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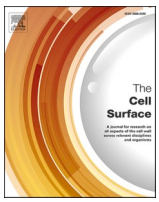

# *Staphylococcus aureus*: Current perspectives on molecular pathogenesis and virulence

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ABSTRACT

*Staphylococcus aureus* has evolved a sophisticated regulatory system to control its virulence. One of the main roles of this interconnected network is to sense and respond to diverse environmental signals by altering the synthesis of virulence components required for survival in the host, including cell surface adhesins, extracellular enzymes and toxins. The accessory gene regulator (agr), a quorum sensing system that detects the local concentration of a cyclic peptide signaling molecule, is one of the well-studied of these *S. aureus* regulatory mechanisms. By using this system, S. aureus is able to sense its own population density and translate this information into a specific pattern of gene expression. In addition to Agr, this pathogen senses specific stimuli through various two-component systems and synchronizes responses with alternative sigma factors and cytoplasmic regulators of the SarA protein family. These different regulatory mechanisms combine host and environmental information into a network that guarantees the best possible response of pathogens to changing circumstances. In this article, an overview of the most significant and thoroughly studied regulatory systems of *S. aureus* is provided, along with a summary of their roles in host interactions.

## 1. Background

*Staphylococcus aureus* (*S. aureus*) is a gram-positive bacterium belonging to the phylum Firmicutes and class Bacilli. *S. aureus* colonizes around 30% of the population, with skin and mucous membranes being the primary sites of colonization (Wertheim et al., 2005). Although *S. aureus* is largely a commensal bacterium, it can cause a variety of diseases that vary greatly in severity. Skin infections are among the most common problems, while necrotizing fasciitis, endocarditis, osteomyelitis and bloodstream infections are among the most serious (Lowy, 1998). *S. aureus* has evolved a complex regulatory network to temporally and locally regulate the production of virulence factors in order to survive and adapt to different environmental niches (Novick, 2003a). Since the virulence factors and regulatory apparatus are not necessary for normal growth, they are referred to as accessory genes. These accessory factors, which include proteins and cell surface components secreted into the extracellular environment, help *S. aureus* establish dominance in the host and contribute to its pathogenicity. These molecules have the ability to attach to host cells, evade the host's defenses, break down nutrients and absorb new ones. Both the chromosome and mobile elements such as phages, plasmids, and pathogenicity islands directly encode these complementary genetic components (Jenul and Horswill, 2019).

The evolution of the bacterial species *S. aureus*, which has a conserved nuclear genome (Feil et al., 2003), was driven primarily by horizontal gene transfer and mutation. One of the most common causes of strain-to-strain variation in *S. aureus* is mobile genetic components, such as incorporated bacteriophages (prophages). Due to their low natural competence, bacteriophage transduction is a common method of DNA transfer between *S. aureus* strains (Xia and Wolz, 2014). Examples of virulence factors on prophages include the immune evasion cluster and Panton-Valentine leukocidin (PVL) (Shallcross et al., 2013); the latter is present on a bacteriophage that has been integrated into the *hlb* gene (Goerke et al., 2006). Exfoliative toxin A (Holochová et al., 2010), cell wall-anchored virulence factor SasX(Li et al., 2012), staphylococcal complement inhibitor (*scn*) (Alibayov et al., 2014), staphylokinase (*sak*), chemotaxis inhibitory protein (CHP) (van Wamel et al., 2006), and the enterotoxins produced by *sea* (Betley and Mekalanos, 1985), *selk2*, and *selp*(Schelin et al., 2011) are important virulence factors encoded by bacteriophages. Another mobile genetic element that can encode pyrogenic toxins toxins, so-called superantigens, are staphylococcal pathogenicity islands (SaPIs). SaPIs encode the superantigen genes for Toxic Shock Toxin (*tsst*) (Novick, 2003b), Enterotoxin B (*seb*), and Enterotoxin-like protein Q (*selq*) (Schelin et al., 2011). Plasmids are

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crucial for the acquisition of antibiotic resistance by *S. aureus*, but there are also some examples showing how important they are for the acquisition of virulence factors. So far, it has been shown that a number of toxins, such as the exfoliative toxin B (Yamaguchi et al., 2001), enterotoxin D (Bayles and Iandolo, 1989), the enterotoxin-like protein SER (Omoe et al., 2003), and enterotoxin-like protein J (Zhang et al., 1998), can be encoded by plasmids. This article focuses on the molecular pathogenesis of *S. aureus*, how it regulates these virulence factors, and the development of antivirulence strategies to address the lack of an anti-*S. aureus* vaccine and the ever-increasing lack of effective antibiotics against this important pathogen.

## 2. The impact of *S. aureus* on human health and its molecular pathogenesis

*S. aureus* is a natural flora of the skin and mucosa and takes advantage of the opportunity to cause opportunistic infections, typically ranging from superficial to invasive infections such as skin infections, bacteremia, pneumonia, etc. (Alonso et al., 2022). The emergence of drug-resistant *S. aureus*, particularly methicillin-resistant *S. aureus* (MRSA) in the late 1990s (Herold et al., 1998) and vancomycin-resistant *S. aureus* (VRSA) in 2002 (Sievert et al., 2008), required careful examination. In 2014, the WHO reported that 86 % of clinical strains of *S. aureus* were methicillin resistant (Organization, 2014). The establishment of MDR strains was facilitated by the frequent use of certain antibiotics in hospital settings. The development of resistant or persistent subpopulations (persister cells) and the regulation of important virulence factors also increase the risk of invasive and recurrent *S. aureus* infections (Rowe et al., 2021). Bacterial attachment to the host cell or tissue is facilitated by the cellular production of surface proteins, which leading to deleterious pathogenesis in humans (Cruz et al., 2021). These proteins were specifically designed to promote the attachment of bacteria to the tissues of their hosts (Arunachalam et al., 2023). In *S. aureus*, a number of structural and secreted virulence components are essential for pathogenesis (Table 1).

## 3. Genetics of virulence in *S. aureus*

In contrast to the core genome, which primarily encodes "housekeeping" tasks, the accessory genome of *S. aureus* often contains virulence factors. Mobile genetic elements (MGEs), such as plasmids, transposons, insertion sequences, prophages and pathogenicity islands, are found in the accessory genome. In addition to virulence factors, these MGEs also carry antibiotic resistance determinants (Malachowa and DeLeo, 2010; Lindsay, 2019). Although transfer mechanisms such as phages or plasmids are missing, the large family of SaPIs relies on helper phages for transduction (Novick, 2019). Also found in the accessory genome are genomic islands (νSAα, νSAβ, νSAγ) that encode a number of virulence factors and appear to originate from MGEs but have lost their ability to be transported in species other than non-MGE-specific. Although many subtypes are associated with different lineages, they are so ubiquitous and stable that their content can be considered diagnostic of the entire species (Kläui et al., 2019). This is in contrast to isolate-specific MGEs, which are often associated with specific diseases (so-called "toxinoses") because they encode the corresponding causative toxins, like the toxic shock syndrome toxin-1(TSST-1) or the enterotoxins that cause food poisoning (Malachowa and DeLeo, 2010; Novick, 2019).

Antibiotic resistance genes are commonly found in plasmids and transposons (for instance mecA (encodes PBP2a, resistant to beta-lactams (Methicillin, Cephalosporins)), vanA (confers resistance to vancomycin) and erm (methylates 23S rRNA, conferring macrolide resistance (Erythromycin, Clindamycin)) genes), but the majority of *S. aureus* toxins and other virulence factors are found on phage and pathogenicity islands (Malachowa and DeLeo, 2010). Panton-Valentine leukocidin (PVL) is a virulence factor produced by certain strains of *S. aureus*, including MRSA. It is a pore-forming toxin that specifically targets and destroys white blood cells (leukocytes), contributing to the severity of infections caused by the bacteria (Alonzo III and Torres, 2014). PVL is a bicomponent toxin consisting of two proteins (LukS-PV (S component) and LukF-PV (F component)). These two subunits work together to form pores in the cell membranes of leukocytes (Spaan et al., 2017). This leads to cell lysis, release of inflammatory mediators, and tissue damage (Shallcross et al., 2013). PVL, the immune evasion proteins chemotaxis-inhibitory protein of *Staphylococcus aureus* (CHIPS) and staphylococcal complement inhibitor (SCIN), the exfoliative toxins A and B, staphylokinase and a number of enterotoxins are among the major *S. aureus* toxins encoded on prophages. It is noteworthy that the insertion of the phage carrying CHIPS, SCIN and staphylokinase (Carroll et al., 1993) renders the gene encoding the β-toxin (β-hemolysin), *hlb*, is associated with virulence functions (Huseby et al., 2007), is not functional in many *S. aureus* strains. This process is commonly referred to as "negative conversion." There is evidence that *hlb* is crucial for thecolonization of infections and can be "repaired" by phage excision (Katayama et al., 2013). SaPIs are mostly known for enterotoxins and TSST. α-toxin, phenol-soluble modulin (PSM) peptides, staphylococcal superantigen-like protein 5 (SSL5), the lipoprotein-like toxins (LPLs), the leukocidin LukDE, and several enterotoxins are among the toxins encoded on genomic islands that often differ only in the expression between isolates (Langley et al., 2010; Malachowa and DeLeo, 2010). It is interesting to note that the genomic island vSAβ also appears to have a complete biosynthesis cluster for the production of lantibiotics although its expression and possible function in bacterial interference have never been demonstrated (Joo et al., 2011). It should also be emphasized that although many MSCRAMMs (microbial surface components that recognize adhesive matrix molecules) play an important rolein virulence, they are typically not encoded in the accessory genome, most likely because they are present in the commensal of *S. aureus* serve

**Table 1**
Important virulence factors and linked genes in the pathogenesis of *S. aureus* (Algharib et al., 2020; Arunachalam et al., 2023).

| Virulence steps/ processes | Associated virulence factors | Linked Genes |
|---|---|---|
| Attachment | Surface proteins such bone sialoprotein-binding protein, fibronectin-binding protein, clumping factors and fibrinogen-binding protein are involved in the recognition of sticky matrix molecules by microbial surface components. | *bbp, fnbA, fnbB, clfA, clfB, sdrD, sasG, fib,* and *cna* |
| Invasion | Lipids, phospholipids, proteins (elastin), DNA and hyaluronic acid can all be broken down by enzymes. | *hysA, nuc, gehB, plc, sepA, sspA,* and V8 |
| Evading the immune system of the host | Toxins that cause pores, such as capsular polysaccharides, leukocidins, phenol-soluble modulins, protein A, CHIPS, Eap, staphyloxanthin and staphylococcal complement inhibitor. | *lukS-PV, hlg, lukF-PV, crtN, spa,* psm-a gene cluster, *chp, scn, eap,* cap5, and 8 gene clusters |
| Persistence and tolerance | Intracellular polysaccharide adhesions and the development of minute colony variations are examples of factors that contribute to intracellular persistence and biofilm formation. | *ica operon, dnaK,* and *hemB* mutation |
| Toxins mediated infections and sepsis | Enterotoxins, exfoliative toxins A and B, α-toxin, lipoteichoic acid and toxic shock syndrome toxin-1 | *sea, hla, tstH, eta,* and *etb* |

**CHIPS:** chemotaxis inhibitory protein of *Staphylococci*; **Eap:** extracellular adherence protein.

different lifestyle purposes.

## 4. *S. aureus* virulence regulation

Numerous regulatory factors can influence the expression of *S. aureus* virulence determinants (Fig. 1). These include global regulators that control a number of virulence genes and are often influenced by certain environmental factors (temperature, pH, NaCl), as well as site-specific regulatory factors such as the icaR gene next to the *ica* operon (Jefferson et al., 2003), which is also subject to numerous regulatory effects (Cerca et al., 2008), or the PSM-sensitive PmtR protein, which controls the PSM exporter Pmt operon (Chatterjee et al., 2013; Joo and Otto, 2016). Here, this overview focuses on a few selected, important international regulators (Fig. 1 and Table 2).

*agr* (accessory gene regulator), a quorum sensing system that upregulates multiple toxins and virulence determinants when cell density reaches a certain threshold, is the most studied staphylococcal virulence regulator (Le and Otto, 2015). This control is thought to delay the expression of virulence determinants during early infection to avoid triggering immunological responses, while simultaneously linking their expression to the state of infection when they are required for immune evasion and nutrition acquisition. Furthermore, *agr*-controlled virulence factors are expressed within a phagosome, most likely as a result of the restricted environment that activates the quorum sensing system through a process known as "diffusion sensing"(Redfield, 2002). *agr* was originally thought to downregulate adhesins, whose primary function was thought to be during early infection. However, this has since been refuted and instead, due to the recognition of many additional functions of MSCRAMMs, *agr* does not regulate the majority of MSCRAMMs in such fashion in clinical strains (Cheung et al., 2011). *agr* most strictly regulates the PSMs and secreted proteases. PSMs are directly controlled by the response regulator of the *agr* two-component system, AgrA, while other *agr* targets are indirectly regulated via the regulatory RNAIII, which is part of *agr* and represents its main intracellular effector molecule (Novick et al., 1993; Queck et al., 2008). The currently most important RNAIII-dependent gene regulation is achieved by blocking the DNA-binding repressor of toxins (Rot) (Geisinger et al., 2006). Rot is a regulatory protein and a 15.6kDa member of the SarA-like family. The name is derives from the fact that mutation of the *rot* locus in an agr-null background restores toxin production and protease activity and consequently restores virulence in a rabbit model of endocarditis (McNamara et al., 2000; Said-Salim et al., 2003). With regard to toxin regulation, Rot acts as a repressor of enterotoxin B (*seb*), alpha-toxin (*hla*), proteases encoded by the *spl* and *ssp* operons, and lipase (*geh*). Enterotoxin B is directly repressed by Rot through binding to the *seb* promoter (Tseng and Stewart, 2005). Rot also acts as a positive regulator of several virulence factors. Protein A (spa) and the SarA family protein SarH1 (Said-Salim et al., 2003) are upregulated by Rot, and through direct binding to its promoter, Rot can positively regulate SSL (Benson et al., 2011). The *agr* system uses a post-translationally modified short thiolactone-containing autoinducing peptide (AIP) as an extracellular quorum sensing signal (Ji et al., 1995). The sequences of the AIP, its modifying enzyme AgrB and the membrane histidine kinase AgrC, to which it binds and which, when activated, causes the phosphorylation of AgrA, vary in at least four *agr* subgroups found in *S. aureus* (Ji et al., 1997). Interbacterial contact in vivo can be influenced by the inhibitory effects of most non-self AIPs, including those from other staphylococcal species (Otto, 2001; Williams et al., 2019). *agr* mutants exhibit notable abnormalities in a variety of animal infection models, including infective endocarditis (Cheung et al., 1994), skin and soft tissue infections (Cheung et al., 2011), pneumonia (Cheung et al., 2011), septic arthritis (Abdelnour et al., 1993), osteomyelitis (Gillaspy et al., 1995), and atopic dermatitis (Nakamura et al., 2020), as would be expected given the control of multiple toxins and other virulence factors.

*agr* mutations refer to changes in the *agr* system, a quorum sensing regulatory mechanism in *S. aureus*. These mutations can disrupt the

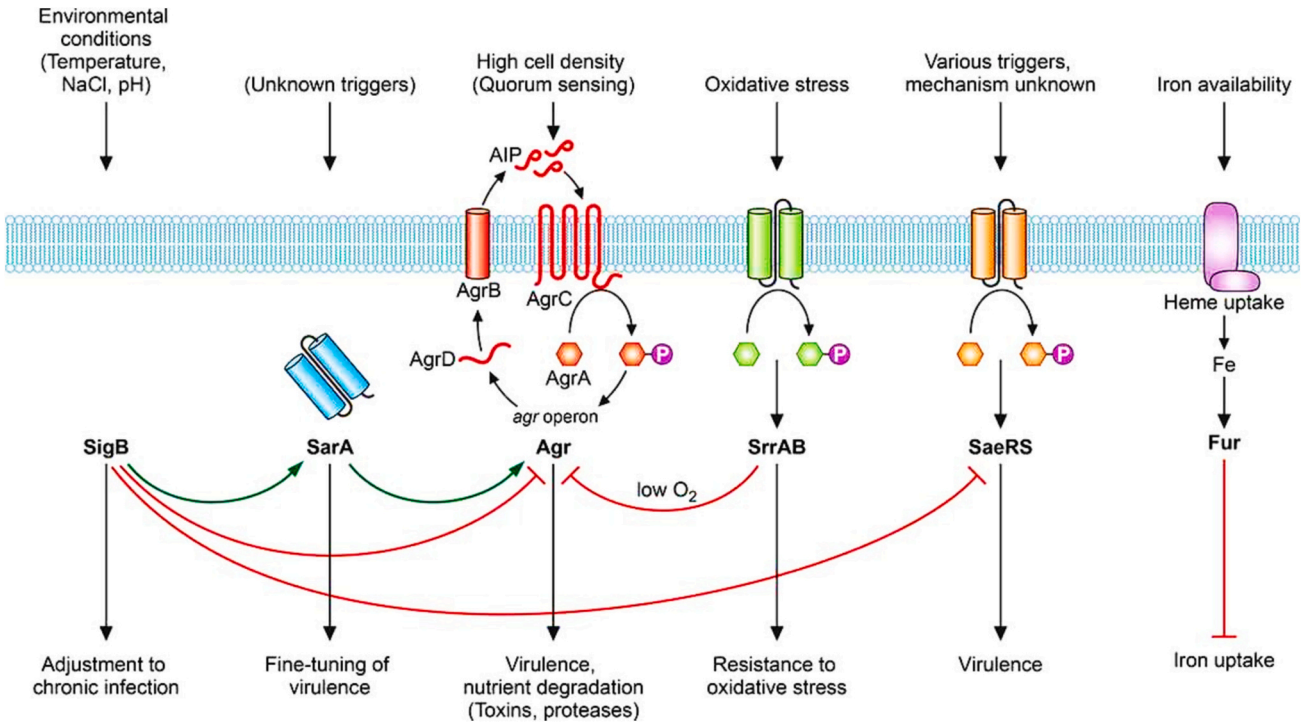


**Fig. 1.** Regulation of *S. aureus* virulence. Numerous regulatory systems mediate the extremely complex regulation of virulence in *S. aureus* and the most significant are shown. The *agr* quorum sensing system, the Sar family of DNA-binding proteins (of which SarA is indicated), the alternative sigma factor SigB and other regulators such as SaeRS all influence a number of virulence variables. The exact triggering mechanisms of these systems are still largely unknown, with the exception of *agr*. fur is a DNA-binding repressor that controls iron uptake and virulence genes, and SrrAB senses oxygen and plays an important role in ROS resistance (Cheung et al., 2021).

**Table 2**
Major virulence regulatory systems of *S. aureus*.

| Regulator system | Role | In vivo | References |
|---|---|---|---|
| *agr* | Cell-to-cell communication (quorum sensing) with AIPs as signal; *agr* activation leads to expression of *exo*-toxins and exo-enzymes | Required for virulence in animal models of skin infection, pneumonia, and endocarditis | (Cheung et al., 1994; Wardenburg et al., 2007; Paharik et al., 2017) |
| SaeRS | Induction of exo-protein production, including many virulence factors | Required for virulence in animal models of skin infection and pneumonia | (Olson et al., 2013; Baroja et al., 2016) |
| SrrAB | Oxygen-responsive TCS; induction of plc and *ica* expression; repression of *agr*, *TSST-1*, and *spa* | Required for defense against neutrophils | (Yarwood et al., 2001; Ulrich et al., 2007) |
| ArlRS | Autolysis and cell surface TCS; induction of MgrA expression and repression of *agr* and autolysis | Required for virulence in animal models of skin infection and endocarditis | (Fournier et al., 2001; Walker et al., 2013) |
| SarA | Cytoplasmic regulator; induction of exo-proteins and repression of *spa* | Required for virulence in animal models of biofilm infection | (Cheung et al., 2004; Zielinska et al., 2012) |
| Rot | Cytoplasmic regulator of toxins and extracellular proteases; *agr* activation prevents Rot translation | Mutation of rot restores virulence in *agr*-null background in rabbit endocarditis model | (McNamara et al., 2000; Said-Salim et al., 2003) |
| MgrA | Cytoplasmic regulator; induction of efflux pumps and capsule expression; repression of surface proteins | Required for virulence in animal models of skin infection and endocarditis | (Gupta et al., 2013; Crosby et al., 2016) |
| SigB | Stationary phase sigma factor; inhibits *agr* activity | Important for the establishment of chronic infection in rat lung model | (Entenza et al., 2005; Tuchscherr et al., 2015) |

system's function, affecting the bacteria's ability to regulate virulence factor expression and adapt to various environments (Boles and Horswill, 2008). Mutations can occur in any of four key components (AgrA, AgrB, AgrC, and AgrD), disrupting the function of the *agr* system. Mutations in AgrA or AgrC often impair signal detection or downstream activation, while mutations in AgrD or AgrB affect AIP synthesis or export, leading to a failure in effective quorum sensing (Geisinger et al., 2012). Mutants in *agr* arise frequently in a process known as "quorum cheating," which describes the situation that specific members of a population mutate *agr* to save energy and benefit from the maintained *agr* function of other cells in the population (Traber et al., 2008; Pollitt et al., 2014; He et al., 2019). *agr*-dysfunctional cell populations, either exclusively or primarily, are advantageous in biofilm-associated infections because of the larger biofilms formed by *agr* mutants and the resulting enhanced resistance to neutrophil attacks (He et al., 2019). The higher frequency of *agr* mutants isolated from bacteremia and chronic infections (Fowler Jr et al., 2004), which typically result from biofilm-associated infection of indwelling medical devices, is thought to be explained by this. Particularly noteworthy is the frequent occurrence of spontaneous mutation in *agr* in the lab, most likely as a result of the lack of selective pressure for virulence factor expression. This, in conjunction with incomplete genetic analysis, can result in incorrect attribution of regulatory functions to other proteins and systems (Adhikari et al., 2007; Chen and Novick, 2007; Villaruz et al., 2009).

fur, which responds to reduced iron availability (Xiong et al., 2000), and SrrAB, an oxygen-responsive regulator (Yarwood et al., 2001), are two important global regulators responsible for the triggering environmental signals recognized. In addition to iron consumption, fur controls a number of virulence factors, including toxins and immune evasion proteins (Horsburgh et al., 2001; Torres et al., 2010; Johnson et al., 2011). Because iron restriction signals entry into the body and the resulting need for these substances, fur is thought to have a role in coordinating the pathogen's attack on the host. Accordingly, fur mutants exhibit a marked decrease in pathogenicity in animal infection models (Horsburgh et al., 2001; Torres et al., 2010). To increase resistance to oxidative stress (Kinkel et al., 2013), the oxygen-sensitive two-component system SrrAB relies on redox-sensitive cysteines (Tiwari et al., 2020). Increased resistance to neutrophil attack results from its down-regulation of *agr* and upregulation of intercellular adhesion (*ica*) expression under anaerobic conditions (Ulrich et al., 2007). Down-regulation of agr while upregulation of *ica* causes *S. aureus* to transition from a highly virulent, toxin-producing phenotype to a persistent, biofilm-forming state. This compromise supports the development of chronic infections but reduces the severity of acute disease manifestations (Jenul and Horswill, 2019).

A series of small proteins (approximately 120 amino acids) containing helix-turn-helix DNA binding sequences belong to the Sar family (Cheung et al., 2008). They are thought to form dimeric winged helical structures with one or two domains and are all homologous to the SarA prototype (Liu et al., 2006). Sar family proteins interact with numerous different regulatory systems and target a variety of virulence factors (Cheung et al., 2008). The effect of one Sar homologue on a particular virulence factor gene can often be the opposite of the effect of another. SarA is most recognized for its potent influence on the production of proteases, which is partially but not completely achieved through the control of *agr* (Beenken et al., 2010). As with many other regulators with a strong and significant influence on the expression of *S. aureus* virulence determinants, such as SaeRS (Liu et al., 2016) and ArlRS (Liang et al., 2005), it is thought that the existence of multiple Sar homologs is to fine-tune virulence factor expression according to various environmental conditions. However, the molecular or environmental triggers of many Sar family regulators are unknown (Cheung et al., 2008). One notable exception is MgrA (Li et al., 2019), which responds to oxygen and reactive oxygen species (ROS) because of its redox sensitive cysteines, and has many effects on virulence (Chen et al., 2006). SarZ, which likewise uses thiol-based oxidation sensing to function as an oxidation sensor, is comparable to MgrA (Chen et al., 2009).

Like many other bacteria, *S. aureus* has another sigma factor called SigB. Its gene is located in a locus that also contains a number of anti-sigma factor genes. These genes are thought to work together to respond to a variety of environmental factors, including heat shock and growth phase (Kullik and Giachino, 1997). SigB has a significant influence on the expression of virulence genes and interacts with numerous other regulators, including agr and SarA (Nicholas et al., 1999). It is thought to adapt *S. aureus* physiology to sustained infection (Tuchscherr et al., 2015).

## 5. Current information on therapeutic strategies against *S. aureus* virulence

Interest in developing alternative treatment techniques for bacterial infections has increased recently, driven by the alarming global spread of antibiotic resistance and, in the case of *S. aureus*, the additional ongoing challenges in discovering a viable vaccine. The translational arm of bacterial pathogenesis research, antivirulence techniques, is often said to be less likely to develop resistance. However, *S. aureus* faces the significant challenge of many, often functionally redundant virulence components (Dickey et al., 2017). Therefore, antivirulence strategies for *S. aureus* either target a virulence determinant that has been shown to have a widespread and highly significant impact on pathogenicity or attempt to eradicate multiple virulence determinants

simultaneously. One or both of these tactics are used in the three primary *S. aureus* antivirulence techniques examined. The first is the development of monoclonal antibodiessuch as MedImmune's MEDI4893 (suvratoxumab) against α-toxin, which is an important virulence factor in many isolates (Diep et al., 2017; Yu et al., 2017). The second strategy targets all leukocidins of *S. aureus,* often in combination with the slightly related α-toxin. For example, the Austrian company Arsanis used this strategy when it developed a monoclonal antibody (mAb) that was cross-reactive against all leukocidins and α-toxin (Rouha et al., 2015; Stulik et al., 2019); nonetheless, clinical trials were unsuccessful. Third, numerous researchers have advocated for quorum sensing blockers targeting *agr* (Khan et al., 2015). They are mainly divided into two classes: those that need to enter the cytoplasm to inhibit the response regulator AgrA and are typically more hydrophobic, such as savirin or apicidin (Sully et al., 2014; Parlet et al., 2019), and those that prevent the binding of AIP to AgrC from the extracellular space, such as AIP analogs (Lyon et al., 2002) and a number of natural substances, including fengycins (Piewngam et al., 2018). Interestingly, *agr* inhibitors have not yet been thoroughly tested with systemic application in models of systemic disease types that may benefit most from antivirulence medications. Furthermore, they may be ineffective in persistent infections, particularly biofilm infections, and would likely need to be limited to acute infections (Khan et al., 2015). As with all antivirulence compounds, it is also necessary to demonstrate that their in vivo effectiveness is due to their antivirulence properties and not to their bactericidal activity, which many of them—especially the more hydrophobic compounds—only show at slightly higher concentrations.

## 6. Conclusion

*S. aureus* is one of the most common infectious agents causing morbidity and mortality worldwide. From mild to catastrophic skin infections to sepsis and pneumonia, this bacteria can cause a variety of illnesses. Antibiotic resistance makes it difficult to treat *S. aureus* infections and there is currently no effective vaccination. The remarkably large number of toxins and other virulence factors produced by *S. aureus* and their effects on disease are the subject of constant attention. To account for the lack of an anti-*S. aureus* vaccine and the increasing shortage of effective antibiotics against this important pathogen, a deeper understanding of the role and contribution of *S. aureus* virulence determinants in *S. aureus* infection will enable the development of antivirulence strategies.

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**Abayeneh Girma:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

## References

Abdelnour, A., Arvidson, S., Bremell, T., Ryden, C., Tarkowski, A., 1993. The accessory gene regulator (agr) controls *Staphylococcus aureus* virulence in a murine arthritis model. Infect. Immun. 61, 3879–3885. https://doi.org/10.1128/iai.61.9.3879-3885.1993.

Adhikari, R.P., Arvidson, S., Novick, R.P., 2007. A nonsense mutation in agrA accounts for the defect in agr expression and the avirulence of *Staphylococcus aureus* 8325–4 traP:: kan. Infect. Immun. 75, 4534–4540. https://doi.org/10.1128/IAI.00679-07.

Algharib, S.A., Dawood, A., Xie, S., 2020. Nanoparticles for treatment of bovine *Staphylococcus aureus* mastitis. Drug Deliv. 27, 292–308. https://doi.org/10.1080/10717544.2020.1724209.

Alibayov, B., Baba-Moussa, L., Sina, H., Zdeňková, K., Demnerová, K., 2014. *Staphylococcus aureus* mobile genetic elements. Mol. Biol. Rep. 41, 5005–5018. https://doi.org/10.1007/s11033-014-3367-3.

Alonso, B., Pérez-Granda, M.J., Latorre, M.C., Sánchez-Carrillo, C., Bouza, E., Muñoz, P., Guembe, M., 2022. Production of biofilm by Staphylococcus aureus: association with infective endocarditis? Enfermedades infecciosas y microbiologia clinica (English ed.) 40, 418–422. https://doi.org/10.1016/j.eimce.2021.03.009.

Alonzo III, F., Torres, V.J., 2014. The bicomponent pore-forming leucocidins of *Staphylococcus aureus*. Microbiol. Mol. Biol. Rev. 78, 199–230. https://doi.org/10.1128/MMBR.00055-13.

Arunachalam, K., Pandurangan, P., Shi, C., Lagoa, R., 2023. Regulation of *Staphylococcus aureus* virulence and application of nanotherapeutics to eradicate *S. aureus* infection. Pharmaceutics 15, 310. https://doi.org/10.3390/pharmaceutics15020310.

Baroja, M.L., Herfst, C.A., Kasper, K.J., Xu, S.X., Gillett, D.A., Li, J., Reid, G., McCormick, J.K., 2016. The SaeRS two-component system is a direct and dominant transcriptional activator of toxic shock syndrome toxin 1 in *Staphylococcus aureus*. J. Bacteriol. 198, 2732–2742. https://doi.org/10.1128/JB.00425-16.

Bayles, K.W., Iandolo, J.J., 1989. Genetic and molecular analyses of the gene encoding staphylococcal enterotoxin D. J. Bacteriol. 171, 4799–4806. https://doi.org/10.1128/jb.171.9.4799-4806.1989.

Beenken, K.E., Mrak, L.N., Griffin, L.M., Zielinska, A.K., Shaw, L.N., Rice, K.C., Horswill, A.R., Bayles, K.W., Smeltzer, M.S., 2010. Epistatic relationships between sarA and agr in *Staphylococcus aureus* biofilm formation. PLoS One 5, e10790. https://doi.org/10.1371/journal.pone.0010790.

Benson, M.A., Lilo, S., Wasserman, G.A., Thoendel, M., Smith, A., Horswill, A.R., Fraser, J., Novick, R.P., Shopsin, B., Torres, V.J., 2011. *Staphylococcus aureus* regulates the expression and production of the staphylococcal superantigen-like secreted proteins in a rot-dependent manner. Mol. Microbiol. 81, 659–675. https://doi.org/10.1111/j.1365-2958.2011.07720.x.

Betley, M.J., Mekalanos, J.J., 1985. Staphylococcal enterotoxin A is encoded by phage. Science 229, 185–187. https://doi.org/10.1126/science.3160112.

Boles, B.R., Horswill, A.R., 2008. Agr-mediated dispersal of *Staphylococcus aureus* biofilms. PLoS Pathog. 4, e1000052. https://doi.org/10.1371/journal.ppat.1000052.

Carroll, J., Cafferkey, M., Coleman, D., 1993. Serotype F double-and triple-converting phage insertionally inactivate the *Staphylococcus aureus* β-toxin determinant by a common molecular mechanism. FEMS Microbiol. Lett. 106, 147–155. https://doi.org/10.1111/j.1574-6968.1993.tb05951.x.

Cerca, N., Brooks, J.L., Jefferson, K.K., 2008. Regulation of the intercellular adhesin locus regulator (icaR) by SarA, σB, and IcaR in *Staphylococcus aureus*. J. Bacteriol. 190, 6530–6533. https://doi.org/10.1128/JB.00482-08.

Chatterjee, S.S., Joo, H.-S., Duong, A.C., Dieringer, T.D., Tan, V.Y., Song, Y., Fischer, E. R., Cheung, G.Y., Li, M., Otto, M., 2013. Essential *Staphylococcus aureus* toxin export system. Nat. Med. 19, 364–367. https://doi.org/10.1038/nm.3047.

Chen, J., Novick, R.P., 2007. svrA, a multi-drug exporter, does not control agr. Microbiology 153, 1604–1608. https://doi.org/10.1099/mic.0.2007/006247-0.

Chen, P.R., Bae, T., Williams, W.A., Duguid, E.M., Rice, P.A., Schneewind, O., He, C., 2006. An oxidation-sensing mechanism is used by the global regulator MgrA in *Staphylococcus aureus*. Nat. Chem. Biol. 2, 591–595. https://doi.org/10.1038/nchembio820.

Chen, P.R., Nishida, S., Poor, C.B., Cheng, A., Bae, T., Kuechenmeister, L., Dunman, P.M., Missiakas, D., He, C., 2009. A new oxidative sensing and regulation pathway mediated by the MgrA homologue SarZ in *Staphylococcus aureus*. Mol. Microbiol. 71, 198–211. https://doi.org/10.1111/j.1365-2958.2008.06518.x.

Cheung, A., Eberhardt, K., Chung, E., Yeaman, M., Sullam, P., Ramos, M., Bayer, A., 1994. Diminished virulence of a sar−/agr-mutant of *Staphylococcus aureus* in the rabbit model of endocarditis. J. Clin. Invest. 94, 1815–1822. https://doi.org/10.1172/JCI117530.

Cheung, A.L., Bayer, A.S., Zhang, G., Gresham, H., Xiong, Y.-Q., 2004. Regulation of virulence determinants in vitro and in vivo in *Staphylococcus aureus*. FEMS Immunol. Med. Microbiol. 40, 1–9. https://doi.org/10.1016/S0928-8244(03)00309-2.

Cheung, A.L., Nishina, K.A., Trotonda, M.P., Tamber, S., 2008. The SarA protein family of *Staphylococcus aureus*. Int. J. Biochem. Cell Biol. 40, 355–361. https://doi.org/10.1016/j.biocel.2007.10.032.

Cheung, G.Y., Wang, R., Khan, B.A., Sturdevant, D.E., Otto, M., 2011. Role of the accessory gene regulator agr in community-associated methicillin-resistant *Staphylococcus aureus* pathogenesis. Infect. Immun. 79, 1927–1935. https://doi.org/10.1128/IAI.00046-11.

Cheung, G.Y., Bae, J.S., Otto, M., 2021. Pathogenicity and virulence of *Staphylococcus aureus*. Virulence 12, 547–569. https://doi.org/10.1080/21505594.2021.1878688.
Crosby, H.A., Schlievert, P.M., Merriman, J.A., King, J.M., Salgado-Pabón, W., Horswill, A.R., 2016. The *Staphylococcus aureus* global regulator MgrA modulates clumping and virulence by controlling surface protein expression. PLoS Pathog. 12, e1005604. https://doi.org/10.1371/journal.ppat.1005604.
Cruz, A.R., Van Strijp, J.A., Bagnoli, F., Manetti, A.G., 2021. Virulence gene expression of Staphylococcus aureus in human skin. Front. Microbiol. 12, 692023. https://doi.org/10.3389/fmicb.2021.692023.
Dickey, S.W., Cheung, G.Y., Otto, M., 2017. Different drugs for bad bugs: antivirulence strategies in the age of antibiotic resistance. Nat. Rev. Drug Discov. 16, 457–471. https://doi.org/10.1038/nrd.2017.23.
Diep, B.A., Hilliard, J.J., Le, V.T., Tkaczyk, C., Le, H.N., Tran, V.G., Rao, R.L., Dip, E.C., Pereira-Franchi, E.P., Cha, P., 2017. Targeting alpha toxin to mitigate its lethal toxicity in ferret and rabbit models of *Staphylococcus aureus* necrotizing pneumonia. Antimicrob. Agents Chemother. 61. https://doi.org/10.1128/AAC.02456-16.
Entenza, J.-M., Moreillon, P., Senn, M.M., Kormanec, J., Dunman, P.M., Berger-Bächi, B., Projan, S., Bischoff, M., 2005. Role of σB in the expression of *Staphylococcus aureus* cell wall adhesins ClfA and FnbA and contribution to infectivity in a rat model of experimental endocarditis. Infect. Immun. 73, 990–998. https://doi.org/10.1128/IAI.73.2.990-998.2005.
Feil, E.J., Cooper, J.E., Grundmann, H., Robinson, D.A., Enright, M.C., Berendt, T., Peacock, S.J., Smith, J.M., Murphy, M., Spratt, B.G., 2003. How clonal is *Staphylococcus aureus*? J. Bacteriol. 185, 3307–3316. https://doi.org/10.1128/JB.185.11.3307-3316.2003.
Fournier, B., Klier, A., Rapoport, G., 2001. The two-component system ArlS–ArlR is a regulator of virulence gene expression in *Staphylococcus aureus*. Mol. Microbiol. 41, 247–261. https://doi.org/10.1046/j.1365-2958.2001.02515.x.
Fowler Jr., V.G., Sakoulas, G., McIntyre, L.M., Meka, V.G., Arbeit, R.D., Cabell, C.H., Stryjewski, M.E., Eliopoulos, G.M., Barth Reller, L., Ralph Corey, G., 2004. Persistent bacteremia due to methicillin-resistant *Staphylococcus aureus* infection is associated with agr dysfunction and low-level in vitro resistance to thrombin-induced platelet microbicidal protein. J. Infect. Dis. 190, 1140–1149. https://doi.org/10.1086/423145.
Geisinger, E., Adhikari, R.P., Jin, R., Ross, H.F., Novick, R.P., 2006. Inhibition of rot translation by RNAIII, a key feature of agr function. Mol. Microbiol. 61, 1038–1048. https://doi.org/10.1111/j.1365-2958.2006.05292.x.
Geisinger, E., Chen, J., Novick, R.P., 2012. Allele-dependent differences in quorum-sensing dynamics result in variant expression of virulence genes in *Staphylococcus aureus*. J. Bacteriol. 194, 2854–2864. https://doi.org/10.1128/JB.06685-11.
Gillaspy, A.F., Hickmon, S.G., Skinner, R.A., Thomas, J.R., Nelson, C.L., Smeltzer, M.S., 1995. Role of the accessory gene regulator (agr) in pathogenesis of staphylococcal osteomyelitis. Infect. Immun. 63, 3373–3380. https://doi.org/10.1128/iai.63.9.3373-3380.1995.
Goerke, C., Wirtz, C., Flückiger, U., Wolz, C., 2006. Extensive phage dynamics in *Staphylococcus aureus* contributes to adaptation to the human host during infection. Mol. Microbiol. 61, 1673–1685. https://doi.org/10.1111/j.1365-2958.2006.05354.x.
Gupta, R.K., Alba, J., Xiong, Y.Q., Bayer, A.S., Lee, C.Y., 2013. MgrA activates expression of capsule genes, but not the α-toxin gene in experimental *Staphylococcus aureus* endocarditis. J. Infect. Dis. 208, 1841–1848. https://doi.org/10.1093/infdis/jit367.
He, L., Le, K.Y., Khan, B.A., Nguyen, T.H., Hunt, R.L., Bae, J.S., Kabat, J., Zheng, Y., Cheung, G.Y., Li, M., 2019. Resistance to leukocytes ties benefits of quorum sensing dysfunctionality to biofilm infection. Nat. Microbiol. 4, 1114–1119. https://doi.org/10.1038/s41564-019-0413-x.
Herold, B.C., Immergluck, L.C., Maranan, M.C., Lauderdale, D.S., Gaskin, R.E., Boyle-Vavra, S., Leitch, C.D., Daum, R.S., 1998. Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identified predisposing risk. Jama 279, 593–598. https://doi.org/10.1001/jama.279.8.593.
Holochová, P., Růžičková, V., Dostálová, L., Pantůček, R., Petráš, P., Doškař, J., 2010. Rapid detection and differentiation of the exfoliative toxin A-producing *Staphylococcus aureus* strains based on ϕETA prophage polymorphisms. Diagn. Microbiol. Infect. Dis. 66, 248–252. https://doi.org/10.1016/j.diagmicrobio.2009.10.008.
Horsburgh, M.J., Ingham, E., Foster, S.J., 2001. In *Staphylococcus aureus*, Fur is an interactive regulator with PerR, contributes to virulence, and is necessary for oxidative stress resistance through positive regulation of catalase and iron homeostasis. J. Bacteriol. 183, 468–475. https://doi.org/10.1128/JB.183.2.468-475.2001.
Huseby, M., Shi, K., Brown, C.K., Digre, J., Mengistu, F., Seo, K.S., Bohach, G.A., Schlievert, P.M., Ohlendorf, D.H., Earhart, C.A., 2007. Structure and biological activities of beta toxin from *Staphylococcus aureus*. J. Bacteriol. 189, 8719–8726. https://doi.org/10.1128/JB.00741-07.
Jefferson, K.K., Cramton, S.E., Götz, F., Pier, G.B., 2003. Identification of a 5-nucleotide sequence that controls expression of the Ica locus in *Staphylococcus aureus* and characterization of the DNA-binding properties of IcaR. Mol. Microbiol. 48, 889–899. https://doi.org/10.1046/j.1365-2958.2003.03482.x.
Jenul, C., Horswill, A.R., 2019. Regulation of *Staphylococcus aureus* virulence. Microbiol. Spectrum 7, 10.1128/microbiolspec.gpp1123-0031-2018. doi:10.1128/microbiolspec.GPP3-0031-2018.
Ji, G., Beavis, R.C., Novick, R.P., 1995. Cell density control of staphylococcal virulence mediated by an octapeptide pheromone. Proc. Natl. Acad. Sci. 92, 12055–12059. https://doi.org/10.1073/pnas.92.26.12055.
Ji, G., Beavis, R., Novick, R.P., 1997. Bacterial interference caused by autoinducing peptide variants. Science 276, 2027–2030. https://doi.org/10.1126/science.276.5321.2027.
Johnson, M., Sengupta, M., Purves, J., Tarrant, E., Williams, P.H., Cockayne, A., Muthaiyan, A., Stephenson, R., Ledala, N., Wilkinson, B.J., 2011. Fur is required for the activation of virulence gene expression through the induction of the sae regulatory system in *Staphylococcus aureus*. Int. J. Med. Microbiol. 301, 44–52. https://doi.org/10.1016/j.ijmm.2010.05.003.
Joo, H.-S., Otto, M., 2016. Toxin-mediated gene regulatory mechanism in *Staphylococcus aureus*. Microbial Cell 4, 29. https://doi.org/10.15698/mic2017.01.553.
Joo, H.-S., Cheung, G.Y., Otto, M., 2011. Antimicrobial activity of community-associated methicillin-resistant *Staphylococcus aureus* is caused by phenol-soluble modulin derivatives. J. Biol. Chem. 286, 8933–8940. https://doi.org/10.1074/jbc.M111.221382.
Katayama, Y., Baba, T., Sekine, M., Fukuda, M., Hiramatsu, K., 2013. Beta-hemolysin promotes skin colonization by *Staphylococcus aureus*. J. Bacteriol. 195, 1194–1203. https://doi.org/10.1128/JB.01786-12.
Khan, B.A., Yeh, A.J., Cheung, G.Y., Otto, M., 2015. Investigational therapies targeting quorum-sensing for the treatment of *Staphylococcus aureus* infections. Expert Opin. Investig. Drugs 24, 689–704. https://doi.org/10.1517/13543784.2015.1019062.
Kinkel, T., Roux, C., Dunman, P., Fang, F., 2013. The *Staphylococcus aureus* SrrAB two-component system promotes resistance to nitrosative stress and hypoxia. mBio 4. https://doi.org/10.1128/mBio.00696-13 e00696–13.
Kläui, A.J., Boss, R., Graber, H.U., 2019. Characterization and comparative analysis of the *Staphylococcus aureus* genomic island v Saβ: an in silico approach. J. Bacteriol. 201. https://doi.org/10.1128/JB.00777-18.
Kullik, I., Giachino, P., 1997. The alternative sigma factor σB in *Staphylococcus aureus*: regulation of the sigB operon in response to growth phase and heat shock. Arch. Microbiol. 167, 151–159. https://doi.org/10.1007/s002030050428.
Langley, R., Patel, D., Jackson, N., Clow, F., Fraser, J.D., 2010. Staphylococcal superantigen super-domains in immune evasion. Crit. Rev. Immunol. 30. https://doi.org/10.1615/CritRevImmunol.v30.i2.40.
Le, K.Y., Otto, M., 2015. Quorum-sensing regulation in staphylococci—an overview. Front. Microbiol. 6, 1174. https://doi.org/10.3389/fmicb.2015.01174.
Li, M., Du, X., Villaruz, A.E., Diep, B.A., Wang, D., Song, Y., Tian, Y., Hu, J., Yu, F., Lu, Y., 2012. MRSA epidemic linked to a quickly spreading colonization and virulence determinant. Nat. Med. 18, 816–819. https://doi.org/10.1038/nm.2692.
Li, L., Wang, G., Cheung, A., Abdelhady, W., Seidl, K., Xiong, Y.Q., 2019. MgrA governs adherence, host cell interaction, and virulence in a murine model of bacteremia due to *Staphylococcus aureus*. J. Infect. Dis. 220, 1019–1028. https://doi.org/10.1093/infdis/jiz219.
Liang, X., Zheng, L., Landwehr, C., Lunsford, D., Holmes, D., Ji, Y., 2005. Global regulation of gene expression by ArlRS, a two-component signal transduction regulatory system of *Staphylococcus aureus*. J. Bacteriol. 187, 5486–5492. https://doi.org/10.1128/JB.187.15.5486-5492.2005.
Lindsay, J.A., 2019. Staphylococci: evolving genomes. Microbiol. Spectrum 7, 10.1128/microbiolspec.gpp1123-0071-2019. doi: 10.1128/microbiolspec.GPP3-0071-2019.
Liu, Y., Manna, A.C., Pan, C.-H., Kriksunov, I.A., Thiel, D.J., Cheung, A.L., Zhang, G., 2006. Structural and function analyses of the global regulatory protein SarA from *Staphylococcus aureus*. Proc. Natl. Acad. Sci. 103, 2392–2397. https://doi.org/10.1073/pnas.0510439103.
Liu, Q., Yeo, W.-S., Bae, T., 2016. The SaeRS two-component system of *Staphylococcus aureus*. Genes 7, 81. https://doi.org/10.3390/genes7100081.
Lowy, F.D., 1998. *Staphylococcus aureus* infections. N. Engl. J. Med. 339, 520–532. https://doi.org/10.1056/NEJM199808203390806.
Lyon, G.J., Wright, J.S., Christopoulos, A., Novick, R.P., Muir, T.W., 2002. Reversible and specific extracellular antagonism of receptor-histidine kinase signaling. J. Biol. Chem. 277, 6247–6253. https://doi.org/10.1074/jbc.M109989200.
Malachowa, N., DeLeo, F.R., 2010. Mobile genetic elements of *Staphylococcus aureus*. Cell. Mol. Life Sci. 67, 3057–3071. https://doi.org/10.1007/s00018-010-0389-4.
McNamara, P.J., Milligan-Monroe, K.C., Khalili, S., Proctor, R.A., 2000. Identification, cloning, and initial characterization of rot, a locus encoding a regulator of virulence factor expression in *Staphylococcus aureus*. J. Bacteriol. 182, 3197–3203. https://doi.org/10.1128/JB.182.11.3197-3203.2000.
Nakamura, Y., Takahashi, H., Takaya, A., Inoue, Y., Katayama, Y., Kusuya, Y., Shoji, T., Takada, S., Nakagawa, S., Oguma, R., 2020. Staphylococcus Agr virulence is critical for epidermal colonization and associates with atopic dermatitis development. Sci. Transl. Med. 12, eaay4068. https://doi.org/10.1126/scitranslmed.aay4068.
Nicholas, R., Li, T., McDevitt, D., Marra, A., Sucoloski, S., Demarsh, P., Gentry, D., 1999. Isolation and characterization of a sigB deletion mutant of *Staphylococcus aureus*. Infect. Immun. 67, 3667–3669. https://doi.org/10.1128/IAI.67.7.3667-3669.1999.
Novick, R.P., 2003a. Autoinduction and signal transduction in the regulation of staphylococcal virulence. Mol. Microbiol. 48, 1429–1449. https://doi.org/10.1046/j.1365-2958.2003.03526.x.
Novick, R.P., 2003b. Mobile genetic elements and bacterial toxinoses: the superantigen-encoding pathogenicity islands of *Staphylococcus aureus*. Plasmid 49, 93–105. https://doi.org/10.1016/S0147-619X(02)00157-9.
Novick, R.P., 2019. Pathogenicity islands and their role in staphylococcal biology. Microbiol. Spectrum 7. https://doi.org/10.1128/microbiolspec.GPP3-0062-2019.
Novick, R.P., Ross, H., Projan, S., Kornblum, J., Kreiswirth, B., Moghazeh, S., 1993. Synthesis of staphylococcal virulence factors is controlled by a regulatory RNA molecule. EMBO J. 12, 3967–3975. https://doi.org/10.1002/j.1460-2075.1993.tb06074.x.
Olson, M.E., Nygaard, T.K., Ackermann, L., Watkins, R.L., Zurek, O.W., Pallister, K.B., Griffith, S., Kiedrowski, M.R., Flack, C.E., Kavanaugh, J.S., 2013. *Staphylococcus aureus* nuclease is an SaeRS-dependent virulence factor. Infect. Immun. 81, 1316–1324. https://doi.org/10.1128/IAI.01242-12.
Omoe, K., Hu, D.-L., Takahashi-Omoe, H., Nakane, A., Shinagawa, K., 2003. Identification and characterization of a new staphylococcal enterotoxin-related

putative toxin encoded by two kinds of plasmids. Infect. Immun. 71, 6088–6094. https://doi.org/10.1128/IAI.71.10.6088-6094.2003.
Organization, W.H, 2014. Antimicrobial resistance: global report on surveillance. World Health Organization.
Otto, M., 2001. *Staphylococcus aureus* and *Staphylococcus epidermidis* peptide pheromones produced by the accessory gene regulator agr system. Peptides 22, 1603–1608. https://doi.org/10.1016/S0196-9781(01)00495-8.
Paharik, A.E., Parlet, C.P., Chung, N., Todd, D.A., Rodriguez, E.I., Van Dyke, M.J., Cech, N.B., Horswill, A.R., 2017. Coagulase-negative staphylococcal strain prevents *Staphylococcus aureus* colonization and skin infection by blocking quorum sensing. Cell Host Microbe 22 (746–756), e745. https://doi.org/10.1016/j.chom.2017.11.001.
Parlet, C.P., Kavanaugh, J.S., Crosby, H.A., Raja, H.A., El-Elimat, T., Todd, D.A., Pearce, C.J., Cech, N.B., Oberlies, N.H., Horswill, A.R., 2019. Apicidin attenuates MRSA virulence through quorum-sensing inhibition and enhanced host defense. Cell Rep. 27 (187–198), e186. https://doi.org/10.1016/j.celrep.2019.03.018.
Piewngam, P., Zheng, Y., Nguyen, T.H., Dickey, S.W., Joo, H.-S., Villaruz, A.E., Glose, K. A., Fisher, E.L., Hunt, R.L., Li, B., 2018. Pathogen elimination by probiotic Bacillus via signalling interference. Nature 562, 532–537. https://doi.org/10.1038/s41586-018-0616-y.
Pollitt, E.J., West, S.A., Crusz, S.A., Burton-Chellew, M.N., Diggle, S.P., 2014. Cooperation, quorum sensing, and evolution of virulence in *Staphylococcus aureus*. Infect. Immun. 82, 1045–1051. https://doi.org/10.1128/IAI.01216-13.
Queck, S.Y., Jameson-Lee, M., Villaruz, A.E., Bach, T.-H.L., Khan, B.A., Sturdevant, D.E., Ricklefs, S.M., Li, M., Otto, M., 2008. RNAIII-independent target gene control by the agr quorum-sensing system: insight into the evolution of virulence regulation in *Staphylococcus aureus*. Mol. Cell 32, 150–158. https://doi.org/10.1016/j.molcel.2008.08.005.
Redfield, R.J., 2002. Is quorum sensing a side effect of diffusion sensing? Trends Microbiol. 10, 365–370. https://doi.org/10.1016/S0966-842X(02)02400-9.
Rouha, H., Badarau, A., Visram, Z.C., Battles, M.B., Prinz, B., Magyarics, Z., Nagy, G., Mirkina, I., Stulik, L., Zerbs, M., 2015. Five birds, one stone: neutralization of α-hemolysin and 4 bi-component leukocidins of Staphylococcus aureus with a single human monoclonal antibody. In: MAbs, pp. 243–254. https://doi.org/10.4161/19420862.2014.985132.
Rowe, S.E., Beam, J.E., Conlon, B.P., 2021. Recalcitrant *Staphylococcus aureus* infections: obstacles and solutions. Infect. Immun. 89. https://doi.org/10.1128/IAI.00694-20.
Said-Salim, B., Dunman, P., McAleese, F., Macapagal, D., Murphy, E., McNamara, P., Arvidson, S., Foster, T., Projan, S., Kreiswirth, B., 2003. Global regulation of *Staphylococcus aureus* genes by rot. J. Bacteriol. 185, 610–619. https://doi.org/10.1128/JB.185.2.610-619.2003.
Schelin, J., Wallin-Carlquist, N., Thorup Cohn, M., Lindqvist, R., Barker, G.C., 2011. The formation of *Staphylococcus aureus* enterotoxin in food environments and advances in risk assessment. Virulence 2, 580–592. https://doi.org/10.4161/viru.2.6.18122.
Shallcross, L.J., Fragaszy, E., Johnson, A.M., Hayward, A.C., 2013. The role of the Panton-valentine leucocidin toxin in staphylococcal disease: a systematic review and meta-analysis. Lancet Infect. Dis. 13, 43–54. https://doi.org/10.1016/S1473-3099(12)70238-4.
Sievert, D.M., Rudrik, J.T., Patel, J.B., McDonald, L.C., Wilkins, M.J., Hageman, J.C., 2008. Vancomycin-resistant *Staphylococcus aureus* in the United States, 2002–2006. Clin. Infect. Dis. 46, 668–674. https://doi.org/10.1086/527392.
Spaan, A.N., van Strijp, J.A., Torres, V.J., 2017. Leukocidins: staphylococcal bi-component pore-forming toxins find their receptors. Nat. Rev. Microbiol. 15, 435–447. https://doi.org/10.1038/nrmicro.2017.27.
Stulik, L., Rouha, H., Labrousse, D., Visram, Z.C., Badarau, A., Maierhofer, B., Groß, K., Weber, S., Kramarić, M.D., Glojnarić, I., 2019. Preventing lung pathology and mortality in rabbit *Staphylococcus aureus* pneumonia models with cytotoxin-neutralizing monoclonal IgGs penetrating the epithelial lining fluid. Sci. Rep. 9, 5339. https://doi.org/10.1038/s41598-019-41826-6.
Sully, E.K., Malachowa, N., Elmore, B.O., Alexander, S.M., Femling, J.K., Gray, B.M., DeLeo, F.R., Otto, M., Cheung, A.L., Edwards, B.S., 2014. Selective chemical inhibition of agr quorum sensing in *Staphylococcus aureus* promotes host defense with minimal impact on resistance. PLoS Pathog. 10, e1004174. https://doi.org/10.1371/journal.ppat.1004174.
Tiwari, N., López-Redondo, M., Miguel-Romero, L., Kulhankova, K., Cahill, M.P., Tran, P. M., Kinney, K.J., Kilgore, S.H., Al-Tameemi, H., Herfst, C.A., 2020. The SrrAB two-component system regulates *Staphylococcus aureus* pathogenicity through redox sensitive cysteines. Proc. Natl. Acad. Sci. 117, 10989–10999. https://doi.org/10.1073/pnas.1921307117.
Torres, V.J., Attia, A.S., Mason, W.J., Hood, M.I., Corbin, B.D., Beasley, F.C., Anderson, K.L., Stauff, D.L., McDonald, W.H., Zimmerman, L.J., 2010. *Staphylococcus aureus* fur regulates the expression of virulence factors that contribute to the pathogenesis of pneumonia. Infect. Immun. 78, 1618–1628. https://doi.org/10.1128/IAI.01423-09.
Traber, K.E., Lee, E., Benson, S., Corrigan, R., Cantera, M., Shopsin, B., Novick, R.P., 2008. agr function in clinical *Staphylococcus aureus* isolates. Microbiology 154, 2265–2274. https://doi.org/10.1099/mic.0.2007/011874-0.
Tseng, C.W., Stewart, G.C., 2005. Rot repression of enterotoxin B expression in *Staphylococcus aureus*. J. Bacteriol. 187, 5301–5309. https://doi.org/10.1128/JB.187.15.5301-5309.2005.
Tuchscherr, L., Bischoff, M., Lattar, S.M., Noto Llana, M., Pförtner, H., Niemann, S., Geraci, J., Van de Vyver, H., Fraunholz, M.J., Cheung, A.L., 2015. Sigma factor SigB is crucial to mediate *Staphylococcus aureus* adaptation during chronic infections. PLoS Pathog. 11, e1004870. https://doi.org/10.1371/journal.ppat.1004870.
Ulrich, M., Bastian, M., Cramton, S.E., Ziegler, K., Pragman, A.A., Bragonzi, A., Memmi, G., Wolz, C., Schlievert, P.M., Cheung, A., 2007. The staphylococcal respiratory response regulator SrrAB induces ica gene transcription and polysaccharide intercellular adhesin expression, protecting *Staphylococcus aureus* from neutrophil killing under anaerobic growth conditions. Mol. Microbiol. 65, 1276–1287. https://doi.org/10.1111/j.1365-2958.2007.05863.x.
van Wamel, W.J., Rooijakkers, S.H., Ruyken, M., van Kessel, K.P., van Strijp, J.A., 2006. The innate immune modulators staphylococcal complement inhibitor and chemotaxis inhibitory protein of *Staphylococcus aureus* are located on β-hemolysin-converting bacteriophages. J. Bacteriol. 188, 1310–1315. https://doi.org/10.1128/JB.188.4.1310-1315.2006.
Villaruz, A.E., Wardenburg, J.B., Khan, B.A., Whitney, A.R., Sturdevant, D.E., Gardner, D.J., DeLeo, F.R., Otto, M., 2009. A point mutation in the agr locus rather than expression of the Panton-valentine leukocidin caused previously reported phenotypes in *Staphylococcus aureus* pneumonia and gene regulation. J. Infect. Dis. 200, 724–734. https://doi.org/10.1086/604728.
Walker, J.N., Crosby, H.A., Spaulding, A.R., Salgado-Pabón, W., Malone, C.L., Rosenthal, C.B., Schlievert, P.M., Boyd, J.M., Horswill, A.R., 2013. The *Staphylococcus aureus* ArlRS two-component system is a novel regulator of agglutination and pathogenesis. PLoS Pathog. 9, e1003819. https://doi.org/10.1371/journal.ppat.1003819.
Wardenburg, J.B., Patel, R.J., Schneewind, O., 2007. Surface proteins and exotoxins are required for the pathogenesis of *Staphylococcus aureus* pneumonia. Infect. Immun. 75, 1040–1044. https://doi.org/10.1128/IAI.01313-06.
Wertheim, H.F., Melles, D.C., Vos, M.C., Van Leeuwen, W., Van Belkum, A., Verbrugh, H. A., Nouwen, J.L., 2005. The role of nasal carriage in *Staphylococcus aureus* infections. Lancet Infect. Dis. 5, 751–762. https://doi.org/10.1016/S1473-3099(05)70295-4.
Williams, M., Costa, S., Zaramela, L., Khalil, S., Todd, D., Winter, H., Sanford, J., O'neill, A., Liggins, M., Nakatsuji, T., 2019. Quorum sensing between bacterial species on the skin protects against epidermal injury in atopic dermatitis. Sci. Transl. Med. 11, eaat8329. https://doi.org/10.1126/scitranslmed.aat8329.
Xia, G., Wolz, C., 2014. Phages of *Staphylococcus aureus* and their impact on host evolution. Infect. Genet. Evol. 21, 593–601. https://doi.org/10.1016/j.meegid.2013.04.022.
Xiong, A., Singh, V.K., Cabrera, G., Jayaswal, R.K., 2000. Molecular characterization of the ferric-uptake regulator, fur, from *Staphylococcus aureus*. Microbiology 146, 659–668. https://doi.org/10.1099/00221287-146-3-659.
Yamaguchi, T., Hayashi, T., Takami, H., Ohnishi, M., Murata, T., Nakayama, K., Asakawa, K., Ohara, M., Komatsuzawa, H., Sugai, M., 2001. Complete nucleotide sequence of a *Staphylococcus aureus* exfoliative toxin B plasmid and identification of a novel ADP-ribosyltransferase, EDIN-C. Infect. Immun. 69, 7760–7771. https://doi.org/10.1128/IAI.69.12.7760-7771.2001.
Yarwood, J.M., McCormick, J.K., Schlievert, P.M., 2001. Identification of a novel two-component regulatory system that acts in global regulation of virulence factors of *Staphylococcus aureus*. J. Bacteriol. 183, 1113–1123. https://doi.org/10.1128/JB.183.4.1113-1123.2001.
Yu, X.-Q., Robbie, G.J., Wu, Y., Esser, M.T., Jensen, K., Schwartz, H.I., Bellamy, T., Hernandez-Illas, M., Jafri, H.S., 2017. Safety, tolerability, and pharmacokinetics of MEDI4893, an investigational, extended-half-life, anti-*Staphylococcus aureus* alpha-toxin human monoclonal antibody, in healthy adults. Antimicrob. Agents Chemother. 61. https://doi.org/10.1128/AAC.01020-16.
Zhang, S., Iandolo, J.J., Stewart, G.C., 1998. The enterotoxin D plasmid of *Staphylococcus aureus* encodes a second enterotoxin determinant (sej). FEMS Microbiol. Lett. 168, 227–233. https://doi.org/10.1016/S0378-1097(98)00423-6.
Zielinska, A.K., Beenken, K.E., Mrak, L.N., Spencer, H.J., Post, G.R., Skinner, R.A., Tackett, A.J., Horswill, A.R., Smeltzer, M.S., 2012. sarA-mediated repression of protease production plays a key role in the pathogenesis of S taphylococcus aureus USA 300 isolates. Mol. Microbiol. 86, 1183–1196. https://doi.org/10.1111/mmi.12048.