



# The staphylococci and staphylococcal pathogenesis

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Over the past 30 years, the scientific literature has been rife with articles that have chronicled the enduring threat and changing nature of *Staphylococcus aureus* as a leading cause of infectious morbidity and mortality to humans (Sheagren, 1984; Archer, 1998; Lowy, 1998; Otto, 2010). The most current surveys indicate that *S. aureus* is responsible for almost 500,000 hospitalizations and 30,000 deaths annually in the USA (Klein et al., 2007). At the turn of the twentieth century, the major threat was hospital-associated strains of methicillin resistant *S. aureus* (HA-MRSA) that are resistant to multiple antibiotics, and reports that some had acquired high level vancomycin resistance (Pearson, 2002; Weigel et al., 2003) seemed to assure the inevitable proliferation of strains that are resistant to all antibiotics. Although this crisis has not yet materialized, we have instead experienced the sudden emergence and global dissemination of hyper-virulent strains of community acquired MRSA (CA-MRSA). Another unexpected threat was the emergence of CA-MRSA in animal adapted strains of *S. aureus*, and their zoonotic transmission to humans. Conversely, some livestock-associated strains have undergone a recent evolutionary transition from human to animal hosts. Amidst this backdrop of newly emergent strains, common clonal types of HA-MRSA and methicillin susceptible *S. aureus* (MSSA) persist in their threat to health care, and attempts to lessen the impact through vaccine development have thus far been unsuccessful.

In this Special Topics issue, recent advances in Staphylococcal research are captured in a collection of research, review, opinion, and methods articles, which we have assigned to the general themes of vaccine development, virulence, and immune evasion, metabolic activity in response to host environment, methods development, and comparative genomics and genome evolution.

## VACCINE DEVELOPMENT

On the front lines of vaccine development, an opinion article from Bagnoli et al. (2012) at Novartis offers plausible explanations for

the vaccine failures that have plagued human clinical trials, and offer optimism that success can be achieved with an appropriate multivalent vaccine that stimulates cellular immunity and opsonophagocytosis, while inhibiting bacterial viability and/or toxicity. Pancari et al. (2012) outline the vaccine strategy and progress at Merck Research labs, defining the mechanistic basis of protection offered by a vaccine that targets the IsdB protein, which is expressed *in vivo* under iron-limited growth conditions.

## METABOLIC ACTIVITY IN RESPONSE TO HOST ENVIRONMENT

The host environment imposes many stresses on bacteria, among them nutrient limitation and oxidative stress imparted by host phagocytes. Proteins involved in iron acquisition are attractive vaccine components, because their expression is promoted by growth in the iron-restricted host environment. Sheldon and Heinrichs (2012) review the biogenesis, substrate specificity, and impact on host innate immune response, of cell envelope lipoproteins that are up-regulated in response to low iron. Gaupp et al. (2012) summarize the cellular targets of oxidative stress, mechanisms employed to sense oxidative stress and damage, oxidative stress protection and repair mechanisms, and regulation of the oxidative stress response. Original research by Fuller et al. (2011) defines the role of a lactate-quinone oxidoreductase (Lqo) in countering oxidative stress imposed by host phagocyte derived nitric oxide, and show that this cytoplasmic protein is essential for virulence in a murine model of sepsis, particularly in association with myocarditis.

## VIRULENCE STUDIES

Although most manifestations of *S. aureus* disease are attributed to its growth as an “extracellular” pathogen, it is gaining new respect for its ability to survive within host cells as a facultative intracellular pathogen. Fraunholz and Sinha (2012) present a guide to recent developments in this emerging

field of study, summarizing the variety of intracellular fates of *S. aureus*, including artwork that appears on the cover of this issue. Original research by Spaulding et al. (2012) shows that major clonal types of *S. aureus* known for causing hospital and community acquired infections, exhibit distinct differences in their capacity for cardiotropic versus lethal sepsis infections, and that production of superantigen toxins and cytolysins account for some of these differences. Expanding on the theme that some strains specialize in certain types of infection, Anderson et al. (2012) describe an *ex vivo* porcine vaginal mucosa model to evaluate the contribution of cytolysins in biofilm formation and tissue damage caused by *S. aureus* strains associated with menstrual toxic shock syndrome. Xu and McCormick (2012) review molecular biology of staphylococcal superantigen toxins, including toxic shock syndrome toxin TSST, and offer a unique perspective on superantigen toxins, which includes a proposed role in colonization, in addition to disease progression. Vandenesch et al. review developments in understanding the potentially redundant arsenal of membrane-damaging virulence factors at the disposal of *S. aureus*, and their interplay with the host immune system (Vandenesch et al., 2012). Hanke and Kielian (2012) have authored a review that summarizes the immune defenses that staphylococcal biofilms evade, and place specific emphasis on the idea that staphylococcal biofilms skew the host immune response away from a proinflammatory bactericidal phenotype toward an anti-inflammatory, pro-fibrotic response that favors bacterial persistence.

## GENE REGULATION

An emerging theme in regulation of gene expression by microbial pathogens is that of regulatory RNA's and control of RNA stability. Morrison et al. (2012) extend this theme, identifying a new role for the SarA transcriptional regulator of *S. aureus*, in binding to and altering the mRNA turnover properties of target transcripts. Cue et al. (2012)

review how various regulatory factors affect production of poly *N*-acetyl glucosamine, an intercellular polysaccharide adhesin that contributes to biofilm related infections in both *S. aureus* and *S. epidermidis*.

## METHODS

An increasing appreciation of the role of biofilms in persistent infection and immune evasion highlights the importance of standard techniques to evaluate biofilm structure and genetics of biofilm formation. Walker and Horswill (2012) describe a simple method for quantitative evaluation of *S. aureus* biofilms on glass coverslips coated with human plasma. Our current and future knowledge of gene function could not be achieved without the less heralded development of efficient techniques for construction of gene deletion mutations. Monk and Foster (2012) review the restriction-modification barrier in Staphylococci, and how knowledge of these systems can be used to develop plasmid vectors that can be used to manipulate previously un-transformable strains.

## COMPARATIVE GENOMICS AND EVOLUTION

A comparative genomics evaluation by Ben Zakour et al. (2012) identifies new directions for research into pathogenesis and patho-adaptation of the *S. intermedius* group of animal pathogens, revealing extensive differences in the accessory genome content between closely related species that nevertheless inhabit distinct host niches. Research by McGavin et al. (2012) reveal three distinct clades within *S. aureus* clonal complex CC30, of which Clade 3 comprised of hospital-associated strains exhibit numerous features that are consistent with evolution through niche adaptation mechanisms. Finally, McCarthy et al. (2012) have analyzed 79 sequenced *S. aureus* genomes to assess the role of bacteriophage in dissemination of toxins and immune evasion genes, finding that horizontal transfer is restricted by bacteriophage family, and lineage of the host bacterium.

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