defending against and breaking down chitin-containing diseases like fungus, nematodes, and insects. It can also serve as an indicator for certain illness conditions.

2. Niemann-Pick Disease

Niemann-Pick disorder (NPD) is a lysosomal storage disorder which is genetically considered as an autosomal recessive disease. It is classified into type major types according to the location of gene mutation as type C1 (NPC1) and type C2 (NPC2) representing NPC1 or NPC2 genetic mutations. Niemann-Pick Disease is identified by the presence of foam cells, also called Niemann-Pick cells, due to their foamy or soapsuds-like appearance. The cells release CHIT1 into the bloodstream. CHIT1 serum levels are significantly increased in Niemann-Pick disease, similar to Gaucher's disease. The activity of CHIT1 which is higher than 4000 nmol/h per mL indicates a prognostic factor for NPD. The significant differences in the CHIT1 activity levels between patients and controls, indicating its potential use as a treatment monitoring tool. The elevated activity of CHIT1 is likely due to the escalated infiltration of tissue macrophages, which may lead to a fluctuation in the CHIT1 levels, depending on the severity of infiltration in the disease (Sheth et al., 2010).

3. Infectious Disease

infectious disease that affects the levels of CHIT1 is Malaria which is characterized by high CHIT1 levels. Anaemia is a common clinical sign in individuals with Plasmodium falciparum infection, caused by the death of red blood cells through phagocytosis and hypersplenism. When the rate of RBC degradation increases, high amount of iron and erythrocyte membrane degradation products within those cells were accumulated in the macrophages which in turn cause an increase in the The CHIT1 production Elevated levels of CHIT1 in the plasma were correlated with haematological factors such as the severity of thrombocytopenia and serum ferritin levels. This finding suggests that elevated plasma CHIT1 levels in malaria may indicate activation of the reticuloendothelial system, akin to people with Gaucher's disease (Kanneganti et al., 2012).

4. Diabetes Mellitus

Research has demonstrated that individuals with recently diagnosed, untreated, and uncomplicated type 2 diabetes mellitus exhibit increased levels of serum chitotriosidase activity. This increase is associated with the age in addition to the patients' levels of plasma glucose, and asymmetric dimethylarginine (ADMA). ADMA is a naturally

occurring compound found in human blood plasma that is produced as a protein breakdown's byproduct in several cell types throughout the body, acting as an analogue of L-arginine. High levels of ADMA can impede the synthesis of nitric oxide and can cause an impairment in the endothelial function, especially in persons with diabetes mellitus. (Sibal et al., 2010). The association between ADMA levels and the high activity of CHIT1 can be used as a significant biomarker for the prediction of endothelial dysfunction in patients with type 2 diabetes mellitus, which is caused by the atherosclerotic lesion's progression. (Di Rosa & Malaguarnera, 2016).

5. Sarcoidosis

It is a systemic disease characterized with an accumulation of mononuclear phagocytes and activated proliferating T lymphocytes in affected areas, leading to the formation of granulomas. The disease's genesis is unknown. Patients with active sarcoidosis typically exhibit significantly elevated levels of CHIT1 in both their serum and bronchoalveolar lavage. In the third and fourth stage, sarcoidosis levels are markedly elevated in comparison to stages 0 and 1. Elevated serum levels of CHIT1 may indicate the progression of the disease to organs beyond the lungs. Most patients have a reduction in CHIT1 activity following therapy with corticosteroids and remission of the condition (Kiszałkiewicz et al., 2015).

6. Atherosclerosis

Atherosclerosis is an inflammatory disorder where lipids and fibrous material gradually build up in the walls of arteries. Atherosclerosis initiation begins with the activation of endothelial cells, which enables monocytes to infiltrate the arterial wall. Once monocytes transform into macrophages, they gather lipids from the bloodstream, stay in the vessel wall, and turn into lipid-filled foam cells. These unique macrophages are stimulated by growth factors and cytokines released by activated endothelial cells and macrophages (Kanneganti et al., 2012). Atherosclerosis patients have a 55-fold increase in serum CHIT1 levels compared to healthy individuals, indicating a strong correlation between lipid-laden macrophages and the levels of CHIT1 expression in arterial walls of atherosclerotic patients. High serum chitotriosidase activity is closely linked to the severity of atherosclerotic lesions, indicating that CHIT1 could serve as a potential marker for the extent of atherosclerosis. High levels of serum CHIT1 activity in atherosclerotic patients indicate the activation of macrophages in these individuals. Individuals with ischemic heart disease (IHD) and atherothrombotic stroke (ATS) showed considerably increased CHIT1 activity compared to healthy control people (Cho et al., 2015).

7. Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), such as Crohn's disease and ulcerative colitis, are chronic inflammatory illnesses that impact patients for their whole lives. Imbalanced interactions between the host and microbes are significant in the onset of IBD. The human large intestine is inhabited by a significant number of commensal anaerobic bacteria, many of which cannot be cultivated using conventional microbiological methods (Kanneganti et al., 2012).

IBD patients typically have a modified commensal bacterial flora characterised by elevated levels of harmful bacteria such as adherent invasive Escherichia coli (AIEC), Peptostreptococcus species, Bacteroides, Eubacterium, intestinal Helicobacter species and Fusobacterium varium,. Some harmful bacteria in the usual microorganisms, such as AIEC and Bacteroides species, are closely linked to the start of intestinal inflammation, especially in Crohn's disease (Kanneganti et al., 2012).

CHI3L1 is actively secreted by colonic epithelial cells and lamina proprial macrophages during inflammation, as reported by Tran et al. in 2011. They have shown a surprising function of CHI3L1 in promoting bacterial attachment and penetration into colonic epithelial cells. CHI3L1 has a high affinity for chitin but does not have the ability to break it down enzymatically, as stated by Eurich et al. (2009).

CONCLUSION

Both active and inactive mammalian chitinases are crucial in the development of chronic inflammation and allergic responses. CHIT1 that is enzymatically active is linked to various illnesses that involve macrophage activation. This review highlights human disorders that provide compelling evidence for the dual and conflicting activities of CHIT1 in regulating and progressing inflammatory and/or infectious diseases. The impact of CHIT1 appears to rely on various parameters, such as the stage of inflammation and the particular cell types and organs affected. Furthermore, the distributions and manifestations of CHIT1 are markedly different. Subsequent research will help us comprehend the significance of this novel chitinase in the progression of inflammatory disorders, viral diseases, and solid tumours.

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