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Review

Synergistic findings from microbiological and evolutional analyses of virulence factors among pathogenic streptococcal species

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ABSTRACT

Background: Members of the genus *Streptococcus* are major constituents of human skin and the mucosal microbiome, among which *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae* are extracellular pathogens that occasionally cause life-threatening infectious diseases. Prior to their successful spread into the blood and deeper organs, pathogenic bacteria must first colonize human epithelial cell surfaces and evade host immunity. Streptococcal extracellular proteins play important roles in this colonization, as they directly interact with the host environment.

Highlight: This review focuses on recent reports of common and specific virulence factors among these species. Most streptococcal virulence factors show multiple functions. For example, conserved essential glycolytic enzymes localize on the bacterial cell surface and in the cytoplasm and contribute to evasion of host innate immunity, while bacterial glycosidases utilize host glycan via the lectin domain or glycosidase activity for survival in the host environment. Furthermore, various streptococcal species and strains show mutually exclusive interactions between the polysaccharide capsule and glycosidase. In addition, phylogenetic and evolutional analysis methods used for determining the importance of virulence factors of the species are introduced. Synergistic findings obtained by microbiological and evolutional analyses enable investigations of the consequence and correlation between genes and infectious phenotypes.

Conclusion: Bacterial pathogens rapidly adapt to clinical intervention, such as antimicrobial agents and vaccination, via horizontal gene transfer, recombination, and/or natural point mutation. It is vital to continue development of innovative analysis methods to counter the mounting threats from evolving bacteria.

Contents

Abbreviations: ECM, extracellular matrix

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1. Introduction

A variety of bacteria and other microorganisms inhabit the human body, of which Streptococci are one of the major genera that colonize skin and mucosa, including the oral cavity. Most streptococcal species are commensal bacteria and some occasionally cause serious infectious diseases. Streptococci are Gram-positive bacterial organisms present in chains or pairs. Phylogenetic analysis results based on the 16 S rRNA sequence were used to divide the genus *Streptococcus* into 6 major clusters: the pyogenic, anginosus, mitis, salivarius, bovis, and mutans groups [1]. A more recent phylogenetic analysis of 136 genes in the core set revealed a similar pattern and divided the genus into 8 groups, with the sanguinis and downei groups additionally classified as distinct clusters [2]. Some streptococcal species, such as *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae*, are known worldwide as important human pathogens that cause serious bacterial infections.

Streptococcus pyogenes is a Lancefield group A bacterium associated with various diseases, such as pharyngitis, scarlet fever, rheumatic heart disease, and invasive necrotizing fasciitis [3]. Its genome is approximately 2 Mbp of a single circular chromosome, which is compact compared to those of other bacteria, such as *Escherichia coli* (4 Mbp) and *Staphylococcus aureus* (3 Mbp). This suggests that *S. pyogenes* utilizes host molecules for its pathogenesis. For example, *S. pyogenes* contains at least 11 fibronectin (Fn)-binding proteins, and the interaction between Fn and Fn-binding proteins promotes bacterial access to host epithelial and endothelial cells [4]. Although approximately 660,000 cases and 163,000 deaths annually are caused by invasive *S. pyogenes* infection, there is no approved vaccine for treatment. In recent epidemiological studies, *Streptococcus dysgalactiae* subsp. *equisimilis* has been increasingly isolated from severe invasive streptococcal infections [5]. This bacterium shares various major virulence factors with *S. pyogenes* [2,5]. Studies of *S. dysgalactiae* subsp. *equisimilis* would also provide valuable insight into streptococcal invasive infections.

Streptococcus agalactiae is a Lancefield group B pathogen known to be a major cause of sepsis and meningitis in neonates [6]. There are 10 different serotypes of the polysaccharide capsule, which shares terminal sialic acids. Type III and Ia are major serotypes among isolates obtained from subjects with invasive diseases. Approximately 50% of infants born to women with *S. agalactiae* colonization in their vagina or rectum become carriers of the bacterium. As with *S. pyogenes*, no approved vaccine is available.

Streptococcus pneumoniae is a leading cause of bacterial pneumonia, sepsis, and meningitis, and is estimated to be responsible for the deaths of at least 800,000 children each year [7,8]. Although a capsule-conjugated vaccine against a subset of pneumococcal serotypes has shown considerable benefits, serotypes not targeted by the vaccine are increasing [8]. A previous study showed that *S. pneumoniae* can adapt to clinical interventions over a remarkably short period of time because of its high rate of recombination [9].

Current streptococcal species diverged from a common ancestor during the evolutional process by host immunity pressure. Some species adapted to the host environment as non-pathogenic commensal bacteria, while others obtained virulence factors and became important pathogens [10]. In this review, recently reported virulence factors of the pathogenic streptococci, *S. pyogenes*, *S. agalactiae*, and *S. pneumoniae*, are discussed.

2. Common factors

2.1. α-Enolase and glyceraldehyde-3-phosphate dehydrogenase (GAPDH)

α-Enolase and GAPDH are essential glycolytic enzymes present in the cytoplasm of many eukaryotic and prokaryotic organisms [11]. Enolase catalyzes the dehydration of 2-phosphoglycerate to phosphoenolpyruvate and GAPDH catalyzes the conversion of glyceraldehyde 3-phosphate to D-glycerate 1,3-bisphosphate in the Embden-Meyerhof-Parnas pathway. Although both are found on bacterial cell surfaces and in the culture supernatant, the proteins do not contain a signal sequence or cell surface-anchoring motifs. α-Enolase interacts with various host proteins, such as plasmin (ogen), fibronectin, collagen mucin, lactoferrin, and cytokeratin-8 [12], and the molecular interaction between bacterial enolase and plasmin notably promotes invasion of *S. pyogenes* into deeper host tissues via tricellular tight junctions [13]. Plasminogen functions as a molecular bridge between streptococcal α-enolase and host tricellulin, a major component of tricellular tight junctions. In addition, α-enolase disrupts the host immune system. Activated neutrophils release DNA fibers with antimicrobial proteins and peptides into the extracellular space, and these fibers function as neutrophil extracellular traps (NETs) to bind, disarm, and kill pathogens [14]. Pneumococcal α-enolase was shown to be capable of inducing neutrophil cell death, NET formation, and NET-dependent bacterial killing in human blood [15].

GAPDH also helps *S. pyogenes* escape detection by the host immune system [16]. *S. pyogenes*-GAPDH and C5a peptidase function synergistically to cleave host complement C5a on streptococcal cell surfaces, and GAPDH interacts with C5a through residues 114–163. It was recently shown that streptococcal GAPDH binds to various host molecules, including fibrinogen, fibronectin, uPAR, plasmin, myosin, enolase, lysozyme, and M-protein, among others [17], giving it moonlighting functions such as colonization and immunity evasion. GAPDH may have additional functions, and thus streptococcal α-enolase and GAPDH are attractive targets for prokaryotic and eukaryotic research.

2.2. Sortase A (SrtA)

A sortase family of transpeptidases is responsible for covalent attachment of bacterial proteins to the peptidoglycan of Gram-positive bacteria and divided into 6 classes based on phylogenetic analysis [18]. Notably, sortase A (SrtA) is found in many Gram-positive bacteria, including those belonging to the genus *Streptococcus* [19], and recognizes proteins containing an LPXTG motif on their C-terminal residues, and then cleaves the proteins between threonine and glycine of the motif. Subsequently, SrtA links the carboxyl group of threonine to the free amino group of the cell wall peptidoglycan via a cross-bridge. Deficiency of *srtA* results in the release of cell wall-anchored proteins into the supernatant and

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