

## Review Article

### Quorum Sensing in *Staphylococcus aureus*

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p-ISSN: 1608-9391

e-ISSN: 2664-2786

#### Article information

Received: 4/ 7/ 2023

Revised: 20/ 9/ 2023

Accepted: 27/ 9/ 2023

DOI: [10.33899/rjs.2024.183429](https://doi.org/10.33899/rjs.2024.183429)

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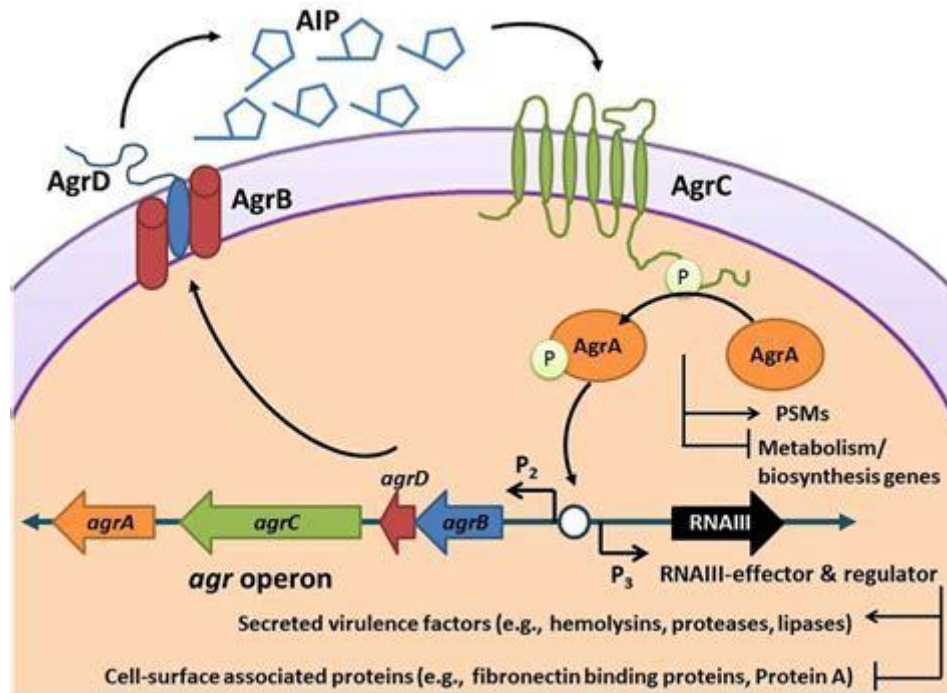
#### ABSTRACT

Staphylococci are common commensals in human beings, yet certain species are pathogenic. *Staphylococcus aureus*, particularly, is a very virulent human pathogen. The capacity of staphylococci to sense the density of bacterial cell, i.e., quorum, and thereafter respond via genetic modifications is attributable to one primary mechanism known as accessory gene regulator (Agr). Agr's extracellular signal is a peptide that is post-translationally modified with a thiolactone molecule. Agr is in charge of the upregulation of numerous exotoxins and hydrolyzing enzymes, as well as the downregulation of many colonization determinants, under circumstances of high cell density. This modulation is critical for the scheduling synthesis of virulence determinants throughout the infection course and the establishment of acute illness, whereas low Agr activity is linked to persistent staphylococcal infections, such as biofilm development. Moreover, Staphylococcal Accessory Regulator A<sub>o</sub> (SarA) controls the establishment of biofilm in *S. aureus* that hinders the production of nuclease and protease via triggering the P2 and P3 promoters resulting in the activation of RNAII and RNAIII, respectively. SarA also endures the transcription of *agrA* and *saeS*, and many virulence determinants including *hla*, *hly*, and *hlg* coding  $\alpha$ -,  $\beta$ -, and  $\gamma$ -hemolysins, respectively. Upon the aforementioned facts, the present review will shed some light on the Quorum Sensing (QS) in *S. aureus*, particularly, the Agr and Sar systems and how these systems control the pathogenicity of this species. Moreover, it will cover the factors that interfere with these systems.

**Keywords:** *Staphylococcus aureus*, quorum sensing, *agr*, *sar*, gene regulation.

## The Agr System

The *agr* locus is about 3500 base and is made up of two distinct transcriptional regions, RNAII and RNAIII, which are activated by the P2 and P3 promoters, respectively (Gupta *et al.*, 2015) as depicted in Fig. (1).



**Fig. 1: A Schematic of the *Staphylococcus aureus* accessory gene regulatory (*agr*) system**

Four genes; *agrB*, *agrD*, *agrC*, and *agrA* are located within the RNAII region, the *agrD* is responsible for expressing the autoinducing peptide (AIP), which serves as a peptide precursor of Agr system signal (Gupta *et al.*, 2015). The mature form of this peptide is made up of 7-9 amino acids that have a distinctive thiolactone ring (Paulander *et al.*, 2018). The transmembrane endopeptidase AgrB modifies thiolactone, cleaves C-terminal, and exports AIP; in the external environment, SspB type I signal peptidase is responsible for the further trimming of AIP (Hazenbos *et al.*, 2017). The *agrC* expresses the histidine kinase sensor; AgrC that once binds with the AIP will be phosphorylated alongside AgrA, the response regulator. Upon stimulation by AgrC-mediated phosphorylation, this response regulator will bind with P2 and P3, the promoter regions for RNAII and RNAIII, respectively. Moreover, phenol-soluble modulins PSMa and PSMb will be regulated as well (Nakagawa *et al.*, 2017).

Even though *agr* is usually maintained in staphylococci, different sequence variants of *agrB*, *agrC*, and *agrD* lead to the generation of AIPs of different signaling characteristics, designed to permit the activation of self as well as cross-inhibition of foreign Agr groups, a phenomenon that may be simply a reflection of phylogenetic selective pressures (Tan *et al.*, 2022). Aside from the AIP, triggering of Agr can be achieved through a number of other regulators, including Staphylococcal Accessory Regulator A (SarA) and Staphylococcal respiratory response AB (SrrAB) as well as external variables like levels of glucose or pH (Burton and McGregor, 2018).

### Gene Regulation via RNAIII-dependent Mechanism

RNAIII as the effector molecule in Agr systems is in charge of controlling Agr targets. It is also an mRNA that contains the delta-toxin. RNAIII governs the expression of target gene primarily through antisense base pairing with 5' untranslated regions, resulting in RNA duplexes. Other than in the instance of alpha-toxin, where RNAIII may indeed function as a post-transcriptional regulator, RNAIII typically inhibits translation (Morales-Fillooy *et al.*, 2020). RNAIII inhibits the synthesis of a number of mainly surface proteins, including protein A. Moreover, RNAIII works by

blocking the translation of the repressor of toxin (Rot), where it corresponds to the Staphylococcal accessory regulator (Sar) transcriptional regulator family (Killikelly *et al.*, 2015; Anderson *et al.*, 2023).

Rot attaches to the promoter of numerous extracellular proteins as well as exotoxins, preventing them from being transcribed. These pathways enable rapid density-dependent up-regulation of enterotoxins, alpha-toxins, leukocidins, degradative exoenzymes, and surface protein down-regulation. Furthermore, genome-wide gene expression studies show that, in parallel to virulence factors, Agr regulation includes a number of metabolic pathways. The above broad physiological changes could help bacteria in adjusting the changing needs throughout infection process (Killikelly *et al.*, 2015).

### **RNAIII-independent Gene Regulation**

Whilst also RNAIII was widely suspected to be the sole pathway through which Agr governs target genes; however, it was discovered that the response regulator AgrA also works by binding to the P2 and P3 promoters, and correspondingly up-regulates the transcription of the *psma* and *psmb* operons through binding to their relevant promoter sequences. PSMs are a class of staphylococcal peptide toxins, which include the delta-toxin. Because the delta-toxin gene is integrated within RNAIII locus, researchers have proposed that the development of RNAIII nearby the delta-toxin gene linked a phylogenetically ancient regulatory network composed of AgrA and potentially quorum-sensing regulation of *psm* determinants to the regulation of additional virulence determinants such as through RNAIII and Rot (Fogel and Bubeck Wardenburg, 2022).

### **The Impact of Agr on Acute Infection and Toxicity**

Upregulation of Agr-mediated virulence factor in *S. aureus* is required for progression of the disease across several lab animals of acute infection, along with infective endocarditis, skin and soft tissue infections (SSTI), pneumonia (Lee *et al.*, 2020), joint infections, and osteomyelitis (Suligoy *et al.*, 2018). In contrast, Agr-mediated down-regulation of PSMs and microbial surface components has indeed been linked to increased biofilm production and bacterial colonization of prosthetics (Jordan *et al.*, 2022). Besides that, Agr impairment is associated with chronic *S. aureus* bacteremia (Lee *et al.*, 2021).

Overall, the Agr-dependent exotoxin up-regulation and enzymatic hydrolysis in one respect and the down-regulation of surface constituents on the opposite end is thought to indicate the distinguishing time-related needs for particular virulence determinants throughout the infection process: At the early stages, low cell density and resultant reduction the Agr expression level leads to higher surface components production necessary for the primary tissues inhabiting (Huber *et al.*, 2020). Once established, bacteria proliferate to increased cell densities, necessitating more nutritional supply and better protection from host immune system that is done by Agr-dependent up-regulation of degradative exoenzymes and toxins. Significantly, this scheduling ensures that the synthesis of exotoxins, a majority of which are pro-inflammatory, is postponed once the developing bacterial population is able to cope with host defense mechanisms that possibly explains the outcomes relevant to the function of Agr and Agr-controlled factors throughout staphylococcal bacteremia (Lee *et al.*, 2020).

Lastly, Agr-regulated production of virulence factors consumes energy, and multiple results indicate that this must be coordinated with development of antimicrobial resistance in resistant variants. Subinhibitory antibiotic doses have been demonstrated to boost Agr expression, incurring a fitness cost that is thought to cause the observed development of Agr-dysfunctional mutations in strains recovered from nosocomial infections (Viedma *et al.*, 2018).

### **Agr-controlled Virulence Determinants**

$\alpha$ -toxin ( $\alpha$ -hemolysin) encoded by the *hla* locus, is one of the most notable Agr-regulated toxins. It is a pore-forming toxin composed of 319 amino acids that attaches to the host cell membrane's disintegrin and metalloprotease 10 (ADAM10) receptor. Hla has also been linked to a number of infections caused by staphylococci. In comparison to the wild-type variants, isogenic *hla*

mutants consistently displayed lower severity of pneumonia *in vivo*, SSTI, and endovascular infection (Krones *et al.*, 2021).

Another class of usually Agr-controlled pore-forming exotoxins is the bi-component leukocidins, that involve Panton-Valentine Leukocidin (PVL), -hemolysin, LukDE, and LukGH (LukAB). Although PVL has now become likely to have a narrower scope in serious infections of *S. aureus* than originally anticipated, LukED has been identified as a key component influencing the development of *S. aureus* infection. Through addressing the CCR5 chemokine receptor on lymphocytes, dendritic cells, macrophages, and LukED promotes phagocytic cell lysis. Additionally, LukGH (LukAB) seems to have a significant part in *S. aureus* infections as it's the sole *S. aureus* exotoxin that promotes the lysis following phagocytosis in addition to the PSM peptides (Le and Otto, 2015).

PSMs belong to peptide toxins class and they are the only Agr-controlled virulence factors that are tightly regulated through AgrA, inferring a possible critical importance in metabolism of *Staphylococcus* species, which is aided through their contribution across the non-infectious way of life of staphylococci microbiota (Chatterjee *et al.*, 2013). PSMs expressed by the *S. aureus* *psm* locus, particularly PSM3, are highly pro-inflammatory in addition to causing breakdown to RBCs as well as to osteoblasts, macrophages, neutrophils, and diverse range of cells. Consequently, PSM peptides have a considerable impact on *S. aureus* acute infections among which osteomyelitis, sepsis, and SSTI (Baldry *et al.*, 2020).

Agr regulates a large number of released enzymes. Particularly, numerous proteases are highly Agr-controlled and are able to influence the pathogen secretome's makeup and consequently its pathogenicity characteristics, in addition to being virulence factors per se (by attributing to the breakdown of tissue and proteins of immune system including antimicrobial peptides) (Vlahos *et al.*, 2022).

Protein A (Spa) stands out amongst the surface proteins that is typically down-regulated by Agr due to its multifaceted role in pathogenesis as well as being constantly Agr-controlled. On contrary, the common notion of Agr-related negative regulation of additional superficial proteins does not necessarily apply throughout staphylococci. Protein A is believed to be linked to several organ system infections, including pneumonia, joint infections, and bacteremia. Protein A activates pro-inflammatory cytokines in the lung parenchyma via the TNF- receptor. Once the protein A is discharged from *S. aureus* cell, it can inactivate the host antibody-mediated immunity upon discharge through attaching the Fc fraction of IgG to hinder the opsonophagocytosis that function through Fc receptor, in addition to provoking apoptosis via connecting to the Fab fraction of IgM (Zhang *et al.*, 2021).

### **Agr Regulates Biofilms and Biofilm-related Infections**

*Staphylococcus aureus* is known for its ability to form biofilms (Sulaiman and Abdulla, 2018). The establishment of biofilms is assumed to take place in three steps: (a) adhesion of bacteria to inanimate or surfaces coated with host proteins; thereafter, aggregates onto multicellular components, (b) propagation and maturation, and (c) dispersal. Given that the *agr* mutants demonstrated prolonged biofilm establishment in staphylococci, the exact processes whereby Agr influences biofilm production is lately come to be obvious (Sauer *et al.*, 2022).

Agr regulates proteolytic enzymes that influence biofilm expansion *in vitro* by destroying protein complexes of the biofilm matrix. Nevertheless, the role of proteases in staphylococcal biofilm development *in vivo* is controversial (Marti *et al.*, 2010).

PSM surfactant function is the sole biofilm-shaping and dispersion process that its significance was verified in animal models and in tests utilizing body fluid. PSMs shape biofilms through generating water channels and result in cell detachment out from the biofilm in a mechanism different from biofilm development, for instance, the biofilm matrix makeup. In animal models, this pathway causes a spread of infection related to biofilm and is accountable for the substantial development of sessile communities found under settings of reduced Agr action, like synovial fluid throughout arthritis (Baldry *et al.*, 2020).

Hence, the Agr influence on biofilm-associated diseases is contradictory: Agr is required for biofilm structure and spread, while its malfunction results in increased biofilm establishment, that could be beneficial to the pathogen living in such situations. As a result, pathogens undergoing a malfunctioning Agr system are frequently colonizing the implanted medical prosthetics. Such colonizers lacked their ability to spread in the body of the patient (Shopsin *et al.*, 2010).

### **Environmental Factors Affecting Regulation of Agr Staphylococcal Respiratory Response AB**

SrrAB is a bi-component system found in *S. aureus*, which is stimulated by oxygen deficiency and nitrosative stress. SrrB is a transmembrane histidine kinase with dimerization, ATPase, and phosphoacceptor domains. The SrrB autophosphorylation is determined by the oxidation-reduction condition of the disulfide bond in the ATP-binding domain. Moreover, SrrA represents an intracellular response regulator, which is able to cohere with DNA and alter transcription in SrrB-related pathways or SrrB-independent pathways (Tiwari *et al.*, 2020).

RNAIII is inhibited upon the binding of SrrAB with regulatory areas of P2 and P3, hence lowering the expression of cell cytotoxic factor in the host under oxygen deficiency circumstances. Because of the oxygen deficiency aspect of bone infections, SrrAB plays an important part in *S. aureus* stress responses throughout the course of abscess development. An srrAB mutant exhibits a significant survival deficiency throughout bone infection, and yet such feature is incompletely recovered by the injection of an anti-lymphocyte antigen 6, indicating the potential influence of SrrAB on response of *S. aureus* to stress stimulated by neutrophil or abscess development *in vivo*. SrrAB controls *psm* that is regulated by Agr system (Yarwood *et al.*, 2001).

SrrAB suppresses  $\alpha$ -PSM synthesis via Agr-dependent mechanism, reducing the death of host cells as well as involving osteoblasts. Simultaneously, SrrAB stimulation causes *S. aureus* central metabolism to shift towards growth when there are no oxidative terminal electron receptors, which might participate in the establishment of persistent small colony variants throughout the osteomyelitis course. *S. aureus* respiratory alterations mediated by SrrAB boost fibronectin-binding protein A expression, disintegration of bacterial cell, and cytosolic DNA discharge, altogether promote biofilm development. Moreover, SrrAB reduces the expression of virulence factors in *S. aureus* by cross-regulation of agr RNAIII and PSMs; however, enhances host tissue survival by promoting metabolic adjustments in response to alterations in the environment in the tissues of infected host (Yarwood *et al.*, 2001).

### **Staphylococcal Accessory Regulator A (SarA)**

SarA acts as a key controller of biofilm development in *S. aureus*, which inhibits the synthesis of nuclease and protease through stimulation of P2 and P3 promoters leading to activation of RNAII and RNAIII. SarA also sustain the transcription of *agrA* and *saeS*, and numerous virulence determinants including *hla*, *hly*, and *hlg* coding  $\alpha$ -,  $\beta$ -, and  $\gamma$ -hemolysins, respectively (Tormo *et al.*, 2005).

Yet, among the SarA's utmost remarkable functions is the suppression of aureolysin and other exoprotease that may destroy PSMs. Because SarA inhibits extracellular proteases, which can breakdown PSMs, the total rise in PSM plenitude hastens both osteoblast and osteoclast death. SarA deactivation, on the other hand, results in suppression of the aforementioned exoproteases and a significant decrease in *S. aureus* pathogenicity. *S. aureus* lacking exoprotease activity is considered extremely virulent; furthermore, a significant drop in mice infected with this variant in a septic model demonstrate a significant drop in survival capacity, independent of the SarA existence (Fujimoto *et al.*, 2009).

### **Two-Component System Regulates Proteases**

SaeRS is a system of two parts made up of SaeS, saeR, saeP and saeQ. The first two express the sensor kinase and the response regulator; whereas, the other two express factors responsible for binding SaeS, thereby stimulate the phosphatase activity. A variety of granulocyte-mediated antibacterial host responses, including phagocytosis-correlated H<sub>2</sub>O<sub>2</sub>, antimicrobial peptides, and

others, have been shown to activate SaeRS. Acidic pH is linked with acidic phagosomes, on the other hand, was proposed to suppress SaeRS in some *S. aureus* isolates. SaeRS, like SarA, decreases post-translational disintegration of PSMs through suppressing the expression of *aur*. This control takes place via a mechanism irrespective of SarA that is depending on active SaeS. In an *ex vivo* osteoblast culture system, the impacts of SaeRS on the disintegration of PSM were revealed. nevertheless *saeRS*-deficient *S. aureus* exhibiting a cytotoxicity absence. Additionally, *saeRS* inhibition reduces cortical bone loss induced by PSM in an animal model throughout the course of bone infection (Liu *et al.*, 2016; Mainiero *et al.*, 2010).

### **Regulation of Metabolism and Virulence**

CodY is a thoroughly preserved global regulator that acts as a transcriptional factor in Gram-positive bacteria throughout stationary phase. It detects metabolites in order to control primary metabolism and expression of virulence determinants. Although it instantaneously controls several genes associated with amino acid production and pathogenicity, it also modulates additional determinants-related pathogenicity through *agr* locus suppression indirectly (Mainiero *et al.*, 2010).

CodY directly activates many adhesion-associated determinants, including *fnbA* and *spa*. CodY indirectly regulates additional virulence determinant mediated via Agr, such as *coa*. Consequently, through inhibiting RNAPIII transcription and directly increasing virulence gene transcription, CodY promotes Agr-controlled virulence determinant-related with *S. aureus* adhesion. CcpA is a second bacterial highly-preserved transcriptional agent in response to catabolism. While glucose is present, CcpA regulates glucose catabolism in addition to the transcription of certain virulence determinants. Regarding *S. aureus*, *ccpA* deletion causes RNAPIII down-regulation, leading in altered *hla* and *spa* transcription patterns (Seidl *et al.*, 2006).

CcpA's effect on virulence factor synthesis adds another critical connection between the production of *S. aureus* exotoxin and the metabolism of host. Such relationship shows that the quantity of glucose in the *S. aureus* environment or a particular host organ might significantly modify *S. aureus* pathogenicity profile. Notwithstanding the extremely metabolism of glucose catabolism in local osteocytes, glycolysis is a crucial mechanism for *S. aureus* survival in bone. When glucose is present, glycolysis takes precedence above other routes including the tricarboxylic acid cycle, the pentose phosphate pathway, and gluconeogenesis (Potter *et al.*, 2020).

CcpA presumably increases *S. aureus*' capacity to infect bone because of the abundance of glucose in bone and defined bacterial glycolysis throughout bone infection, although this yet to be proven. Apart from catabolite responsive regulators, there is accumulating indications that some metabolites, particularly pyruvate, are able to affect Agr action (Harper *et al.*, 2018).

### **CONCLUSION**

The pathogenicity of *Staphylococcus aureus* is regulated by complex mechanisms involving quorum sensing. Agr and SarA systems play crucial roles in the modulation of virulence determinants and biofilm formation. The upregulation of exotoxins and hydrolyzing enzymes, as well as the downregulation of colonization determinants, under high cell density conditions, are critical for the establishment of acute illness. On the other hand, low Agr activity is linked to persistent staphylococcal infections, such as biofilm development. The SarA system controls the establishment of biofilm in *S. aureus* and the transcription of many virulence determinants. Understanding the regulation of these systems and the factors that interfere with them is crucial for the development of effective therapies against *S. aureus* infections.

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## استشعار النصاب في العنقوديات الذهبية

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### الملخص

تعد العنقوديات من المتعايشات الشائعة في البشر، مع ذلك هناك انواع معينة تكون ممرضة. وتعد العنقوديات الذهبية، على الخصوص، ممرضات بشرية ضارية جدا. تعزى قابلية العنقوديات على استشعار كثافة الخلايا البكتيرية (النصاب) ومن ثم الاستجابة عن طريق التحويرات الوراثية الى الية اساسية تدعى منظم الجين الملحق. الاشارة خارج خلوية لمنظم الجين الملحق عبارة عن ببتيد محور في عمليات ما بعد الترجمة مع جزيئة ثايولاكتون. عندما تكون كثافة الخلايا عالية يكون منظم الجين الملحق مسؤولا عن تنشيط العديد من اليفانات الخارجية والانزيمات الحالة وكذلك تثبيط العديد من محددات الاستيطان. هذا التعديل ضروري جدا لجدولة تخليق محددات الفوعة اثناء الاصابة وانشاء العدوى الحادة، في حين ترتبط الفعالية المنخفضة لمنظم الجين الملحق بالإصابات المستمرة الناجمة عن العنقوديات مثل الغشاء الحيائي. إضافة لذلك، يتحكم المنظم العنقودي الملحق أ بتكوين الغشاء الحيائي الذي يكبح انتاج الانزيمات الحالة للمادة النووية والبروتينات عن طريق تحفيز المحفزين P2 و 3P مما يؤدي الى تنشيط RNAI و RNIII على التوالي. وكذلك يكون المنظم العنقودي الملحق مسؤولا عن استنساخ *agrA* و *saeS* والعديد من محددات الفوعة مثل *hla* و *hly* و *hlg* المشفرة لحالات الدم الفا و بيتا و كما على التوالي. بناءً على الحقائق المذكورة في اعلاه، ستسلط هذه المقالة بعض الضوء على نظم استشعار النصاب في العنقوديات الذهبية، لا سيما Agr و Sar وكيف تتحكم هذه الانظمة في امراضية هذا النوع البكتيري. علاوة على ذلك، ستتم تغطية العوامل التي تتداخل مع هذه الانظمة.

الكلمات الدالة: البكتريا العنقودية الذهبية، استشعار النصاب، Agr، Sar، التعبير الجيني.