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Research paper

Mouse models for infectious diseases caused by *Staphylococcus aureus*

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ABSTRACT

Staphylococcus aureus – a commensal of the human skin, nares and gastrointestinal tract – is also a leading cause of bacterial skin and soft tissue infection (SSTIs), bacteremia, sepsis, peritonitis, pneumonia and endocarditis. Antibiotic-resistant strains, designated MRSA (methicillin-resistant *S. aureus*), are common and represent a therapeutic challenge. Current research and development efforts seek to address the challenge of MRSA infections through vaccines and immune therapeutics. Mice have been used as experimental models for *S. aureus* SSTI, bacteremia, sepsis, peritonitis and endocarditis. This work led to the identification of key virulence factors, candidate vaccine antigens or immune-therapeutics that still require human clinical testing to establish efficacy. Past failures of human clinical trials raised skepticism whether the mouse is an appropriate model for *S. aureus* disease in humans. *S. aureus* causes chronic-persistent infections that, even with antibiotic or surgical intervention, reoccur in humans and in mice. Determinants of *S. aureus* evasion from human innate and adaptive immune responses have been identified, however only some of these are relevant in mice. Future research must integrate these insights and refine the experimental mouse models for specific *S. aureus* diseases to accurately predict the failure or success for candidate vaccines and immune-therapeutics.

1. *Staphylococcus aureus*

Staphylococcus aureus is a Gram-positive bacterium that colonizes the skin, nares and gastrointestinal tract of humans (Lowy, 1998). Approximately 20% of the human population are stably colonized while 30% are colonized in a variable manner (Lowy, 1998; von Eiff et al., 2001). *S. aureus* is also a pathogen that causes invasive disease, predominantly skin and soft tissue infections (SSTI), but also bacteremia, sepsis, pneumonia, osteomyelitis and endocarditis (Lowy, 1998). The pathological hallmark of *S. aureus* infection is the formation of purulent abscess lesions that are formed around a nidus of the pathogen, primarily via the infiltration of neutrophils (Cheng et al., 2009). In humans, *S. aureus* infection does not lead to the development of protective immune responses and chronic persistent or recurrent infections are common (Lessa et al., 2010). Some isolates of *S. aureus* cause toxic-shock syndrome, exfoliative skin disease, and enteritis in humans (Lowy, 1998). Secreted toxins are the key virulence determinants for these diseases (Bukowski et al., 2010; McCormick et al., 2001) and transfer of the corresponding genes among staphylococcal strains involves specific bacteriophages (Novick et al., 2010). (See Fig. 1.) (See Table 1.)

S. aureus is also an important pathogen of live-stock, causing large scale infections in ruminants (sheep, goats, cows), poultry and pigs (Fluit, 2012). Molecular epidemiological data suggest that a common pathogenic *S. aureus* clone associated with ruminants originated in humans (Fitzgerald, 2012a). This strain adapted to its chosen niche more than 11,000 years ago, at a time when farming domesticated animals became common practice, and then diversified (Fitzgerald, 2012a). Similar jumps from humans to new hosts occurred for several different clinical lineages (Fitzgerald, 2012b). Adaptation to new hosts required a combination of gene loss, allelic diversification, and acquisition of mobile genetic elements, for example elements that support the expression of unique von-Willebrand factor binding protein

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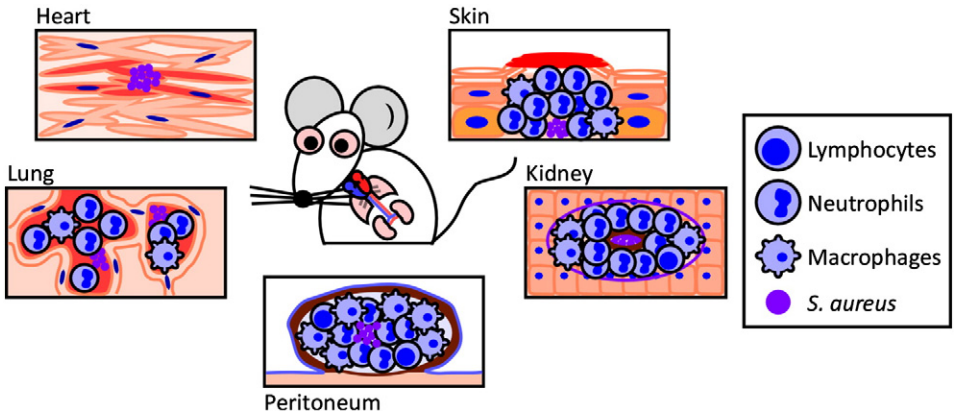

Fig. 1. Mouse models for *S. aureus* infections. Mice are susceptible to *S. aureus* infections. Staphylococci can be administered by four different routes: intravenous, intraperitoneal, subcutaneous and intranasal inoculation. Intravenous delivery of staphylococci generates metastatic infectious lesions in multiple internal organs including heart and kidneys. In heart, agglutinated staphylococci (staphylococcal abscess community; SAC) are surrounded by necrotic cardiac myocytes (red). In renal tissue, SAC are surrounded by fibrin deposits (brown – eosinophilic pseudocapsule) which separate bacteria from massive immune cell infiltrates (purple). Injection of staphylococci into the peritoneum creates a lesion comprised of a large number of immune cells with staphylococci. This lesion is attached to the peritoneal lining and surrounded by an inner layer of fibrin deposits (brown) and an outer layer of collagen (blue). Subcutaneous injection of staphylococci generates a subcutaneous abscess and dermonecrotic (red) lesions on the overlying skin. Lower respiratory tract infection caused by intranasal inoculation of staphylococci is characterized by obstruction of airspace (red) by inflammatory cell infiltrates and aggregates of *S. aureus*.

alleles in *S. aureus* strains that infect ruminants and horses (Viana et al., 2010). Nevertheless, the core genome of ruminant associated *S. aureus* is stable and can lead to reciprocal transmission of newly emerging clones into the human population (Spoor et al., 2013). This type of pathogen introduction occurs on a global scale and is associated with transport of live-stock or people (Price et al., 2012). It has led to outbreaks of human *S. aureus* disease in countries that otherwise have low prevalence for staphylococcal disease (Fitzgerald, 2012a).

The genome of *S. aureus* strains varies in size (2.6–2.9 MB), based on the presence of prophages and pathogenicity islands (Kuroda et al., 2001; Harris et al., 2010). Nevertheless, all *S. aureus* isolates encompasses a core genome for the functional expression of genes that are shared by most if not all clinically relevant strains (McCarthy and Lindsay, 2010). For example, *S. aureus* isolates generally coagulate blood, agglutinate in plasma, and bind to animal immunoglobulin (Cheng et al., 2011). Although nasal colonization is asymptomatic for most individuals, it represents a risk factor for hospital-acquired infection (Gorwitz et al., 2008). Other risk factors for nosocomial infection include indwelling catheters, endotracheal intubation, medical implants, trauma, diabetes, immunosuppression and immunosuppressive therapy, hemodialysis and peritoneal dialysis (Miller et al., 2007; Kallen et al., 2010). In the United States, *S. aureus* is the single most frequent cause of hospital-acquired infectious disease mortality (Klevens et al., 2008).

Massive use of antibiotics in animals and humans led to the selection of drug-resistant strains, designated MRSA for methicillin-resistant *S. aureus* (DeLeo and Chambers, 2009). Broad spectrum β-lactam resistance is caused by MecA, a penicillin-binding protein that cannot be inhibited by β-lactamase resistant β-lactam or cephalosporin compounds (DeLeo and Chambers, 2009). Recommended therapeutics against MRSA strains are vancomycin, daptomycin and linezolid (Liu et al., 2011; Arbeit et al., 2004; Stevens et al., 2002). However, vancomycin-resistant (VRSA) strains, which acquired genes for the synthesis of altered peptidoglycan precursors from enterococci, have been isolated (Chang et al., 2003; Fridkin, 2001; Weigel et al., 2003). *S. aureus* strains have also evolved resistance mechanisms to daptomycin and linezolid shortly after these compounds were approved for clinical use (Weigel et al., 2003; Richter et al., 2013; Sader et al., 2013). MRSA infections occur frequently in American hospitals and in

Table 1
Summary of mouse models for *S. aureus* infection.

Disease model	Infection route	Infectious dose (CFUs)	Phenotype	References
Skin infection	Subcutaneous	1×10^7–1×10^9	Dermonecrosis caused by secreted toxins	(Kennedy et al., 2010; Malachowa et al., 2013)
Metastatic abscess formation	Intravenous	1×10^6–1×10^7	Abscess formation in most internal organs	(Cheng et al., 2009)
Sepsis	Intravenous	5×10^7–5×10^8	Acute lethal disease within 48 hours of infection; formation of multiple lesions in heart	(Cheng et al., 2010b; McAdow et al., 2011)
Peritonitis	Intraperitoenal	5×10^8 (LD_{50}) 6×10^9 (LD_{90})	Acute lethal disease within 12 hours of infection; formation of abscess lesions on peritoneal surfaces	(Rauch et al., 2012)
Pneumonia	Intranasal	2–4×10^8	Acute lethal disease within 72 hours of infection; infiltration of inflammatory cells into alveolar air space	(Bubeck Wardenburg et al., 2007)