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Review

Chitin and chitinase: Role in pathogenicity, allergenicity and health

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ABSTRACT

Chitin, a polysaccharide with particular abundance in fungi, nematodes and arthropods is immunogenic. It acts as a threat to other organisms, to tackle which they have been endowed with chitinase enzyme. Even if this enzyme is not present in all organisms, they possess proteins having chitin-binding domain(s) (ChtBD). Many lethal viruses like Ebola, and HCV (Hepatitis C virus) have these domains to manipulate their carriers and target organisms. In keeping with the basic rule of survival, the self-origin (own body component) chitins and chitinases are protective, but that of non-self origin (from other organisms) are detrimental to health. The exogenous chitins and chitinases provoke human innate immunity to generate a deluge of inflammatory cytokines, which injure organs (leading to asthma, atopic dermatitis etc.), and in persistent situations lead to death (multiple sclerosis, systemic lupus erythromatosus (SLE), cancer, etc.). Unfortunately, chitin-chitinase-stimulated hypersensitivity is a common cause of occupational allergy. On the other hand, chitin, and its deacetylated derivative chitosan are increasingly proving useful in pharmaceutical, agriculture, and biocontrol applications. This critical review discusses the complex nexus of chitin and chitinase and assesses both their pathogenic as well as utilitarian aspects.

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1. Introduction

Mankind is overwhelmed by pathogenic and allergenic health issues. In this regard, chitin, an insoluble, linear β-1, 4-linked polymer of *N*-acetylglucosamine (GlcNAc) monosaccharide units seems to have a pivotal role [1]. This polymer is an essential component of fungi (*Neurospora*, *Rhizopus*, *Ustilago*, *Saccharomyces*, *Candida*, *Aspergillus*, *Trichoderma*, *Cryptococcus* etc.) [2], diatoms (*Thalassiosira*, *Cyclotella*) [3], zooplanktons [4], nematodes (*Schistosoma*) [5], molluscs (*Atrina rigida*) [6] and arthropods (*Drosophila*, mosquitoes, cockroaches) [7–9]. The cell walls, shells, exoskeletons (cuticle) and peritrophic membranes of these organisms are made of chitin [10,11]. It also serves as the food and energy source for several bacteria such as *Pseudomonas aeruginosa*, *Listeria monocytogenes*, *Serratia marcescens*, *Vibrio harveyi*, *Vibrio cholerae*, *Bacillus circulans etc.* [12–14]. Chitin is the second most abundant polysaccharide following cellulose [15]. Chitin synthase is the enzyme responsible for chitin synthesis [16]. This enzyme is a member of CAZy database (Carbohydrate-Active EnZymes) (http://www.cazy.org), belonging to the glycosyltransferase-2 (GT-2) family, clustered along with cellulose synthase and hyaluronan synthase [17,18]. It is located in the plasma membrane and it

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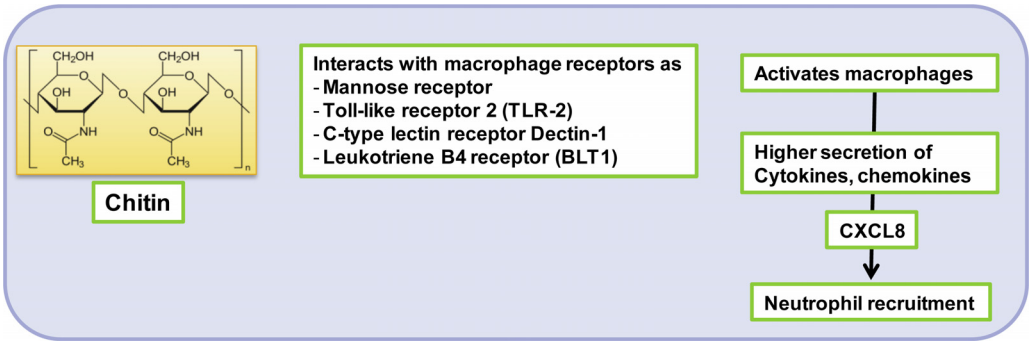

Fig. 1. Chitin and its immune activation mechanism.

transfers *N*-acetylglucosamine units to the growing chitin chain [16]. Chlorovirus CVK2 infecting Chlorella cells elaborate the chitin synthase enzyme, which leads to the deposition of chitin outside the cell wall of the blue-green alga [19]. Whether this exogenous chitin is protective or harmful for the alga depends on its equilibrium with the virus. Genome-wide analyses of chitin synthase-coding genes (chs) in bacteria revealed their sharing by horizontal gene transfer (HGT). As per the study, several of the recipient bacteria are plant pathogens such as *Agrobacterium vitis*, *Pseudomonas cichorii*, *Dickeya* spp, *Pectobacterium* spp and *Brenneria* spp. [20]. Antifungal agents of echinocandin class that inhibit cell wall β-(1, 3)-glucan synthesis are perceived as a threat to some fungi. In retaliation, the fungus *Candida albicans* upregulated the chitin synthase gene expression, via PKC (protein kinase C), HOG (osmolarity glycerol response), and Ca^{2+}-calcineurin signaling pathways [21]. SMART (Simple Modular Architecture Research Tool)-based domain architecture analysis of the enzyme chitin synthase revealed the presence of several transmembrane passes, coiled coil region and a Cyt-b5 domain [22]. Cyt-b5 (cytochrome b5-like heme/steroid binding domain) is present in human cytochrome P450 (CYP) enzymes and it play roles in drug metabolism [23].

Chitin is the substrate of enzyme chitinase (EC 3.2.1.14) belonging to family 18 and 19 glycoside hydrolase (GH) as described in CAZy database [18,24]. Chitinase, the depolymerizing enzyme has been discovered in virus [25], bacteria [26], fungi [27], protozoa [28], arthropods [29] and plants [30]. These organisms from diverse phylogenetic hierarchies employ chitinases for 'defense and offense' functions [28,31,32]. A number of reviews have discussed diverse aspects of chitinases [33]. Bacterial chitinases from *Erwinia*, *Serratia*, *Bacillus* [34,35], *Vibrio* [36], *Pyrococcus* [37], *Francisella* [32], *Streptomyces*, *Alteromonas* sp. and *Nocardiopsis* [38,39] have been well-studied. *Francisella tularensis* secretes chitinase for infecting the arthropod (ticks, mosquitos etc.) vectors for spreading tularemia [32]. Even the GRAS (generally recognized as safe) lactic acid bacteria *Lactococcus lactis* and *Lactobacillus plantarum*have chitinolytic enzymes [40].

Malaria parasite (*Plasmodium* sp.) secretes chitinase to cross the chitin-containing peritrophic matrix of host mosquito, to gain access to its mid gut [28]. Plants such as rubber (*Hevea brasiliensis*) and tobacco (*Nicotiana tabacum*) elaborate the enzyme for defense purpose [41,42]. Other plants as moringa (*Moringa oleifera*) (seed) [43], stinging nettle (*Urtica dioica*) (rhizome) [44], Indian mustard (*Brassica juncea*) (stems and leaves) [45] etc. have chitin binding or chitinase activity. These proteins and enzymes secreted/accumulated by the plants deter fungi and insects by disrupting their chitin walls. So, chitinases act as antimicrobial, antifungal and anti-herbivory agents.

Several sponges from the Phylum Porifera possess chitins. The spongin of demosponges *Aplysina* sp. *Aiolochroia crassa*, and *Verongula gigantea* have α-chitin [46,47]. The freshwater sponge *Spongilla lacustris* and *Lubomirskia baicalensis* have this polymer in their skeletal scaffold as well [48,49]. Chitin has also been detected in the fossil forms of sponges as *Vauxia gracilenta* [50]. The siliceous cell wall of diatom *Thalassiosira pseudonana* has a chitin-based network [51,52].

For a long time, this notion remained that chitins do not occur in vertebrates [53]. Current evidences are refuting those concepts and redefining the understanding on chitin. This polymer has been detected in the gut, scales, appendages of zebrafish, salmon and salamander [53]. In fact, chitin chains are converted to hyaluronan in mammals, for the neural toxicity of endogenous chitin [54]. The detection of chitin in human or other mammals is recent, but the elaboration of chitinases is adequately proven. Chitinase is secreted in mammals to counter exogenous chitins. These polymers from molds, nematodes, and arthropods can be sensed by macrophages, which can activate innate immunity, leading to cytokine release and neutrophil infiltration. Fig. 1 illustrates the mechanism of human innate immune activation by chitin. Human chitinase includes chitotriosidase and acidic mammalian chitinase (AMCase) [24]. Macrophages, neutrophils, epithelial cells and chondrocytes elaborate chitinase that interacts with polysaccharides or extracellular matrix glycoproteins (Ujita et al., 2003). This enzyme defends human body against bacteria and fungi. However, it exerts self-damaging effects in inflammatory non-homeostasis conditions. Chitinase expression is upregulated in allergic conditions which take part in tissue remodeling [56]. Chitinases contain Glyco_18 domains and these domain-harboring proteins are pathology biomarkers [57]. High serum chitinase level has been discovered in asthma, atherosclerosis, worm infections, Gaucher's disease (hepatosplenomegaly), cancer, Alzheimer's disease, multiple sclerosis etc. [58,59]. Chitinases can behave differently under different situations [60]. YKL-40 (chitinase-3-like protein 1), YKL-39 (chitinase 3-like protein 2), SI-CLP (stabilin-1 interacting chitinase-like protein) are some other disease-associated proteins with the Glyco_18 domain [57]. These proteins have lost the chitinase activity, yet are virulent. The chitinase-3-likeprotein 1 or YKL-40 levels were high in Schistosoma-infected population; however, antihelmintic drugs could reduce its level [5]. This critical review was pursued to garner insights on the lesser- investigated aspects of the chitin and chitinase in pathogenicity and health.

1.1. Chitin deacetylases and chitosan

Chitins are thermo-stable, and templates for biomineralization, thus ideal for nanocomposites development [61,62]. Chitin deacetylases secreted by bacteria, fungi and insects catalyze the deacetylation of chitin, which results in chitosan [63]. The deacetylation renders the polymer more elastic, and less immunogenic,