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Generic determinants of *Streptococcus* colonization and infection

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ABSTRACT

Bacteria within the genus *Streptococcus* have evolved to become exquisitely adapted to the colonization of humans and other animals. These bacteria predominantly live in harmony with their hosts, but all have capacity to cause disease should prevailing conditions allow. Streptococci express a myriad of colonization and virulence attributes that promote their survival at a variety of ecological sites. Many of these factors are surface-expressed adhesins that exhibit conservation at structural or functional levels across the genus. This reflects the importance of adherence interactions with a multitude of host substrata, such as epithelia or extracellular matrix components, to streptococcal survival. Other important factors are more restricted in their distribution, often conferring pathogenic capabilities associated with immune evasion or host tissue destruction. Evidence suggests that dissemination of these streptococcal attributes has frequently been driven by the movement of genetic material via lateral gene transfer, reflecting ecological pressures. Such recombination events have simultaneously facilitated extensive diversification, resulting in distinct tropisms at the species- or strain- level. These generic determinants offer significant potential as targets for combating streptococcal disease. However, this will depend upon better understanding of their mechanistic basis, and refined mapping of their distribution by epidemiological and metagenomic studies.

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1. Introduction

There are over 100 defined species of *Streptococcus* and many of these are natural inhabitants of the human oral cavity and nasopharynx. A commensal microorganism is currently defined as being able to survive at harmony with the host in an arrangement that may be beneficial to one or both. By this definition, these streptococcal inhabitants are commensals, but they do all have the ability to cause some kind of disease, be it superficial or systemic, and so they may be better termed opportunistic pathogens. Since the environmental components present in the human mouth and nasopharynx are complex, the streptococci have evolved a myriad of factors and mechanisms for colonization of these sites. However, the structures and functions of these factors, and their mechanistic properties, have often been to a large degree well-conserved. Their genes have been selectively retained and evolved in the generation of species, and this has been mediated by DNA-mediated transformation, phage-mediated transduction, and conjugal transfer. There is now evidence to suggest that DNA-mediated transformation following the development of competence may be a widely shared mechanism in *Streptococcus* gene transfer (Mashburn-Warren et al., 2010), when it was previously believed that, for example, group A streptococci (GAS) were non-transformable.

In general, *Streptococcus* infections begin by interaction of the bacterial cells with host tissues through adhesin-receptor reactions (Fig. 1). Streptococci express a spectrum of adhesins that can exhibit broad specificity e.g., fibronectin binding, or unique specificity for a molecular ligand, such as sialyl T-antigen (Takamatsu et al., 2005). These adhesins often drive bacteria to the initial colonization site, for example the tooth surface, buccal or lingual mucosae, tonsils, etc. that express the available receptors. The outcome of initial adherence is the growth of the bacterial cells, provided environmental conditions are favorable, to form an early biofilm (Nobbs et al., 2009). This may attract different species of bacteria to adhere and form a community, such as in the development of dental plaque (Wright et al., 2013), or stimulate host cellular tissue to become susceptible to bacterial cell invasion (Fig. 1).

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Intracellular streptococci may then remain in a benign (or latent) state, to re-emerge later (Fig. 1), divide within the tissue to generate localized damage, or become disseminated throughout the body and infect multiple organs. Differential gene expression accompanies these processes, but many of the adhesins and invasins show common structures and properties, and the transcriptional regulators involved share similar structures and recognition motifs.

This article will consider some, but by no means all, of the generic determinants in the genus *Streptococcus* that are involved in mediating colonization and virulence. The focus will be on known factors that are expressed by oral streptococci and that are shared across the genus that promote adhesion to host surfaces, from a genetic and functional standpoint.

2. *Streptococcus* genomes

The streptococci include human pathogens, commensals, animal pathogens, fish pathogens, and non-pathogenic species used within the dairy industry (e.g., *Streptococcus thermophilus*). A recent analysis of 46 genome sequences has provided insight into the evolutionary history of the genus. Gene gain/loss analyses revealed a dynamic pattern of genomic evolution. Firstly with a period of gene gain, and then with gene loss, the major groups of the genus diversified. Then, a period of gene expansion led to the origins of the present species. A large proportion of the pan-genome has experienced lateral gene transfer (LGT), but despite this, a number of biochemical characteristics of groups have been retained, suggesting genomic cohesiveness through time (Richards et al., 2014). Proteolysis appears to be a defining feature of the mitis group, and also enrichment for *N*-acetyltransferase activity, which has been associated with resistance to aminoglycoside antibiotics. The salivarius group was enriched for urease, urea metabolism, and transposase activity, suggesting potential for high levels of recombination.

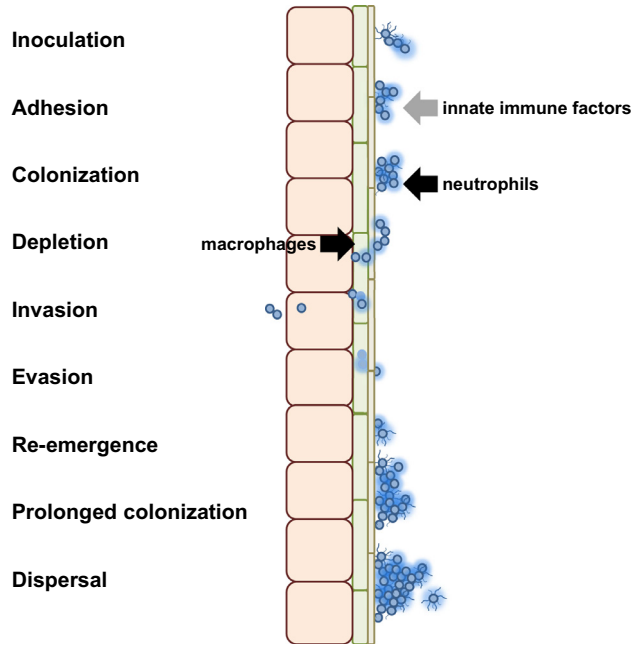

Fig. 1. Model for the establishment of longer-term mucosal colonization by streptococci. Following adhesion of bacteria to epithelium, and initial transient colonization, depletion of bacterial cell numbers occurs associated with host immune responses. These include innate factors, such as antimicrobial peptides, agglutinins, mucins, neutrophils and macrophages. A small number of streptococci successfully evade these responses, perhaps associated with internalization by epithelial cells. Bacteria may reside dormant within epithelial cells, or replicate, or become internalized by macrophages within which they survive and become spread systemically. Expression of factors that have anti-phagocytic properties and biofilm-enhancing activities may allow the streptococci to re-emerge to form a biofilm community, from which streptococci may be dispersed to colonize new sites.

2.1. Core genome

The *Streptococcus* genomes can be best described as consisting of core and accessory genomes. In *Streptococcus pneumoniae* (pneumococcus), for example, the core genome represents those genes that are common to all human pneumococcal isolates. These include key colonization and virulence genes as well as genes that enable niche adaptation and regulation of metabolism in response to alterations in available carbon sources, cations and amino acids, and anaerobic conditions. The core genome size is dependent on the number of isolates used during the analysis, and this gradually decreases with the addition of new genomes until a plateau is reached. To reach the absolute plateau and thus the definitive core genome size for *S. pneumoniae*, a decaying function analysis has to be undertaken (Tettelin et al., 2005).

By fitting a double-exponential decaying function model it has recently been shown that meningitis- versus bacteremia-associated pneumococci share a common core set of genes and that there is no difference in the core genome content from these disease manifestations (unpublished). This supports the requirement for a range of previously described virulence factors for these meningitis and bacteremia causing pneumococci. This high-resolution view of the core genome suggests that despite considerable competency for genetic exchange, the pneumococcus is under considerable pressure to retain key components that are presumably advantageous for colonization and transmission, and are essential for access and survival following invasion. A better understanding of the tropism of the pneumococcus for the blood and the brain will require more detailed analysis of allelic variation and gene expression.

The accessory genome represents the set of genes specific to a particular isolate(s), which are not shared in their entirety across the whole pneumococcal population. These may include, for example, genes associated with antibiotic resistance or novel virulence determinants.

2.2. Lateral gene transfer

LGT is a fundamental process in the genome evolution of bacteria (Gogarten and Townsend, 2005). LGT occurs by transformation, transduction or conjugation. It enables bacteria to evolve rapidly through the acquisition of novel genetic determinants, or genetic determinants that are homologous to existing DNA, which were not previously resident within the recipient's genome. The transfer of DNA via homologous recombination (HR) leads to the replacement of a region of the genome of a recipient cell by the corresponding region from the donor cell (Smith et al., 1991).

For pathogenic bacteria, interaction with the human immune system remains a constant battle and leads to some major changes in their genetic makeup. Adaptation of the pneumococcus, for example, to the host environment is facilitated by mutations and by frequent transfers of genetic material between isolates and across bacterial species (Hanage et al., 2009; Croucher et al., 2011; Golubchik et al., 2012). This genetic variability contributes to the considerable redundancy in the range of tools available to the pneumococcus to target host receptors, overcome the mucosal barrier and survive within the nasopharynx (Jedrzejas, 2001; Weiser et al., 2003; Bergmann and Hammerschmidt, 2006; Selva et al., 2009).

As such, LGT contributes to the remarkable plasticity of the pneumococcus through this intra- and inter-species genetic exchange. Due to this natural transformability LGT, for example,

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