Staphylococcus aureus (subsp. *aureus*)

Host species

- wide range of domestic and wild mammalian animals, birds, humans
- various species of laboratory animals (National Research Council 1991, Shimizu 1994, Harkness & Wagner 1995, Percy & Barthold 2007)

Properties

- *S. aureus* exists in the environment such as dust, water, food or on food equipment and environmental surfaces, and it is relatively resistant to a variety of environmental conditions such as drying, UV light, and heat (National Research Council 1991, Shimizu 1994, Harkness & Wagner 1995). This environmental resistance and the broad host spectrum make it difficult to control spread of infection.
- *S. aureus* easily develops antibiotic resistance (Shimizu 1994, Winn *et al*. 2006). This is particularly a problem in *S. aureus* strains derived from hospitalized humans. They are typically resistant to multiple antibiotics including methicillin and oxacillin. The prevalence of such strains is lower in the community and in animal facilities, because antibiotic selective pressure is much lower than in hospitals.

Organotropism

- common inhabitant of the skin and mucous membranes (nasopharynx, lower intestinal tract, lower genital tract)
- entry into the body occurs most probably through breaks in the oral mucosa or skin

Clinical disease

- animals and human carriers usually remain asymptomatic (National Research Council 1991, Shimizu 1994, Harkness & Wagner 1995, Winn *et al*. 2006, Percy & Barthold 2007); clinical disease is common in immunocompromised hosts
- clinical signs (other than sudden death from pneumonia, septicaemia, or toxaemia) in laboratory animals include fever, anorexia, depression, various forms of dermatitis, foot swelling, reddening of the conjunctiva, lacrimation, subcutaneous lumps, enlarged mammary glands, and purulent discharge

- skin lesions are frequently accompanied by pruritus resulting in scratching and self-mutilation

Pathology

A variety of distinct disease processes have been reported in laboratory animals (National Research Council 1991, Shimizu 1994, Harkness & Wagner 1995, Percy & Barthold 2007), including the following:

- mouse: suppurative or ulcerative dermatitis, furunculosis, conjunctivitis, facial abscesses, botryomycotic granulomas, subcutaneous abscesses, preputial gland abscesses, bulbourethral gland abscesses, balanoposthitis, urinary cystitis
- rat: ulcerative dermatitis, pododermatitis, keratoconjunctivitis, panophthalmitis, subcutaneous abscesses
- guinea pig: exfoliative dermatitis, pododermatitis ("bumblefoot"), conjunctivitis, pneumonia, mastitis, osteoarthritis
- rabbit: conjunctivitis, subcutaneous abscesses, bronchopneumonia, lymphadenitis, mastitis
- hamster: dermal abscesses
- Mongolian gerbil: dermatitis ("sore nose").

In humans, a variety of suppurative inflammatory conditions and toxinoses are found (Winn *et al*. 2006):

- suppurative inflammation: skin lesions (e.g. furunculosis, impetigo), pneumonia, mastitis, phlebitis, meningitis, osteomyelitis, endocarditis, etc.
- toxinoses: toxic epidermal necrolysis, toxic shock syndrome, food poisoning.

Morbidity and mortality

Morbidity and mortality are highly variable and influenced by host, bacterial, and environmental factors:

- strain differences in susceptibility to *S. aureus* infection and associated disease are found among immunocompetent mice (Shults *et al*. 1973, Needham & Cooper 1976, Hong & Ediger 1978, von Köckritz-Blickwede *et al*. 2008); e.g. in the latter study, C57BL/6 mice were the most resistant in terms of control of bacterial growth and survival, A/J, DBA/2, and BALB/c mice were highly susceptible, and C3H/HeN, CBA, and C57BL/10 mice exhibited intermediate susceptibility levels

- immunodeficient hosts such as splenectomized or neutrophil-depleted mice (Teixeira *et al.* 2008, Robertson *et al*. 2008), athymic nude mice (Sano *et al.* 1988), iNOS-deficient mice (McInnes *et al*. 1998), TLR2-deficient and MyD88-deficient mice (Takeuchi *et al*. 2000) are highly susceptible to *S. aureus* infection or associated disease; likewise, certain mutant strains of mice without (known) inmmunodeficiency such as mice deficient in urokinase-type plasminogen activator have an increased susceptibility to staphylococcal disease (Shapiro *et al*. 1997)
- the genetic background strain may influence outcome of disease in mutant mice such as *S. aureus*-triggered sepsis and arthritis in IL-4-deficient mice (Hultgren *et al*. 1999)
- female and castrated CD-1 mice are more susceptible to infection with certain strains of *S. aureus*, suggesting a hormonal influence on resistance (Yanke *et al*. 2000)
- other contributing host factors are age (Girgis *et al*. 2004), physical injuries, e.g. as a result of fighting or surgery, and behavioural dysfunctions such as trichotillomania (Jacoby *et al*. 2002, Percy & Barthold 2007)
- *S. aureus* strains can express a diverse arsenal of virulence factors and differ in virulence (Mizobuchi *et al*. 1994, Benton *et al*. 2004, Sibbald *et al*. 2006)
- predisposing environmental factors include stress, e.g. provoked by experimental procedures, nutritional deficiencies (Galler *et al*. 1979, Chew *et al*. 1985, Wiedermann *et al*. 1996), concurrent infections, e.g. with mites (Percy & Barthold 2007) or *Pseudomonas aeruginosa* (Hendricks *et al*. 2001), and the prevalence of *S. aureus* in the environment

Zoonotic relevance

- transmissible between species
- transmission mainly by contact with infected animals or humans and their excretions
- humans are a reservoir: ~20% of people persistently carry *S. aureus* in the anterior nares, and ~60% are intermittent carriers (Kluytmans *et al*. 1997)

Interference with research

S. aureus could principally interfere with research by induction of disease (as described above). In addition, natural infection with *S. aureus* could compromise numerous studies using experimental animal models of *S. aureus* infection (e.g. models of implant-related infection, surgical wound infection, infected burn wounds, septic shock, infective endocarditis, and bone infection). It also has to be considered that *S. aureus* produces a

variety of biologically active products, including protein A, catalase, coagulase, fibrinolysins, hyaluronidase, lipases, hemolysins, leucocidin, exfoliatins, enterotoxins, and toxic shock syndrome toxin (Winn *et al.* 2006). The effects of these products and their metabolites are numerous and are not covered by this monograph. The following list provides examples of potential research complications due to entire *S. aureus* organisms:

Physiology

- *S. aureus* induces serum α_2-macroglobulin in rats (Jinbo *et al.* 2001)
- *S. aureus* causes contractile dysfunction in the mouse heart (Knuefermann *et al.* 2004) and aorta (Cartwright *et al.* 2007)

Pathology

- immunocompromised animals are at increased risk for pathological lesions caused by *S. aureus*, e.g. kidney abscesses have been observed in infected rats following treatment with corticosteroids (Simmons & Simpson 1977)
- inapparent wound infection with *S. aureus* increases plasma fibrinogen levels, total leukocyte counts, and wound histology scores in rats (Bradfield *et al.* 1992)
- *S. aureus* and its peptidoglycan ameliorate glucocorticoid-induced impaired wound healing in rats (Chang *et al.* 1997)
- *S. aureus* and its peptidoglycan stimulate macrophage recruitment, angiogenesis, fibroplasia, and collagen accumulation in wounded rats (Kilcullen *et al.* 1998)
- *S. aureus* enhances inflammation, endothelial injury, and blood coagulation in mice with streptozotocin-induced diabetes (Tsao *et al.* 2006)
- *S. aureus* elicits marked alterations in the mouse airway proteome during early pneumonia, including an increase in antimicrobial peptides, opsonins, pro-inflammatory mediators, and coagulation proteins (Braff *et al.* 2007, Ventura *et al.* 2008)
- spontaneous arthritis in MRL/*lpr* mice is aggravated by *S. aureus* infection (Salinas-Carmona *et al.* 2009)

Cell biology

- infection with *S. aureus* induces a pro-inflammatory state in endothelial cells, as determined by expression of cytokines (Yao *et al.* 1995, Yao *et al.* 1996, Söderquist *et al.* 1998,

Strindhall *et al*. 2005), Fc receptors (Bengualid *et al*. 1990), and adhesion molecules (Strindhall *et al*. 2002)

- *S. aureus* enhances expression of Toll-like receptor 2 and MyD88 in microglia (Esen & Kielian 2006)
- *S. aureus* induces release of TNF-α and nitric oxide in murine macrophages (Paul-Clark *et al*. 2006)
- *S. aureus* enhances secretion of TNF-α, IL-1β and nitric oxide, and up-regulates expression of nitric oxide synthase and Toll-like receptor 2 in epididymal epithelial cells (Zhao *et al*. 2008)
- *S. aureus* induces expression of IL-6 and IL-12 (Bost *et al*. 1999), MHC class II molecules (Schrum *et al*. 2003a), CD40 (Schrum *et al*. 2003b), receptor activator of NF-κB ligand and prostaglandin E2 in osteoblasts (Somayaji *et al*. 2008)
- *S. aureus* induces apoptosis in osteoblasts (Tucker *et al*. 2000)
- *S. aureus* activates the early response genes c-fos and c-jun and activator protein-1, and induces proapoptosis genes Bad and Bak in pleural mesothelial cells (Mohammed *et al*. 2007)

Immunology

- *S. aureus* inhibits contact sensitivity to oxazolone by activating suppressor B cells in mice (Benedettini *et al*. 1984)
- *S. aureus* induces production of IFN-γ, TNF, and IL-6 in the bloodstreams, spleens, and kidneys of systemically infected mice (Nakane *et al*. 1995)
- systemic *S. aureus* infection induces a Th2 response (IL-4, IL-10) in the spleens of mice (Sasaki *et al*. 2000)

Interactions with other infectious agents

- low concentrations of *Pseudomonas aeruginosa* enhance the ability of *S. aureus* to cause infection in a rat model of orthopaedic wounds, while at the same time *S. aureus* lowers the rate of *Pseudomonas aeruginosa* infection (Hendricks *et al*. 2001)
- *S. aureus* serves as an iron source for *Pseudomonas aeruginosa* during in vivo coculture (Mashburn *et al*. 2005)
- *S. aureus* synergizes with Kilham rat virus infection to induce diabetes in BBDR rats (Zipris *et al*. 2005)

- co-infection of the cotton rat with *S. aureus* and influenza A virus results in synergistic disease and increased induction of both pro- and anti-inflammatory cytokines (IL-1β, IL-6, IL-10, IFN-γ) (Braun *et al.* 2007)

Behaviour

- rats with inapparent wound infection show decreased activity in open-field testing and shorter duration of freezing behaviour (Bradfield *et al.* 1992)

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