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In silico analysis of a family of extracellular polysaccharide deacetylases involved in virulence of pathogenic gram-positive cocci

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Background

Pathogenic bacteria incessantly evolve mechanisms to resist their host's innate immunity. One such mechanism is molecular camouflage: the modification of bacterial surface molecules to make them unrecognizable by the host's immune system or resistant to its effector molecules. Recently, a peptidoglycan deacetylase (PgdA) was discovered in *Streptococcus pneumoniae* that renders bacterial peptidoglycan resistant to human lysozyme, thus preventing host-mediated cell wall damage [1-3]. In addition, polysaccharide deacetylases with different substrate specificities were identified in other

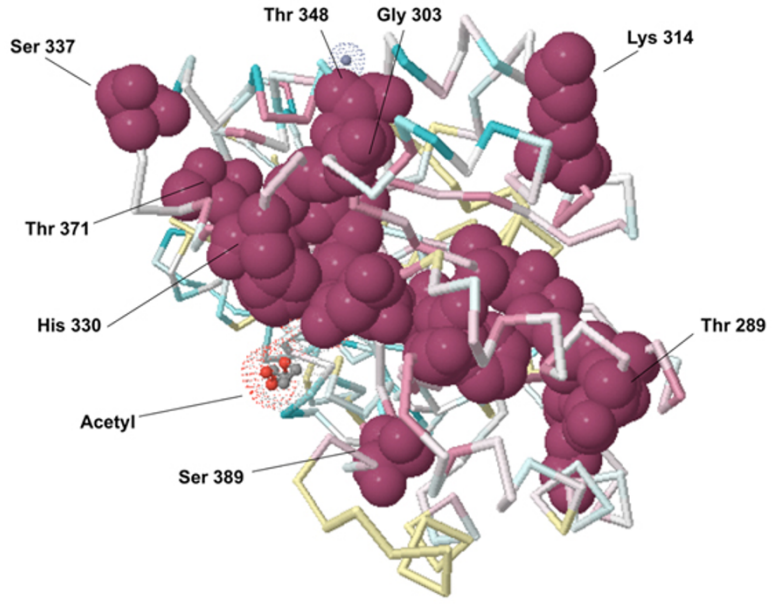

Figure 1 ConSurf [7,8] analysis of peptidoglycan and polysaccharide deacetylases of gram-positive cocci. The analysis involves the surface mapping of aligned amino acid sequences to the three-dimensional structure of *S. pneumoniae* PgdA (Protein Data Bank ID 2c1g). Highly conserved residues are shown in red (some are labeled for reference). These residues, conserved among the aligned proteins, are located within one region of the enzyme, surrounding the acetyl-binding groove.

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gram-positive bacteria and shown to contribute to virulence (e.g., IcaB of *Staphylococcus epidermidis* [4] and Pdi or *Streptococcus iniae* [5]).

Materials and methods

In this study, genomes of streptococci and other representative gram-positive cocci were screened for the presence of functional homologs of PgdA, the prototypic pneumococcal peptidoglycan deacetylase. Subsequently, amino acid sequences of homologous proteins were aligned[6] and mapped to the three-dimensional structure of PgdA (Protein Data Bank ID: 2c1g). The ConSurf tool[7,8] was used for surface mapping of the phylogenetic information calculated from the multiple sequence alignments.

Results

Primary screening identified at least one intact *pgdA* orthologous gene in every sequenced pathogenic streptococcal species and other paralogous polysaccharide deacetylases. Multiple sequence alignment of PgdA homologs proteins, phylogenetic analysis, and chromosomal context analysis suggest that these proteins are under host selective pressure. All PgdA orthologs share a conserved Pfam protein domain (PF01522), and 40 amino acid residues are 100% identical, but non-randomly distributed in beta-sheets in the C-terminal half of each streptococcal PgdA. ConSurf structural conservation analysis revealed that highly conserved residues in PgdA orthologs and paralogs surround the enzyme's acetyl-binding groove (Figure 1).

Conclusion

Taken together, these data suggest the conservation of PgdA in pathogenic streptococci, the presence of PgdA orthologs and paralogs in gram-positive cocci, and the high conservation of amino acid residues surrounding the active site of these enzymes. These residues may be tested as potential targets for the rational design of novel, immune-assisted antibacterial agents.

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