GV-SOLAS
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Expert Information

From the Working Group on Hygiene

Implication of infectious agents on results of animal experiments

Staphylococcus aureus

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Authors: GV-SOLAS Working Group on Hygiene

Contents

Staphylococcus aureus

Background

- *Staphylococcus (S.) aureus* is a commensal and opportunistic pathogenic bacterium, being one of the more important causes of naturally occurring skin lesions in mice and rats.[1,2]

Prevalence

- Humans are a reservoir: ~20% of people persistently carry *S. aureus* in the anterior nares, and ~60% are intermittent carriers.[3]
- *S. aureus* was found to be the most prevalent agent (18.8% in mouse facilities, 58.6% in rat facilities) in experimental facilities in Japan.[4]
- A large retrospective study revealed prevalences of 6.07 % in laboratory mice and 23.61% in laboratory rats in North America and Europe.[5]
- Laboratory mice from various vendors have recently been found to be colonized with *S. aureus* at varying rates (0-20.9%).[6]

Host species

- Wide range of domestic and wild mammalian animals, birds, humans[7-10]
- Various species of laboratory animals[1,2,11,12]

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.[1,11,12] This environmental resistance and the broad host spectrum make it difficult to control spread of infection.
- *S. aureus* easily develops antibiotic resistance.[11,13] 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.[6,14]

Susceptibility

- Strain differences in susceptibility to *S. aureus* infection and associated disease are found among immunocompetent mice.[15-18] For example, 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.
- 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.[19]
- Immunodeficient hosts such as splenectomised or neutrophil-depleted mice[20,21], athymic nude mice[22], iNOS-deficient mice[23], TLR2-deficient and MyD88-deficient mice[24,25], IL-1-deficient and TNF-α-deficient mice[26], IL-1R-deficient mice[25], γδ T cell-deficient mice[27], complement component 3-deficient mice[28], cytochrome b-245 beta

polypeptide-deficient mice[29], interferon-inducible protein 204-deficient mice[30] and cathelicidin-deficient mice[31] are highly susceptible to *S. aureus* infection or associated disease. Likewise, certain mutant strains of mice without (known) immunodeficiency such as mice deficient in urokinase-type plasminogen activator[32] or DS-*Nh* mice[33] have an increased susceptibility to staphylococcal disease.

- 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.[34]
- Female and castrated CD-1 mice are more susceptible to infection with certain strains of *S. aureus*, suggesting a hormonal influence on resistance.[35]
- Other contributing host factors are age[36], physical injuries, e.g., as a result of fighting or surgery, and behavioural dysfunctions such as trichotillomania.[2,37]
- *S. aureus* strains can express a diverse arsenal of virulence factors and differ in virulence.[38-40]
- Predisposing environmental factors include stress, e.g., provoked by experimental procedures, nutritional deficiencies[41-43], concurrent infections, e.g. with ectoparasites[2], *Pseudomonas aeruginosa*[44] or *Candida albicans*[45], and the prevalence of *S. aureus* in the environment.

Organotropism

- Common inhabitant of the skin and mucous membranes (nasopharynx, lower intestinal tract, lower genital tract)[1,12,14]
- Entry into the body occurs most probably through breaks in the oral mucosa or skin[1,11,12,14]

Clinical disease

- Animals and human carriers usually remain asymptomatic.[1,2,11-14] 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.[1,11,12,14]
- Skin lesions are frequently accompanied by pruritus resulting in scratching and self-mutilation.[1,2,12]

Pathology

A variety of distinct disease processes have been reported in laboratory animals[1,2,11,12,14], 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, osteomyelitis
- 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[13]:

- 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 (see section 'susceptibility').

Zoonotic potential

- Transmissible between species[10]
- Transmission by contact with infected animals and humans or contaminated food, faeces, cages, and bedding[6,11,12,46-49]
- Genetic studies of *S. aureus* populations suggest that *S. aureus* lineages are largely host-specific.[10, 50-54]
- Laboratory mice are predominantly colonized with *S. aureus* lineages of the clonal complex (CC) 1 and CC15, which are common in the human population, as well as CC88, which is only occasionally found among human and animal isolates.[6,55] Adaption of *S. aureus* to the murine host may involve the loss of mobile genetic elements (MGEs) encoding human-specific virulence factors (such as immune evasion gene cluster-encoding Sa3int phages and superantigen-encoding MGEs).

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* vaccination and infection (e.g. models of implant-related infection, surgical wound infection, infected burn wounds, septic shock, infective endocarditis, and bone infection).[6,55] 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.[13,56] 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.

Oncology

- Intratumor injection of *S. aureus* delays glioma growth in C57BL/6 mice by activating microglia.[57]

Teratology

- *S. aureus* L-forms exert a teratogenic effect on cultured mouse embryos *in vitro*.[58]

Infectiology / 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.[44]
- *S. aureus* serves as an iron source for *Pseudomonas aeruginosa* during *in vivo* coculture.[59]
- *S. aureus* synergizes with Kilham rat virus infection to induce diabetes in BBDR rats.[60]
- 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).[61]
- Levels of nasal colonization (and hence the possible risk of invasive disease) by *H. influenzae* are increased in neonatal rats pre-colonized with *S. aureus*.[62]
- Probiotics treatment decreases the number of *S. aureus* organisms from ascites in septic rats.[63]
- The gut microbiota mediate protective effects against *S. aureus*-induced pneumonia, mastitis and endometritis in mice.[64-66]
- Oral administration of lactobacilli may alleviate *S. aureus*-induced inflammation.[67,68]
- *S. aureus* impacts *Pseudomonas aeruginosa* chronic respiratory disease in murine models.[69]
- Feeding mice *Bacillus subtilis* spores abrogates colonization of *S. aureus* in the faeces and intestines.[70]

Immunology

- *S. aureus* inhibits contact sensitivity to oxazolone by activating suppressor B cells in mice.[71]
- *S. aureus* induces production of IFN-γ, TNF, and IL-6 in the bloodstreams, spleens, and kidneys of systemically infected mice.[72]
- Infection with *S. aureus* induces a pro-inflammatory state in endothelial cells, as determined by expression of cytokines[73-76], Fc receptors[77], and adhesion molecules.[78]
- *S. aureus* induces expression of IL-6 and IL-12[79], MHC class II molecules[80], CD40[81], receptor activator of NF-κB ligand and prostaglandin E2 in osteoblasts.[82]
- Systemic *S. aureus* infection induces a Th2 response (IL-4, IL-10) in the spleens of mice.[83]
- Following *S. aureus* brain infection in mice, gene expression of multiple pro-inflammatory cytokines and chemokines (including IL-1β and CCL9) are upregulated, leading to macrophage recruitment.[26]
- *S. aureus* enhances expression of Toll-like receptor 2 (TLR-2) and MyD88 in microglia.[84]
- *S. aureus* induces release of TNF-α and nitric oxide in murine macrophages.[85]
- *S. aureus* enhances inflammation, endothelial injury, and blood coagulation in mice with streptozotocin-induced diabetes.[86]
- *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.[87,88]
- *S. aureus* phagocytosis by mouse peritoneal macrophages leads to c-Jun N-terminal kinase (JNK) activation in a TLR2-dependent manner; JNK activation causes

inhibition in superoxide production, resulting in the prolonged survival of engulfed bacteria.[89]

- *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.[90]
- Infection of rats with *S. aureus* results in rapid increased expression of most cytokine, chemokine, and inflammatory receptor gene transcripts studied in the lung.[91]
- Spontaneous arthritis in MRL/lpr mice is aggravated by *S. aureus* infection.[92]
- γδ T cells produce IL-17 upon infection of mice with *S. aureus*.[27,93,94]
- *S. aureus* activates the NLRP3 inflammasome in rat conjunctival goblet cells.[95]
- *S. aureus* infection results in increased hydrogen peroxide production in rat macrophages and osteoblasts, increased superoxide anion production in macrophages, lower alkaline phosphatase activity in osteoblasts, and higher phagocytosis activity in macrophages.[96]
- Serum nitric oxide levels are decreased in early *S. aureus* infection in Syrian hamsters.[97]
- Chronic infection with *S. aureus* induces strong peripheral systemic inflammation (enhanced T- and B-cell counts and increased concentrations of IFN-γ, IL-6, and TNF-α in peripheral blood), but prevents clinical symptoms of experimental autoimmune encephalomyelitis in rats. Moreover, *S. aureus* infection reduces autoimmune inflammation of the central nervous system and reduces the severity of autoimmune optic neuritis.[98]
- Transcripts encoding IL-8, IL1β, oncostatin M-like, CCR1, CXCR1 (IL8RA), CCL4 (MIP-1β) and CCL3 (MIP1α)-like proteins are among the most highly up-regulated transcripts during *S. aureus* abscess formation in the rabbit skin.[99]
- In rats, the local innate immune response of mammary glands is activated after *S. aureus* inoculation during the initial stage of infection, characterized by up-regulation of gene expression of TLR2, NOD2, TNF-α, IL-1β, IL-6, IL-10, and CXCL1. TGF-β1 expression is suppressed at an early phase and IFN-γ mRNA expression increases at a later stage.[100]
- Rat fallopian tube *S. aureus* infection activates neutrophils formed extracellular traps, elevates citrullinated histone H3, and decreases high molecular weight kininogen.[101]
- Following systemic *S. aureus* infection of mice and rats, there is a shift from secreted anti- to proinflammatory adipokines and cytokines in serum and on the level of gene expression in adipose tissue at sites distinct from infection.[102]
- *S. aureus* colonization primes the murine immune system, including a systemic IgG response specific for numerous *S. aureus* proteins.[6,103]
- *S aureus* biofilms in the rabbit maxillary sinus mucosa are associated with increased IL-1β, IL-8, and TNF-α expression, and decreased IL-4 and IL-5 expression.[104]
- *S. aureus* drives expansion of low-density neutrophils in diabetic mice.[105]
- Mouse peritoneal macrophages infected with *S. aureus* show elevated ROS production, secretion of TNF-α, IL-1β, and CXCL8, along with increased expression of surface receptors (TNFR1, IL-1R, and CXCR1), and inflammatory markers (iNOS and COX-2).[106]
- Mice with *S. aureus* pneumonia have elevated CD5L levels in the lungs.[107]
- Levels of granulocyte colony-stimulating factor are increased in the bone marrow and serum from *S. aureus*-infected mice.[108]

- Intra-tracheal *S. aureus* infection induces a significant increase in IL-21 in the mouse lung.[109]
- *S. aureus* can induce toll-like receptor/mitogen-activated protein kinase/NF-κB signalling in mouse peritoneal macrophages.[110]
- *S. aureus* induces cathelicidin gene transcription in murine mammary glands.[31]

Toxicology

- High dose infection with methicillin-resistant *S. aureus* increases the oxidative stress and inflammatory response in the mouse kidney, leading to a decrease in the expression of renal drug-metabolizing enzymes.[111]

Physiology

- Inapparent wound infection with *S. aureus* increases plasma fibrinogen levels, total leukocyte counts, and wound histology scores and decreases activity in open-field testing and duration of freezing behaviour in rats.[112]
- *S. aureus* and its peptidoglycan ameliorate glucocorticoid-induced impaired wound healing in rats.[113]
- *S. aureus* and its peptidoglycan stimulate macrophage recruitment, angiogenesis, fibroplasia, and collagen accumulation in wounded rats.[114]
- *S. aureus* induces serum α_2-macroglobulin in rats.[115]
- *S. aureus* causes contractile dysfunction in the mouse heart[116] and aorta.[117]
- Peripheral (local) RANTES and central PGE_2 production are involved in *S. aureus*-induced fever in rats.[118]
- *S. aureus* infection impairs glucose tolerance in mice via the secretion of the insulin-binding factor eLtaS.[119]

Cell biology

- *S. aureus* induces apoptosis in osteoblasts.[120]
- *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.[121]
- Infection of murine 3T3-L1 cells with *S. aureus* increases macrophage chemoattractant protein-1, visfatin, and IL-6 secretion, whereas resistin and adiponectin are decreased. Infected cells have higher intracellular triacylglycerol concentrations and larger lipid droplets because of a decreased lipolysis.[122]
- Peripheral blood gene expression and pathways involved in the response to *S. aureus* infection in mice have been analysed by Ahn et al.[123] Many of these pathways belong to the category of immune response such as CD28, ICOS, MEF2, CD40 and NF-κB pathways. Others include cytoskeletal remodeling (TGF and WNT), apoptosis and clathrin-coated vesicle transport.
- Brain infection with *S. aureus* leads to high extracellular levels of glutamate, aspartate, γ-aminobutyric acid, and zinc in rats.[124]
- *S. aureus* induces formation of dynamic tubular structures that protrude from the bacteria-containing phagosome at early times post-infection in CHO cells.[125]
- *S. aureus* biofilm elicits the expansion, activation and polarization of myeloid-derived suppressor cells *in vivo* and *in vitro*.[126]
- A total of 634 up-regulated and 401 down-regulated genes were identified in rat middle ear mucosa colonized with *S. aureus*.[127]

- The coagulation cascades pathways are upregulated in mice with *S. aureus*-induced chronic rhinosinusitis.[128]
- *S. aureus* infects osteoclasts and replicates intracellularly.[129]

Assisted reproductive technology

- *S. aureus* may affect reproductive health through induction of endometritis and mastitis.[65,66,130]

Special considerations

- For detailed information on immune responses against *S. aureus* infections in the skin, the reader is referred to the review articles by Miller & Cho[131] and Krishna & Miller.[132]
- Mice have been used as experimental models for infectious diseases caused by *S. aureus*. These models and several factors impacting their outcome have been reviewed by Kim et al.[133], Parker[134] and Mrochen et al.[135]

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