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Chitinase-like proteins as regulators of innate immunity and tissue repair: helpful lessons for asthma?

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Abstract

Chitinases and chitinase-like proteins (CLPs) belong to the glycoside hydrolase 18 (GH18) family of proteins. Chitinases are expressed in mammals and lower organisms and facilitate chitin degradation, hence act as host-defence enzymes. Gene duplication and loss-of-function mutations of enzymatically active chitinases has resulted in the expression of a diverse range of CLPs across different species. CLPs are genes that are increasingly associated with inflammation and tissue remodelling, not only in mammals but also across distant species. Whilst the focus has remained on understanding the functions and expression patterns of CLPs during disease in humans, studies in mouse and lower organisms have revealed important and overlapping roles of the CLP family during physiology, host-defence and pathology. This review will summarise recent insights into the regulatory functions of CLPs on innate immune pathways and discuss how these effects are not only important for host-defence and tissue injury/repair after pathogen invasion, but also how they have extensive implications for pathological processes involved in diseases such as asthma.

Chitinase-like proteins - functions within an ancient protein family

Glycoside hydrolase family 18 (GH18) proteins encompass the enzymatically active chitinases and enzymatically inactive chitinase-like proteins (CLPs). Chitinases hydrolyse glycosidic bonds of chitin, an abundant polysaccharide found as a structural component of the fungal and bacterial cell wall, and within the exoskeleton of crustaceans, arthropods and helminth parasites [1]. In insects, chitin is an integral part of the cuticle and as such, expression of chitinases are essential for a successful cuticle molt and reorganisation of the chitin-extracellular matrix architecture [2-4]. Aside from developmental roles, chitinases are also used by pathogens to invade or exploit chitin-containing structures within lower organisms [5], highlighting the importance of chitinases during host-pathogen interactions. However, highly conserved chitinases are expressed across all species, even mammals that lack endogenous chitin and these species, chitinases are considered an evolutionary ancient form of host defence against chitin-containing pathogens and chitinous material [6-8]. CLPs on the other hand, are a diverse set of proteins often expressed in a species specific manner, and have arisen from gene duplication of chitinases followed by mutation and loss of function of the chitinolytic domain [9]. CLPs are strongly, but not exclusively, associated with T helper 2-type inflammatory pathologies that include helminth infection [10], asthma [11] and fibrosis [12], and as such a lot is known about their expression patterns during disease. However, the individual roles of CLPs during physiology versus inflammation and pathology are not well understood. Extensive phylogenetic analysis on the chitinase and CLP families has provided detailed insights into protein diversification across species, conserved protein features and gene specialisation [9,13-15]. CLPs are evolving at a remarkably rapid rate, which appears to be beyond the extent of natural genetic drift, and rather points toward positive selection forces that drive their genetic variation. However, whole CLP sequence estimations of synonymous versus non-synonymous mutations ($\omega < 0.5$) did not support such selection pressures [9]. Rather, it appears that there are specific sites within the CLP protein structure that are under positive selection pressures ($\omega > 1$) that drive the high functional diversity of CLPs across species, yet allow for conservation of the sugar-binding barrel structure [13]. This diversity is particularly highlighted between humans and mice (Figure 1) and scientists have questioned whether studies in mice yield useful information for human pathologies. However, despite the large diversity and whilst lacking

chitin-degrading activity, mammalian CLPs are all widely associated with immune-modulating activities important for both pathogen control and corresponding host-damage [10,16]. These innate host-defence roles also extend to species other than mammals. For example, *Drosophila* express imaginal disc growth factor (IDGF) proteins, which are ~25% homologous to mammalian CLPs (**Figure 1**) and recent studies have characterised functional readouts for IDGFs during nematode infection, wound injury and healing [17,18]. Similarly mollusk CLPs including *My-Clp1* from Japanese scallops and *Cg-Clp1* and *-Clp2* from oysters appear equally involved in developmental tissue remodelling and immune defence [19,20]. CLPs across species are also broadly expressed in similar cell types (**Table 1**). In humans and mice, CLPs are expressed in both immune and structural cells whilst data from lower organisms points toward expression in haemocytes (immune cells) and structural tissues like larval body fat. Thus, despite the diversity, it is clear that a lot can be gained from studying CLP molecules across multiple species. Such experiments will provide a strong link between CLP functions and the evolutionary development of this fascinating family of proteins. Herein, this review will give examples of the innate immune responses influenced by CLPs, highlighting how these regulatory roles are important for balancing host-pathogen responses and the implications for disease pathology when this balance is not maintained.

Disease association and molecular mechanisms of CLPs

A brief search of the literature quickly highlights CLP expression in an enormous variety of pathologies or models suggesting broad generalised functions. The exception seem to be YKL-39 in humans and Ym2 in mice which appear to have restricted roles during arthritis/osteoarthritis [21-23] and airway induced inflammation [24-26] respectively. However, YKL-39 and Ym2 are not widely studied, so there may be key information missing that links these proteins to other physiological or pathological processes. At least in mice, studies are hampered by limited tools to detect or analyse Ym2, as this protein has high sequence similarity (~95%) to Ym1 (**Figure 1**) and is the least abundant murine CLP [10,27].

YKL-40 is the best studied CLP in terms of disease associations with increased expression levels found in infection [28,29], fibrosis [30,31], multiple sclerosis [32], lung disease [33] and many more pathologies. Probably not surprisingly, BRP-39 in mice is often referred to as the “prototypical” CLP

because it is the genetic orthologue of YKL-40 in humans. However, whilst BRP-39 is upregulated in various mouse models of infection and pathology, Ym1 seems to more closely mimic the effects of YKL-40 as it is often upregulated to a greater degree than BRP-39 and seems to share functional similarities to YKL-40 [10]. For example, both YKL-40 and Ym1 levels are greatly increased in the serum following injury, inflammation or in unbalanced immune responses [28,34]. Additionally, these two CLPs are expressed in neutrophils [35] and are increased following either IL-4/IL-13 or IFN γ stimulation [36]. It is clear from both an evolutionary standpoint and from an immunological basis, that studying all CLPs in mice; Ym1, Ym2 and BRP-39 and the crossover of functions in other species; will be critical for understanding the driving forces behind CLP diversification and their role in disease.

A lot of current research aims to address the use of CLPs as indicators of pathology and/or disease severity [37-39], but are they more than just biomarkers of disease? The molecular mechanisms of CLPs that have so far been discovered support a diverse array of functions from altering collagen synthesis/degradation [40,41] to regulating pro-inflammatory cytokine levels important for control of infection [10,16]. Primarily CLPs are carbohydrate binding molecules, but individual proteins often differ in the complexity of sugars they bind [42]. For instance, resolution of the Ym1 crystal structure and additional biochemical analysis revealed specific binding to heparin/heparan sulfate proteoglycans and possible interactions with glucosamine oligomers [43,44]. Although, later structural analysis appeared inconsistent with a monoglucosamine-binding site [45]. In contrast, YKL-39 binds chito-oligosaccharides, with sugar length determining binding strength [46]. Considering its apparent specialised functions, it is somewhat surprising that further studies have not begun to unlock mechanistic details of YKL-39.

Whilst one protein, 12/15-lipoxygenase, has been identified to bind Ym1/Ym2, an interaction thought to mediate Ym1/Ym2 effects on Th2-immune regulation [47], the spotlight has remained on understanding receptor-ligand interactions of YKL-40/BRP-39 and numerous binding partners have already been identified. Initially studies focussed on IL-13R α 2 as a receptor for YKL-40/BRP-39 after an interaction was revealed using yeast two-hybrid screening [48]. However, many more targets were identified by this and later screening approaches. Prostaglandin D2 receptor (CRTH2) [49], receptor for advance glycation end product (RAGE) [50] and type I collagen [40,41] have also been shown to interact

with YKL-40/BRP-39. Some of these interactions appear to at least in part, be responsible for the regulatory actions of CLPs on innate immune responses and tissue remodelling and will be discussed in more detail below. However, it is clear that there are still actions of CLPs that have not yet been attributed to receptor-ligand interactions suggesting that there are likely more CLP receptors or alternative functions yet to be identified.

CLP regulatory roles during innate inflammation

Some of the most extensive functional or characterisation studies of CLPs has centred around asthma and related lung diseases. CLPs are highly upregulated in the lungs of asthmatic patients [33,51,52] and in murine models of allergic airway inflammation [7,24,53]. The majority of studies have focused on how CLPs may be regulating adaptive Th2 responses during allergic inflammation [47,53]. However, YKL-40 expression positively correlates to neutrophilic and IL-17-driven inflammation in asthmatic patients [38,54], suggesting CLPs may also be important for non-Th2 asthma phenotypes that are often strongly associated with innate immune responses. Recently, we demonstrated that Ym1 (and to some extent Ym2) stimulates cytokine IL-1 β to drive IL-17A production in innate $\gamma\delta$ T cells, resulting in the accumulation of neutrophils [10]. Ym1-induced neutrophilia was important for host-defence against nematode *N. brasiliensis* larvae that were migrating through the lung on route to the gastrointestinal tract. Whilst yet to be demonstrated directly, the influence of Ym1 on IL-1 β was proposed to occur through activation of the inflammasome [10,55], a hypothesis consistent with the ability of Ym1 to form crystals under acidic and highly inflammatory conditions [35,56]. BRP-39 (*Chil1*) has also been shown to have pro-inflammatory effects, albeit during bacterial infection. Following *Staphylococcus aureus* infection of the bone and bone marrow, inhibition of *Chil1* via shRNA delivery dampened IL-1 β and TNF α cytokine levels [57]. Similarly, *Chil1*-deficient mice had significantly lower levels of TNF α , IL-6 and IL-22 in the large intestine following *Salmonella enterica ser. Typhimurium* infection [58]. Yet, unlike Ym1 where pro-inflammatory effects were associated with enhanced host-defence, BRP-39 in the gut and bone appears to be a pathogenic mediator enhancing bacterial survival [57,58] and invasion [59]. Interestingly, in the lung BRP-39 inhibits caspase-1-dependent macrophage pyroptosis and thereby augments macrophage killing

of *Streptococcus pneumoniae* [60]. BRP-39 not only limited pathogen survival/colonisation but also reduced IL-1 β production in a way that was consistent with inhibition of inflammasome activation, and thereby was important for the control of inflammation-induced pathology [16,60]. Whilst these findings are contradictory, differences may relate to contrasting BRP-39-protein interactions in different tissues or during different infections. For example, BRP-39 suppression of bacterial growth in the lung was found to be IL-13R α 2-dependent [48], whereas bacterial adherence and invasion in the colon required direct binding of bacteria to epithelial cell derived BRP-39 [59,61]. Regardless, these studies highlight the complex nature of CLP regulatory roles and further studies are clearly needed to understand the mechanisms through which CLPs mediate pathogen related effects.

Overall studies in mice point toward Ym1 playing important innate defence roles during nematode infections [10,62,63], whilst BRP-39 appears to have a greater role in bacterial infections [16,60], adding to speculations that host-pathogen interactions may have influenced evolutionary divergence of CLPs in rodents. Examining the effects of CLPs in humans would suggest an overarching role of YKL-40 during infection, inflammation and pathology. Serum levels of YKL-40 increase during helminth [28,64] and bacterial infection [29,65] and whilst this hasn't necessarily been translated into a functional output, the absence of other similarly upregulated CLPs in humans suggests a dominant role for YKL-40 in these scenarios. Additionally, YKL-40 levels positively correlate with IL-1 β expression following brain injury [66]. However, administration of recombinant YKL-40 to *Streptococcus pneumoniae* infected peritoneal macrophages from BRP-39-null mice reduced IL-1 β secretion [48], again highlighting dual roles of CLPs during different innate immune responses. The ability of CLPs to influence innate immunity has also been described for organisms other than mammals. In particular the *Drosophila* IDGF family are critical regulatory molecules during innate immunity. Mutation of *IDGF3* leaves its host more susceptible to nematode or bacterial infection [17] and microarray analysis demonstrated that *IDGF2* expression resulted in activation of innate immune genes associated with phagocytosis [18]. Similarly, following bacterial infection, mollusks rapidly upregulate *My-Clp1*, a CLP gene with implicated roles in innate defence and pathogen recognition [19]. The complexities of specific CLP functions still need to be untangled but overall data suggests prominent roles in regulating innate immune responses and/or pathogen recognition.

Not only important for host-defence, there is growing evidence that the innate immune system, in particular IL-1 β /inflammasome activation, play a pathogenic role during severe asthma [67-69]. Therefore, it is exciting to speculate a role for CLPs in such disease settings, where therapeutic inhibition of CLPs may be beneficial to pathological outcomes in asthma. In this respect, CLP functions already associated with infection-induced innate immune responses will help direct studies into diseases like asthma.

Dual roles of CLPs in balancing tissue remodelling: protection from injury versus pathology

CLPs have diverse effects on inflammation and immune regulation, but a lot of earlier studies often described CLP expression in relation to tissue injury, repair and remodelling [70-73]. In *Drosophila*, *IDGF* genes are increased upon septic injury [74] and *IDGF3* regulates expression of genes required for wound closure after infectious nematodes force entry into the host [17]. In contrast in mice, BRP-39 levels increase after bacterial induced inflammation and injury [16,60] and expression of Ym1 triggers innate responses that contribute to tissue injury as a trade off to parasite killing [10]. However, increased levels of CLPs are not purely attributed to pathogen induced insult, as CLPs are also upregulated during sterile injury [18,66,72,75,76] suggesting fundamental roles in tissue repair. It would appear that Ym1, and similarly other CLPs, have dual roles during injury and repair (**Table 2**). Th2-type immune responses have been shown to be critical for tissue repair following helminth infection [77]. Data strongly suggests that Ym1 can promote rapid lung regeneration by influencing Th2 cytokine production during *N. brasiliensis* infection, despite contributing to innate injury initially [10]. Additionally, Ym1 is highly expressed in neutrophils and is part of the neutrophil transcriptional signature that is critical for aiding the development of wound healing macrophages [78].

Current research has largely focused on the ability of CLPs to indirectly regulate tissue remodelling by influencing innate and/or adaptive immune responses. However, it is clear that CLPs can also influence the extracellular matrix (ECM) through direct interactions with ECM molecules, including collagen and heparan sulfate proteoglycans [41,43,44]. In vitro studies show that YKL-40 is mitogenic for fibroblasts [79] and it can induce cellular responses directly leading to enhanced collagen production [80]. Such responses likely relate to the combined effects of YKL-40 binding to and stimulating collagen fibril

formation [41], in addition inhibiting collagen degradation [40]. In fact enhanced expression of YKL-40 correlates with fibrotic disorders of the lung [30,49,81] and liver [31,82]. Interestingly, YKL-40 also regulates the epithelial-mesenchymal transition (EMT) [83], a process which involves a phenotypic shift of epithelial cells towards a mesenchymal fibroblast-like cell that is highly migratory and secretes enhanced amounts of ECM proteins like collagen. EMT is not only a critical mechanism allowing cancer metastasis but has also been shown to be a key driver of airway remodelling in asthma [84]. Overall it is evident that CLPs affect the ECM both through immunoregulatory effects as well as through directly affecting ECM deposition and turnover. This has wide stretching consequences for tissue injury, repair and remodelling, not just as a consequence of host-defence responses but also as a pathological response in disease.

Concluding remarks

CLPs exert complex effects on tissue processes that are important for defence against pathogens and protection from the often destructive processes that occur after pathogen invasion. However, aberrant immune responses and prolonged and excessive CLP expression more often than not lead to detrimental disease outcomes. Understanding how CLPs maintain a balance between protective versus pathological responses (**Figure 2**) will be a critical step in determining how, when and what CLP functions can be targeted for disease therapy. Parallels between the roles of CLPs from lower organisms and mammals allow a unique opportunity to study how these proteins and particularly the functional domains of these proteins can act as over-arching molecules in development, homeostasis and pathology. There is still a long way to go before we will grasp the full repertoire of CLP effects, but analysis of functionalities across species and mechanism(s) of action will be a crucial step forward. Numerous protein-CLP receptor/ligand interactions have already been described and suggest CLPs have a somewhat promiscuous nature but also pose several interesting questions; (1) Do CLPs act on common receptor(s); (2) CLPs are expressed in such vast quantities and circulate throughout the body even during normal physiology. In these scenarios are innate CLPs pathogen sensing molecules and can these effects be attributed to receptor/ligand interactions?; and lastly (3) genetic mutations of YKL-40 have been associated with worse disease outcomes [85], but do these mutations alter protein binding interactions? Considering the

duplication/mutation of chitinases to form the CLP family, it might be logical to assume that CLPs have evolved to recognise and interact with chitin-containing pathogens and initiate an immune response to deal with the threat. However, there must be alternative functions, as not all CLPs bind chitin and different CLPs expressed within one species can have quite dissimilar functions (Ym1 and BRP-39 in mice; YKL-39 and YKL-40 in humans). Perhaps multiple CLP genes evolved within a species to deal with different types of infectious agents and associated damage to the host, yet when produced in vast quantities in the absence of a concurrent infection, CLPs can lead to pathological consequences. Further experiments will be needed to answer these questions and those posed above and future CLP research will likely aim at discovering the true importance and therapeutic value of CLP molecules.

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Completing Interests

The author declares that there are no competing interests associated with the manuscript.

Abbreviations

CLP, chitinase-like protein; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; GH18, Glycoside hydrolase family 18 IDGF, imaginal disc growth factor.

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Table 1: Expression of chitinase-like proteins in different cell types

Cell type	YKL-40	BRP-39	Ym1	IDGF	My-Clp1
Macrophages	Differentiated macrophages [96]	[97]	[98]	N/A	N/A
Neutrophils	[99]	[100]	[35]	N/A	N/A
Epithelial cells	[101]	[97]	[102]	N/A	N/A
Dendritic cells	[103]	[104]	[105]	N/A	N/A
Chondrocytes	[106]	[107]	[108]	N/A	N/A
Astrocytes	[109]	[110]	[111]	N/A	N/A
Larval Fat Body	N/A	N/A	N/A	[112]	?
Haemocytes (white blood cell equivalent)	N/A	N/A	N/A	[113]	[19]

Table 2: Chitinase-like protein expression/activity during injury and repair

CLP	Species	Organ	Expression/role	Receptor interaction
YKL-40	Human	Brain	Increased during brain acute injury and expression sustained long after injury onset [66]	Unknown
		Kidney	Increased expression during acute kidney injury [86-88]	Unknown
		Liver	Increased expression during acute and chronic liver injury [89]	Unknown
		Joint	Increased expression during joint trauma [90,91]	Unknown
BRP-39	Mouse	Lung	Limits lung injury in response to bacterial infection [16,60]	Anti-inflammatory effects during bacterial infection partly IL-13R α 2 dependent
			Protective role during acute injury after bleomycin treatment [92]	Unknown
			Prevents neonatal lung injury [93]	
		Bone	BRP-39 Inhibition leads to less tissue destruction following bacterial infection [57]	Unknown
		Kidney	Sensor of degree of injury and aids repair [94]	Unknown
Ym1	Mouse	Skin	Temporal expression after wounding [75,76]	Unknown
		Lung	Innate expression limits parasite burden at expense of lung injury [10]	Unknown
		Brain	Increased expression after stab wound [72]	Unknown
		Kidney	Increased expression in mice with severe acute kidney injury [95]	Unknown
IDGF2	Drosophila	Haemolymph component	Increased expression induced by injury [18]	Unknown
IDGF3	Drosophila	Haemolymph component	Mutation of <i>Idgf3</i> results in defective haemolymph clotting upon nematode entry and larvae injury [17]	Unknown

Figure 1: Protein homology between different chitinase-like proteins and chitinases. Protein sequences (UniProt ID) of individual chitinase-like proteins (CLPs) or chitinases were aligned and the percentage identity was estimated using Cluster-Omega. Colour of the square corresponds to degree of homology, red = 100% identical and yellow = 0% identity. DmIDGF₃, *Drosophila melanogaster* Imaginal disc growth factor 3 (IDGF₃); DmIDGF₂, *Drosophila melanogaster* IDGF₂; Cg-Clp1, *Crassostrea gigas* Clp1 protein; mBRP-39, *Mus musculus* BRP-39 (*Chil1*); mYm1, *Mus musculus* Ym1 (*Chil3*); mYm2, *Mus musculus* Ym2 (*Chil4*); hYKL-39, *Homo sapiens* YKL-39 (*CHI3L2*); hYKL-40, *Homo sapiens* YKL-40 (*CHI3L1*); hAMCase, *Homo sapiens* Acidic mammalian chitinase AMCase (*CHIA*); hCHIT1, *Homo sapiens* Chitotriosidase CHIT1 (*CHIT1*); mAMCase, *Mus musculus* Acidic mammalian chitinase AMCase (*Chia*); mChit1, *Mus musculus* Chitotriosidase Chit1 (*Chit1*).

Figure 2: Proposed roles of chitinase-like proteins in the lung. CLPs either keep host-defense and tissue repair balanced during infection or cause unbalance in immune regulation and tissue remodeling contributing to pathology during asthma. In the lung, host-defence responses include innate inflammation to control pathogen growth and alterations of the extracellular matrix to rapidly repair the tissue and infection induced injury. CLPs regulate type 2 and type 17 immune responses and inflammasome activation leading to pathogen killing. Additionally CLPs contribute to the balance of injury and repair by influencing collagen deposition and immune regulation. During chronic inflammatory pathologies, such as asthma, CLPs are secreted in abundance. In such situations CLPs also regulate type 2 and type 17 immune responses, but this inflammation tips the balance of regulation toward tissue remodeling and fibrosis.

Figure 1

Figure 2