Chapter

Introductory Chapter: An Overview of the Genus *Staphylococcus* and *Streptococcus*

Anıl Cebeci and Sahra Kırmusaoğlu

1. Introduction

We live in a world that inhibits many life forms including microorganisms. Bacteria, an important member of these microorganisms, sometimes become a very tough enemy of the human being with the stimulation of the conditions and environment. Bacterial infections that are sourced from pathogenic bacteria are one of the leading causes of the human death worldwide. For instance, lower respiratory infections killed 3 million people globally in 2016 [1].

Among the most pathogenic bacteria for human, genera of *Staphylococcus* and *Streptococcus* come forward with their pathogenicity. Staphylococci and Streptococci are grouped as Gram-positive cocci. Staphylococci form clumps, whereas Streptococci grow in chains. They can be discriminated by catalase test because Staphylococci have the capability to produce catalase [2].

Staphylococci and Streptococci are together responsible of the pathogenesis of a variety of diseases such as wound infections, mastitis, toxic shock syndrome, scarlet fever, cystic fibrosis, nosocomial and community-acquired infections, periodontitis, and indwelling device-associated infections [3, 4].

2. Virulence factors of *Staphylococcus* spp. and *Streptococcus* spp.

2.1 Toxins

As a major human pathogenic bacterium, *Staphylococcus aureus* (*S. aureus*) has many virulence factors including staphylocoagulase (SC), protein A, staphylococcal enterotoxins (SEs), and leukotoxins.

SC is the cause of acute bacterial endocarditis. It binds to the blood prothrombin, and this complex induces the number and the colonization of bacteria via transformation of fibrinogen to fibrin [5]. Protein A is the vehicle of *S. aureus* for binding to Fc region of IgG. By this mechanism, pathogenic bacterium is surrounded by IgG and will not be recognized by the cells of human immunity system [6].

SEs belong to a huge family of staphylococcal and streptococcal exotoxins and are shown to be the main cause of toxic shock syndrome. These superantigens show their pathogenicity via binding to class II major histocompatibility complex (MHC) molecules that are located on the surface of the antigen-presenting cells and causing a toxic shock with stimulation of high numbers of T cells [7].

Additionally, leukotoxins of *S. aureus* can eliminate phagocytic cells of the mammalian immune system by killing them selectively [8].

Although they are the hosts of the mucosal surfaces of human, streptococci are associated with many infectious diseases like tonsillitis, endocarditis, pharyngitis, meningitis, and glomerulonephritis [9]. Group A streptococcus (GAS) which is known as the main cause of necrotizing fasciitis produce streptococcal pyrogenic exotoxins (Spes). Streptococcal toxic shock syndrome (STSS) is associated with various Spe proteins, including SpeA, SpeS and SpeG, streptococcal superantigen A (SSA), and streptococcal mitogenic exotoxin Z (SMEZ) and SMEZ2. As mentioned before, these superantigens induce T cells to proliferate massively and cause abnormal production of cytokines [10].

Hemolysin from *Streptococcus pyogenes* (*S. pyogenes*) and its equivalent, pneumolysin, from *S. pneumoniae*, not only form pores but also activate the inflammatory system elements. Again, streptolysin O (SLO) and streptolysin S (SLS) belong to this superantigen family [10].

2.2 Biofilm formation

Bacterial biofilm is the optimum environment for bacteria to survive. More than a nutrient poll, biofilm provides protection for its residents against harsh conditions, antibiotics, and other antimicrobial chemical agents. From the vision of indwelling device-associated infections and nosocomial and community-acquired infections, *Staphylococcus epidermidis* (*S. epidermidis*) and *S. aureus* are the main responsible organisms with the ability of forming biofilm [11].

S. aureus strains can bear the *ica* operon that express polysaccharide intracellular adhesin (PIA) which is termed as the main molecule in biofilm formation [12, 13]. With its positively charged molecular structure, PIA enhances the intercellular binding of negatively charged bacterial surface [14].

However, the biofilm can be structured without the adhesive effect of PIA. PIA-independent biofilms may be formed by different surface proteins such as biofilm-associated protein (Bap) and accumulation-associated proteins (Aap) of *S. epidermidis* [12, 13]. More than that, protein A and some members of the fibronectin-binding proteins, cell wall-anchored proteins, and autolysins can help the formation of biofilm [14].

3. Antibiotic resistance of *Staphylococcus* and *Streptococcus*

Antibiotic resistance becomes a worldwide serious health threat due to the inappropriate prescribing, overuse, and the extensive agricultural use of antibiotics [15]. *S. aureus*, a well-known pathogenic bacterium, exhibits resistance to the some of the important and widely used antibiotics such as β-lactam antibiotics, tetracycline, and methicillin through its genome and extrachromosomal elements [16].

The genetic elements of *S. aureus* play a critical role in antibiotic resistance. *S. aureus* can hydrolase the β-lactam ring of penicillin by using the penicillinase which is expressed from the *bla*Z gene localized in *S. aureus* plasmid. This emerging feature can be observed more than 80 percent of the *S. aureus* strains [17].

Another example of plasmid-originated antibiotic resistance can be observed for tetracycline in *S. aureus*. *Tet* gene in conjugative plasmid of *S. aureus* encodes ribosomal protection protein which prevents the binding of tetracycline to ribosome and thus the inactivation of it [18].

The occurrence of *S. aureus* isolates that are resistant to β-lactam antibiotics provide the discovery of penicillinase-stable penicillins. One of these molecules, methicillin, is the medication of choice to treat β-lactam-resistant *S. aureus* infections. But some of the *S. aureus* isolates are also resistant to methicillin and different types

of antibiotics such as macrolides and cephalosporins. Methicillin-resistant *S. aureus* (MRSA) isolates demonstrate their characteristics of multi-antibiotic resistance through their chromosomes and extrachromosomal elements. Penicillin binding protein 2a which is encoded by chromosomal *mec*A gene is the main reason of methicillin resistance of *S. aureus* [19, 20].

Enterococci are the members of the microflora of the intestinal system. But they are also opportunistic and nosocomial pathogens. Especially, they are accused of sepsis, endocarditis, and urinary tract infections in immunosuppressed patients [21].

These pathogens demonstrate a different feature compared to other Gram-positive cocci: adaptation to different antimicrobials such as vancomycin quickly and exhibition of multidrug resistance [21].

Vancomycin is a member of glycopeptide antibiotics. It targets the precursors of peptidoglycan, while this system is crucial for the enterococcal cell wall biosynthesis. By binding to these precursors and preventing the transglycosylation and transpeptidation, vancomycin prevents the building and growing of bacterial cell wall [22]. But enterococci overcome this destructive problem with different *van* operon systems, for instance, *vanA*, *vanB*, *vanC*, and *vanD*. The common feature of these systems is to alter the peptidoglycan biosynthesis pathway with different molecules so that vancomycin cannot identify the molecule thus cannot interfere [22].

Author details

Anıl Cebeci and Sahra Kırmusaoğlu*
Faculty of Arts and Sciences, Department of Molecular Biology and Genetics, Halic University, Istanbul, Turkey

*Address all correspondence to: kirmusaoglu_sahra@hotmail.com

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