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MINIREVIEW

Bacterial Chitinases and Their Role in Human Infection

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ABSTRACT It has been widely appreciated that numerous bacterial species express chitinases for the purpose of degrading environmental chitin. However, chitinases and chitin-binding proteins are also expressed by pathogenic bacterial species during infection even though mammals do not produce chitin. Alternative molecular targets are therefore likely present within the host. Here, we will describe our current understanding of chitinase/chitin-binding proteins as virulence factors that promote bacterial colonization and infection. The targets of these chitinases in the host have been shown to include immune system components, mucins, and surface glycans. Bacterial chitinases have also been shown to interact with other microorganisms, targeting the peptidoglycan or chitin in the bacterial and fungal cell wall, respectively. This review highlights that even though the name "chitinase" implies activity toward chitin, chitinases can have a wide diversity of targets, including ones relevant to host infection. Chitinases may therefore be useful as a target of future anti-infective therapeutics.

KEYWORDS bacterial chitinase, chitinases, chitin-binding protein, lytic polysaccharide monooxygenase, host-pathogen interaction, glycans

Chitin is the second-most-abundant biopolymer in nature. It is virtually omnipresent, as it represents a major component of the cuticle of insects and crustaceans and can also be found in the fungal cell wall (1). Given the abundance of chitin, it is not surprising that enzymes degrading this biopolymer can be found throughout the tree of life, from bacteria to mammals (2). Chitin-degrading enzymes are called chitinases. They are glycosyl hydrolases that function by liberating *N*-acetylglucosamine (GlcNAc) subunits in chitin polymers (3). Many bacterial species produce chitinases to degrade this environmental chitin as a source of nutrients (4). Some bacterial chitinases have activity toward the chitin present in fungi and insects and have been proposed as a method to protect crops from pests (5). Chitinases are therefore clearly an important area of study in environmental microbiology and biotechnology. However, bacteria that infect mammalian hosts also express chitinases even though mammals do not produce chitin. These bacterial chitinases may interact with chitin present in the bacterium's environmental niche outside the human host. However, chitinase activity inside the human host suggests that the mammalian host provides alternative molecular targets for these chitinase domains. Indeed, an increasing number of studies have revealed that chitinases can target other GlcNAc-containing molecules, such as peptidoglycan and mammalian glycans (6–9). In this review, we will summarize the current knowledge regarding the roles of bacterial chitinases during mammalian infection of different body sites, including skin, gut, airway, and systemic infection (Fig. 1). The biotechnological applications of bacterial chitinases have been recently discussed in other reviews (5, 10).

CHITINASE CLASSIFICATION AND FUNCTION

Chitinases are generally classified in the glycosyl hydrolase (GH) family 18 or 19 (3, 11). This classification is usually not based on experimental evidence. Rather, GH families classify enzymes that hydrolyze carbohydrate polymers based on their amino acid

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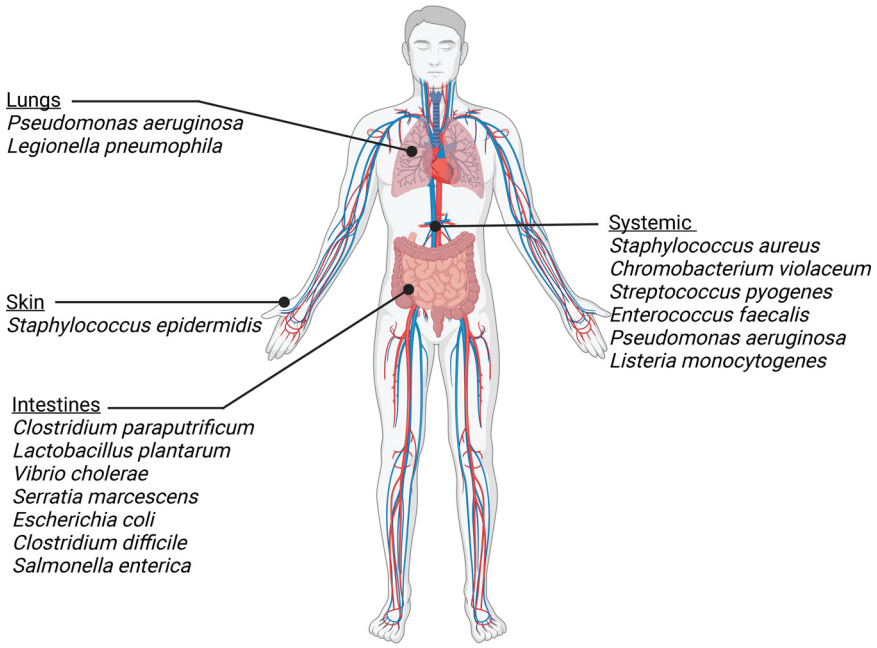

FIG 1 Bacterial species that express chitinases/CBP during colonization or infection of various locations of the human body.

sequence similarities (12). Even though certain glycosyl hydrolases share homology and are classified in the same GH family, that does not necessarily mean that they share the same substrate specificities. Members of the same GH families can demonstrate divergent substrate specificity, while there are also examples of members of separate GH families sharing similar substrate specificity (12). For example, the GH48 family mostly contains cellulases; however, one GH48 enzyme produced by the beetle *Gastrophysa atrocyanea* demonstrates chitinase activity (13). For this reason, glycosyl hydrolases are further classified after experimental analysis based on their target substrate, catalytic mechanism, or the location on the glycosidic chain that is targeted (12). GH18 chitinases cleave chitin polymers and retain the configuration of the anomeric carbon (retaining mechanism), while GH19 chitinases cleave the polymers with an inversion of the anomeric configuration (inverting mechanism) (14, 15). Chitinases can have exo-activity, cleaving glycosidic bonds on the ends of chitin polymers and oligomers, or endo-activity, cleaving internal glycosidic bonds (3). Chitin-binding proteins (CBP) maintain chitin-binding ability but lack catalytic activity. Most chitin-binding proteins contain either the carbohydrate-binding module (CBM) 33 or CBM5/12. While CBM33 was originally thought to contain no chitinase activity, some CBPs with this domain have been shown to break chitin chains by oxidative cleavage. These CBPs have been reclassified as lytic polysaccharide monooxygenases (LMPOs) (4, 16).

BACTERIAL CHITIN UTILIZATION

A variety of bacterial species produce chitinases for the purpose of degrading chitin. Some of these bacterial species can also colonize human tissue as pathogenic invaders (4). The ability to utilize environmental chitin as a carbon source via chitinase expression is likely important for the persistence and transmittance of these pathogens outside hosts. The bacterial pathogens *Listeria monocytogenes* (17–19), *Vibrio cholerae* (20), *Enterococcus faecalis* (21–23), *Escherichia coli* (24), and *Serratia marcescens* (25, 26) all express chitinolytic machinery for the purpose of using chitin as a carbon source. The opportunistic pathogen *S. marcescens* expresses a complex set of machinery for the degradation of chitin polymers, involving three GH18 chitinases (ChiA, ChiB, and ChiC) and a lytic polysaccharide monooxygenase (CBP21) (25, 26). Expression is controlled by ChiR, a member of the LysR-type transcriptional regulator family (27). In order to degrade extracellular chitin, these chitinases have to be secreted from the bacterial cell. In *S. marcescens*, secretion of the chitinase

machinery was shown to require proteins that partially destabilize the bacterial cell membrane. Without the holin-like protein ChiW and the L-alanyl-D-glutamate endopeptidase ChiX, chitinases cannot be released into the supernatant (28). ChiW likely facilitates the translocation of ChiX to the periplasm, where it can access peptidoglycan (28). ChiX demonstrates catalytic activity toward bacterial peptidoglycan and could therefore facilitate chitinase secretion (29). *L. monocytogenes* also expresses chitinases, ChiA and ChiB, and the lytic polysaccharide monooxygenase LPMO10. All three proteins are involved with chitin degradation *in vitro*, but LPMO10 may not be important for *in vivo* chitin degradation since it is not expressed in chitin-containing media (17–19). *V. cholerae* expresses chitinolytic machinery that allows growth on a chitin-containing medium (30). Chitin utilization in *Vibrio* species is thought to involve the coordination of secreted chitinases, porins, transporters, and carbohydrate-specific enzymes (20). The expression of a number of these factors was shown to be regulated by the two-component sensor/kinase ChiS, which senses environmental chitin (30, 31). The zoonotic pathogen *Francisella tularensis* subsp. *novicida* forms biofilms on chitinous surfaces and uses chitin as a carbon source via the production of chitinases (32). *F. tularensis* type B expresses an additional chitinase (ChiD) that promotes infection of ticks, one of the main vectors of transmission, potentially by utilizing chitin present in their exoskeleton as a carbon source (33). *E. faecalis* expresses two chitinolytic enzymes, EfChiA18A and EndoE, and a chitin-binding protein, EfCBM33A, that work in tandem to degrade chitin and utilize it as a carbon source (21–23). Lastly, *E. coli* can also utilize chitin as a carbon source through the expression of chitinase machinery (24). The ability of these bacterial pathogens to utilize environmental chitin likely does not impact pathogenesis in the host environment. However, chitinases have also been shown to be directly important for mammalian infection.

CHITINASE ROLES DURING INFECTION

Over recent years, bacterial chitinases have been shown to exhibit alternative roles not involving the direct cleavage of chitin polymers (16, 34) (Fig. 2). A meta-genomic analysis of pathogenic species revealed that the chitin-binding domain 3, a common domain in chitinases, is evolutionarily conserved in virulence factors and co-occurs with peptidase, glycosyl hydrolase, kinase, hemagglutinin-acting, and collagen-binding domains (35). The presence of a chitin-binding domain alongside domains with known pathogenic function indicates that interactions with chitin or chitin-like molecules within mammalian hosts may be important for infection. Various bacterial chitinases and chitin-binding proteins that have been implicated in or suggested to play a role in infection will be discussed in the following sections.

SKIN COLONIZATION

The skin is an epithelial barrier that serves as vertebrate animals' first line of protection against the outside world. The role of bacterial chitinases during skin colonization and infection has not been studied in great detail, but there is some evidence for their involvement. The opportunistic pathogen *Staphylococcus epidermidis* expresses the putative chitinase SE0760 during skin colonization but not during colonization of the nasal cavity (36). It has therefore been suggested that this chitinase is involved in the invasion of skin tissue (37). However, this hypothesis has not been confirmed yet by experimental studies. Future research needs to be performed to fully understand the role of this chitinase for skin colonization. While other bacterial skin pathogens, such as *Staphylococcus aureus* and *Streptococcus pyogenes*, carry chitinases, their role in skin infection has not been elucidated. These chitinases were studied for their role during systemic infection, which will be discussed in the following section.

SYSTEMIC INFECTION

Bacterial chitinases have been shown to directly contribute to bacterial pathogenesis during systemic infections. In numerous pathogens, chitinase expression leads to enhanced virulence. Specific targets and functions of chitinases in mammals have

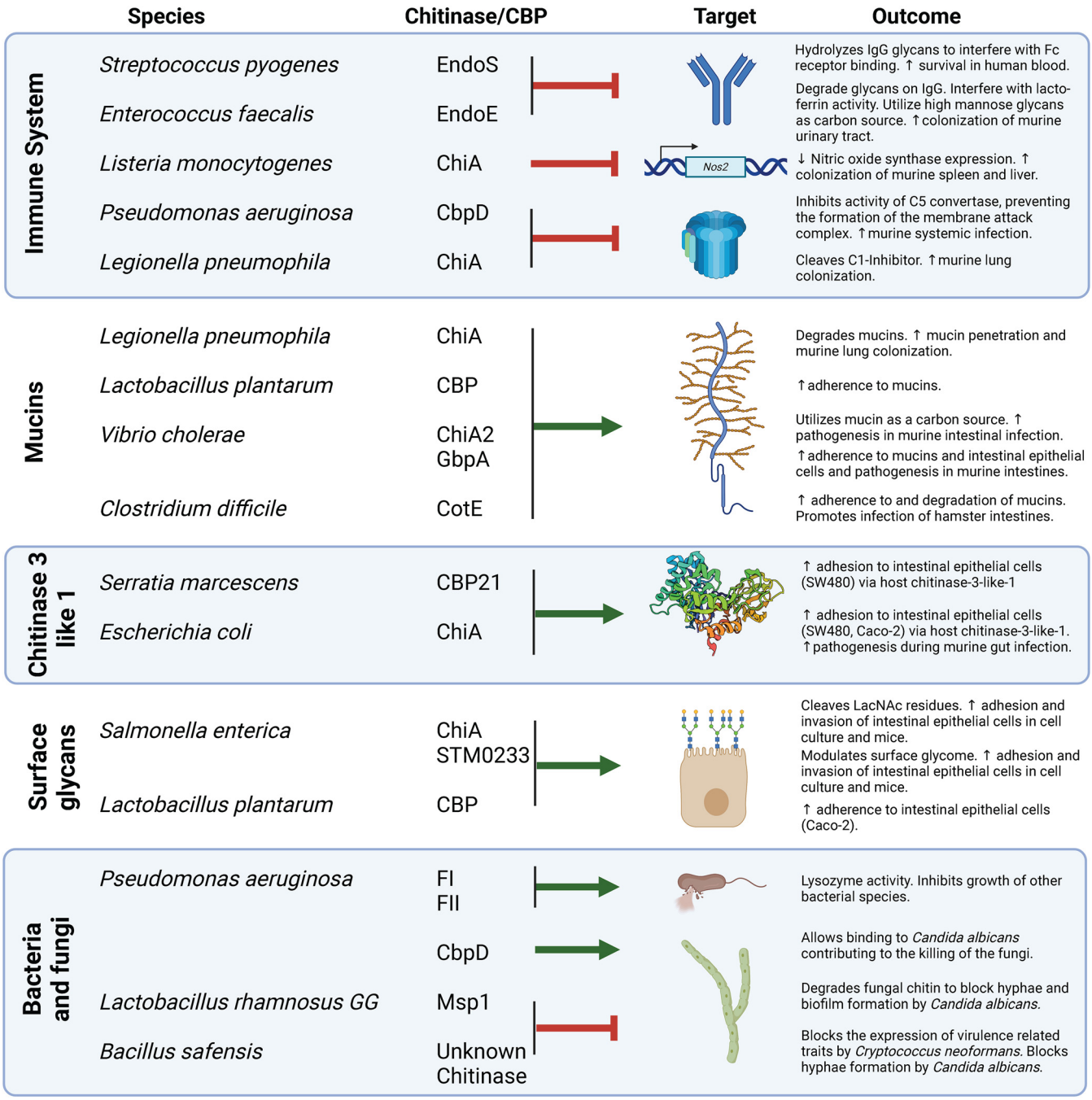

FIG 2 Bacterial chitinases/CBPs with activity toward alternative molecular targets that are relevant to human infection.

been described for multiple pathogens, as we will detail below. However, we will first describe chitinases with undefined targets that have been associated with bacterial pathogenesis. For example, a mouse model of *Staphylococcus aureus* sepsis revealed the chitinase-related protein SAUSA300_0964 as a potent virulence factor that is upregulated in a hypervirulent protease-deficient strain of *S. aureus* (38). SAUSA300_0964 expression is regulated by the Sae system alongside other virulence factors and is upregulated in the presence of the antibiotic colistin, but its function during infection is still unknown (39, 40). The pathogen *Chromobacterium violaceum* expresses the putative chitinase CV_4240, which is indirectly linked to virulence. Expression of virulence genes in *C. violaceum* is regulated by the CviR/CviI quorum sensing system. The same system was shown to regulate expression of CV_4240, indicating a potential role for

the chitinase during infection (41). This putative chitinase was also found to be secreted and likely also contributes to chitin degradation by *C. violaceum* (42, 43). It is still unclear if chitinase activity contributes to *C. violaceum* pathogenesis or if it is only required for degradation of environmental chitin outside a human host. Additionally, the zoonotic pathogen *Francisella tularensis* type A upregulates a GH18 family chitinase in the spleen of infected mice (44). The chitinases ChiA and ChiB expressed by *F. tularensis* subsp. *novicida* have been reported to regulate biofilm production, affecting the ability of *F. tularensis* subsp. *novicida* to adhere to, invade, and replicate inside lung epithelial cells (32, 45).

Many bacterial chitinases seem to be involved in the modulation of the host immune response to infection, interfering with antibody function, the complement cascade, or phagocyte function. Their function therefore enables pathogenic microbes to efficiently infect their hosts, as we will describe in the following sections.

Targeting of glycans present on IgG and other immune system components. A well-characterized GH18 glycosyl hydrolase that interferes with antibody function during systemic infection is endoglycosidase S (EndoS) of *Streptococcus pyogenes*. This enzyme hydrolyzes core GlcNAc residues on IgG glycans in human serum (46). EndoS contains a GH18 chitinase domain and a CBM. Mutation of the active residue of the GH18 chitinase domain blocks catalytic activity (47), while deletion of the CBM slows the rate of glycan degradation (48). The modification of IgG glycans by EndoS promotes survival of *S. pyogenes* in human blood by interfering with Fc receptor binding (49). A similar mechanism is exploited by the animal pathogen *Corynebacterium pseudotuberculosis*, which mainly infects sheep and goats. This bacterium expresses a GH18 chitinase domain-containing enzyme, CP40, that shares homology with EndoS of *S. pyogenes* (50). CP40 does not show activity toward chitin but, instead, degrades biantennary glycans on IgG (50). *Enterococcus faecalis* expresses one chitin-binding protein (EfCBM33A) and three chitinase domain-containing enzymes (EndoE, EfChi18A, and EfEndo18A). *E. faecalis* upregulates EfCBM33A and EfChi18A when exposed to horse blood and human urine (51, 52), but their functions during infection are still unclear. EndoE and EfEndo18A are better characterized and have been shown to interfere with different arms of the immune response. EndoE and EfEndo18A are characterized as β-1,4 endo-β-*N*-acetylglucosaminidases and demonstrate activity toward mammalian glycans. EndoE contains a GH18 chitinase domain and a GH20 domain. The GH18 domain of EndoE is responsible for cleaving high-mannose glycans, which was determined based on *in vitro* activity toward glycans present on RNase B, a model high-mannose protein (53, 54). EfEndo18A also demonstrates activity toward these high-mannose glycans. The liberated mannose can then be utilized as a carbon source by *E. faecalis* (55, 56). Complex glycans on IgG are also cleaved by EndoE, but there are conflicting reports on whether this activity is due to the GH18 or GH20 domain (53, 55). A recent study suggests that the GH18 and GH20 domains work in conjunction to degrade complex glycans, with GH20 targeting GlcNAc residues on branches and GH18 targeting core GlcNAcs (57). Finally, EndoE is capable of deglycosylating lactoferrin, thereby blocking its activity (58). This host protein normally interferes with bacterial biofilm production. *E. faecalis* can utilize the glycans released from lactoferrin as a carbon source (58). Deletion of all three *E. faecalis* GH18 enzymes results in reduced colonization of the pathogen in a murine urinary tract infection model (55).

Complement inactivation. *Pseudomonas aeruginosa* secretes a chitin-binding protein, CbpD, which has now been demonstrated to have lytic polysaccharide monooxygenase activity (59, 60). The catalytic activity of CbpD is protective against the host complement cascade during systemic infection of mice. Activation of the host complement cascade on bacterial surfaces results in the deposition of a membrane attack complex and subsequent lysis of Gram-negative bacteria. CbpD inhibits a crucial step in this cascade by preventing the assembly of the C5 convertase and therefore the formation of the membrane attack complex. This study also suggests an additional role for CbpD in influencing the expression of multiple proteins, including other virulence factors (60). Studies have found that CbpD can carry various types of post-translational modifications, such as phosphorylation, succinylation, and acetylation (61, 62). Some of

the lysine residues found in CbpD can exhibit more than one modification, and there are even changes in the overall levels of phosphorylation depending on if CbpD is intracellular or extracellular (62). This variation in post-translational modifications could lead to conformational changes and different protein interactions (62), which may explain the seemingly dual functions of CbpD in inhibiting C5 convertase and modulating protein expression (60).

Interference with macrophage function. The gastrointestinal pathogen *Listeria monocytogenes* produces two chitinases (ChiA and ChiB) and a chitin-binding protein (lmo2467) that surprisingly do not seem to contribute to intestinal infection (63, 64). Instead, they are required for colonization of systemic sites such as the spleen and liver in an intravenous mouse model of infection (63). It appears that chitinase activity is intricately linked to virulence based on the fact that the Mour transcription factor regulates chitinase activity as well as the virulence-associated processes of biofilm formation and cell invasion (65). However, chitinase expression during infection could be regulated differently, since strains lacking Mour did not display a colonization defect during intravenous infection (65). This alternative regulatory system could involve the putative internalin/autolysin Lmo0327 and the putative transcriptional activator Lmo0325. The deletion of either of these genes blocks chitinase transcription (66). Other potential regulators of chitinase expression during *L. monocytogenes* infection are the virulence factor regulator PrfA, the sigma factor σ^B, the small RNA (sRNA) LhrA, and the *agr* quorum sensing system (64, 67, 68). ChiA is also upregulated during infection of murine macrophages (69). Further, it has been shown that ChiA promotes systemic infection through the downregulation of nitric oxide synthase expression (70). The role for ChiB during infection is still not well understood. An *L. monocytogenes* strain deficient in ChiB production was isolated from a clinical gastroenteritis infection, confirming data from intestinal epithelial cell (63, 64) infections that ChiB is likely not required for intestinal infection (71).

RESPIRATORY INFECTION

Chitinases are also emerging as virulence factors for respiratory pathogens. *Pseudomonas aeruginosa* expresses an active chitinase, ChiC, even though *P. aeruginosa* cannot use chitin as a carbon source *in vitro* (72, 73). ChiC production by *P. aeruginosa* is regulated by the GacS/GacA two-component system, which also regulates virulence in the lungs of mice with cystic fibrosis (74–76). ChiC is likely clinically relevant, as expression was upregulated in artificial-sputum medium, a model for cystic fibrosis sputum (77), and in hypervirulent strains isolated from cystic fibrosis patients (78, 79). ChiC is known to be secreted, but its actual functions during infection are still unknown (73). The chitin-binding protein CbpD, whose role for inhibiting the complement cascade during systemic infection we described in the previous section, was also found to be upregulated in artificial-sputum medium (80). CbpD is regulated by a quorum sensing system required for virulence in the lungs of rats, indicating that its role in complement cascade interference may extend to lung infection (81, 82). Further studies are required to explore if CbpD contributes to lung infection.

Legionella pneumophila expresses a chitinase (ChiA) that is secreted via the type II secretion system and is also contained within outer membrane vesicles (83, 84). While ChiA has activity toward chitin, it also has peptidase activity that degrades mammalian mucins to promote mucin layer penetration, and it cleaves the complement component human C1-inhibitor, potentially interfering with activation of the complement cascade (9, 83). This function could explain why a ChiA-deficient *L. pneumophila* strain does not persist as long as a wild-type strain in murine lungs (83). ChiA was also shown to be translocated to the cytosolic side of the *Legionella*-containing vacuole within infected macrophages (85). However, the function of this chitinase within a host cell is unclear since it was not required for intracellular replication (83).

GASTROINTESTINAL INFECTION

The roles of bacterial chitinases in mammals have usually been studied in the context of bacterial pathogens. However, some commensal bacteria also produce chitinases. For

instance, the gut commensal *Clostridium paraputrificum* produces several active chitinases, one of which, Chit62J4, shows optimal activity at pH 5.5, which is relevant to the intestinal tract (86). This indicates that *C. paraputrificum* may target dietary chitin or intestinal glycans as a carbon source during gastrointestinal colonization. Another gut commensal, *Lactobacillus plantarum*, expresses a chitin-binding protein that promotes adhesion to mucins and intestinal epithelial cells (87).

Numerous gastrointestinal pathogens express chitinases that have been implicated in promoting intestinal infection. In *Vibrio cholerae*, two chitinases (ChiA1, ChiA2) and the chitin-binding protein GbpA have been fairly well characterized in their roles during infection. They are known to be secreted via the type II secretion system (88, 89). ChiA1 is conserved in *V. cholerae* strains isolated from pandemics but is not conserved in nonpandemic strains, strongly suggesting a potential role for this chitinase during infection (90). The chitinase ChiA2 was shown to be required for intestinal infection, as it releases nutrient sources from intestinal mucins and promotes intestinal survival (8). ChiS, the main regulator of chitinase expression, is activated not only in the presence of chitin (30, 31), but also by mucins, which leads to higher expression of ChiA2 (91). The expression of ChiS, ChiA1, and ChiA2 is ultimately regulated by the transcription factor CytR, which also regulates other virulence factors to promote intestinal pathogenicity (92). In addition to chitinases, the chitin-binding protein GbpA also plays a role during infection. Deletion of *gpbA* results in less adherence of *V. cholerae* to intestinal epithelial cells and less fluid buildup in the intestines of infected mice (89, 93). Further studies revealed that this phenotype is due to GbpA's ability to bind GlcNAc residues present on intestinal mucins (93, 94). Interestingly, GbpA may only be required for early attachment and infection, since its expression is downregulated at high cell density (95). GbpA may also function as a toxin during infection, as treatment of colonic epithelial HT29 cells with purified GbpA induced necrosis (96). GbpA expression was found to be uniquely regulated by a complex interaction between the Vc1 riboswitch, c-di-GMP, and cAMP receptor protein (CRP) signaling systems (97, 98). Similar to some of the other bacterial chitin-binding proteins, GbpA demonstrates lytic polysaccharide monooxygenase activity (99).

We discussed the role of CBP21 in chitin degradation by *Serratia marcescens*; however, CBP21 has an additional role during infection. CBP21 can promote adhesion to colonic epithelial cells through interactions with the host chitin-binding protein chitinase-3-like-1 (100). The chitinase ChiA, produced by adherent-invasive *Escherichia coli*, also interacts with a glycan on chitinase-3-like-1 to promote adhesion to intestinal epithelial cells (101). *Clostridium difficile* incorporates the bifunctional enzyme CotE onto the surface of spores to promote colonization of the intestines (102). CotE demonstrates chitinase and peroxiredoxin activity, allowing *C. difficile* spores to bind to and degrade intestinal mucins, leading to enhanced pathogenicity in a hamster model of intestinal infection (102–104). CotE has been proposed as a therapeutic target, either for use in vaccines (105, 106) or as a potential target for inhibiting spore formation (107).

Chitinases produced by *Salmonella enterica* have recently been shown to contribute to intestinal infection (108, 109). Chitinase gene expression is upregulated during infection of HeLa cells, murine macrophages, and the gastrointestinal system of chickens (110–112). One of the chitinases, ChiA, demonstrates activity toward a common component of mammalian glycoproteins, *N*-acetyllactosamine (7, 113). Our group has shown that the chitinase ChiA and the putative chitinase STM0233 are upregulated in the gastrointestinal tract of mice and are required for the efficient invasion of small intestinal tissue by *S. enterica* serovar Typhimurium (108). This invasion phenotype is likely due to the targeting of surface glycans, since the presence of these chitinases induces specific changes in the abundance of GlcNAc-containing glycans (108). In a simultaneously published study, Chandra et al. confirmed the role for ChiA in promoting invasion and interaction with surface glycans and further showed that ChiA of *S. enterica* serovar Typhi has a similar function (109). That same group also revealed roles for ChiA in maintaining *Salmonella*-containing vacuoles during intracellular infection

and modulating the host immune response during infection with *S. Typhi* and *S.* Typhimurium (109).

INTERACTIONS BETWEEN BACTERIAL CHITINASES AND OTHER MICROBES

We have discussed multiple examples of how bacterial chitinases interact with the host. However, there are also examples of bacterial chitinases that interact with other bacteria or fungi. *Pseudomonas aeruginosa* chitinases (FI and FII) demonstrate lysozyme activity, targeting the cell wall of other bacterial species and inhibiting their growth (114). Bacterial species have also demonstrated activity toward chitin present in the cell wall of fungal pathogens. *P. aeruginosa* has been shown to bind and kill *Candida albicans* hyphae (115). It was later shown that the chitin-binding protein CbpD allows binding of *P. aeruginosa* to *C. albicans* hyphae, likely contributing to this killing mechanism (116). The probiotic *Lactobacillus rhamnosus* GG also interacts with *C. albicans* by blocking hyphal morphogenesis and biofilm formation (117). It was further shown that the peptidoglycan hydrolase MspI blocks hyphal formation by degrading fungal chitin (117). The soil bacterium *Bacillus safensis* has also been shown to block biofilm production, capsulation, and melanization by *Cryptococcus neoformans*. Additionally, *B. safensis* can bind to and block hyphal formation by *C. albicans*. Both of these antifungal mechanisms were shown to be dependent on chitinase activity (118).

SUMMARY AND OUTLOOK

Despite the target limitation that is hinted at with the name "chitin"ase, bacterial chitinases interact with a broad range of molecular targets and play an important role in infection. We have highlighted evidence that chitinases interact with mammalian N-linked surface glycans, mucins, and immune system components to promote epithelial cell adhesion, liberate nutritional resources, or interfere with the host immune response. The activity of GH18 and GH19 glycosyl hydrolases toward GlcNAc-containing molecules explains their important but divergent roles during infection of different body sites with different pathogens.

While we continue to learn more about the roles of chitinases during pathogenesis, much remains unknown, such as the targets of many bacterial chitinases. Purified glycans are commonly used to assess the activity of bacterial chitinases, but recent advances in glycome analysis techniques can be applied to further understand the role of these chitinases in interacting with host glycans (119). Glycan arrays can be used to detect binding across a wide range of glycan structures (120–122). Fluorescently tagged lectins can be used to detect specific saccharide moieties on the surface of cells. Ma et al. have incorporated metal-conjugated lectin staining into a cytometry time of flight technique to detect surface glycans at a single-cell level (123). While mass spectrometry has been largely used to quantify glycan abundance in a total sample, mass spectrometry imaging can identify the spatial distribution of glycans in tissue (124). With the help of these novel methods, researchers might more easily and comprehensively understand the roles of chitinases during infection.

Targeting bacterial chitinases may be a useful method for designing antivirulence therapeutics. It has been proposed that the spore-inhibiting antibiotic fidaxomicin may target CotE on *C. difficile* (107). One potential strategy to limit bacterial infections is designing small molecules to inhibit chitinase activity in order to limit adhesion or block interactions with the immune system and treat active infections. Targeting chitinases may also be an effective way to limit the spread of foodborne pathogens in livestock. Humans express two chitinases, chitotriosidase 1 (CHIT1) and acid mammalian chitinase (AMCase), which are thought to contribute to the type 2 immune response to environmental chitin and chitin-containing pathogens, such as helminths (125, 126). Therefore, care must be taken to ensure that a potential inhibitor would not interfere with the ability of these host chitinases to contribute to an effective innate immune response.

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