The high command of the staphylococcal war: the *Staphylococcus aureus* virulence and antimicrobial resistance regulatory nets

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Introduction

The gram-positive bacterium *Staphylococcus aureus* is a member of the normal skin and nasal microbiome in 30% of humans. However, in specific conditions, this microorganism can become a very common opportunistic pathogen, which can be responsible of lesser skin infections to bacterial endocarditis (1).

The expression of virulence factors of S. aureus is modulated during the different steps of the infection process. The main virulence regulatory machineries are growth-dependent therefore implies the action a two-component system (TCS) that generates an intracellular signal when de population density reaches a specific concentration, and so the main regulators of the system modify the expression of certain genes, allowing the generation of some virulence factors and repressing others (2). Moreover, the antimicrobial resistance genes presented in Methicillin-resistant *S. aureus* (MRSA) and Vancomycin-resistant *S. aureus* (VRSA) also present a strong regulation based on other types of TCS) by which the bacteria can sense the presence of the antibiotic in the environment and thereby activate its resistance mechanisms (3). The present study summarizes these molecular events in several figures, focusing on the regulation of virulence determinants and its relationship with the growth phase of the microbial population.

1. Virulence and antimicrobial resistance mechanisms

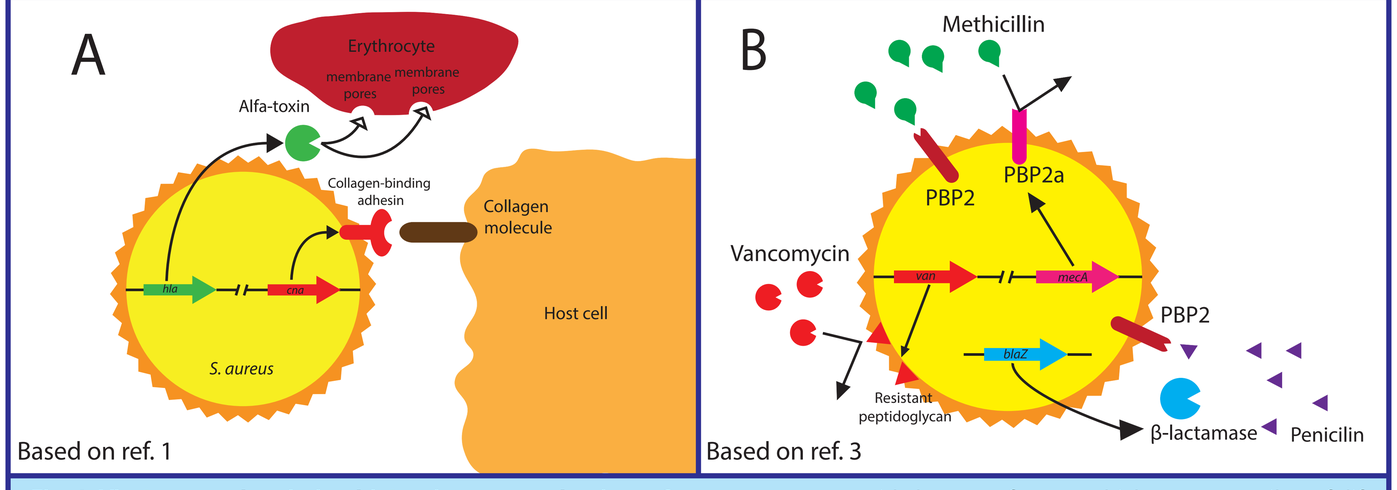


Fig. 1. Virulence and antimicrobial resistance mechanisms. *S. aureus* presents a wide battery of genes which are responsible of different steps of the infection process or are the basis of the resistance to antimicrobial agents. This figure represents a scheme of some of them.

In Fig. 1A are represented the genes *cna* and *hla* which codify a collagen-binding adhesin and the alfa-toxin respectively. The first one is responsible of the attachment to the host cell by contacting with a collagen molecule and the second is mainly used by the pathogen to generate membrane pores in the human erythrocytes, in order to obtain molecules from them (2).

The Fig. 2A summarizes the most important antimicrobial resistance mechanisms against cell wall antibiotics. The β-lactams penicillin and methicillin attach to the penicillin binding protein 2 (PBP2), which are responsible of the synthesis of the cell wall, and stop their activity. The gene *blaZ* codifies a β-lactamase which breaks actively the β-lactam antibiotic, and mecA is responsibale of the synthesis of PBP2a, a PBP which is resistant to the binding of all types of β-lactams, such as methicillin.

The last cell wall drug represented here are the glycopeptides (i.e. vancomycin). These peptides have the ability of binding to the bacterial cell wall precursors, and avoid its polymerization in order to form the wall. The *van* cassette provide all the enzymatic machinery to synthesize vancomycin resistant peptidoglycan (3).

2. Model of infection

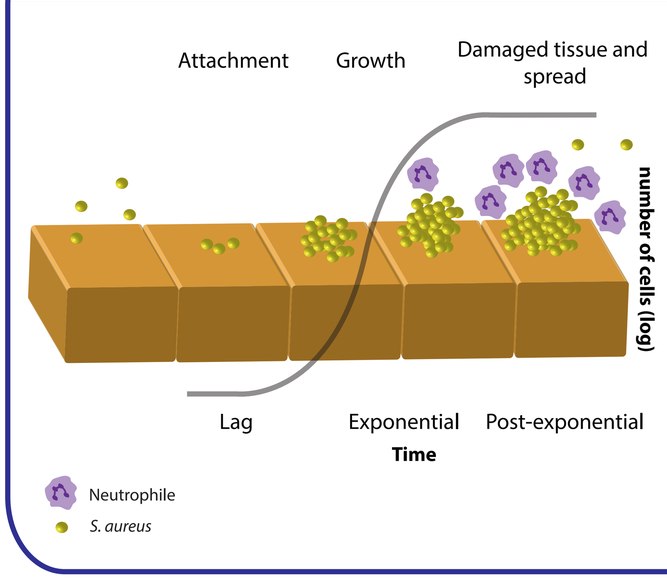


Fig.2. Model of infection. This figure represents the main steps of the *S. aureus* infection process: attachment to host cells, population growth and spread (which implies damaging the nearby tissues). These steps can be correlated with the general phases of a microbial culture: lag, exponential and post-exponential as it is presented in the image. The level of the global regulator molecules that coordinate all the system is different during these culture phases because it depends on the population density in a specific moment. Thus, the general regulation of virulence is growth-dependent (2).

Antimicrobial resistance regulation

MRSA and VRSA strains contain different genetic elements that confer their resistant phenotypes, and their expression is controlled by different TCS that are specific to each resistance mechanism (Fig. 1B). The expression of these genes is repressed without extracellular antibiotics, but when the drugs are present, the sensor protein of the TCS is activated and transduce its signal to the regulatory proteins, allowing the transcription of the repressed genes (3,4).

Fig. 3. Regulatory mechanisms during lag phase

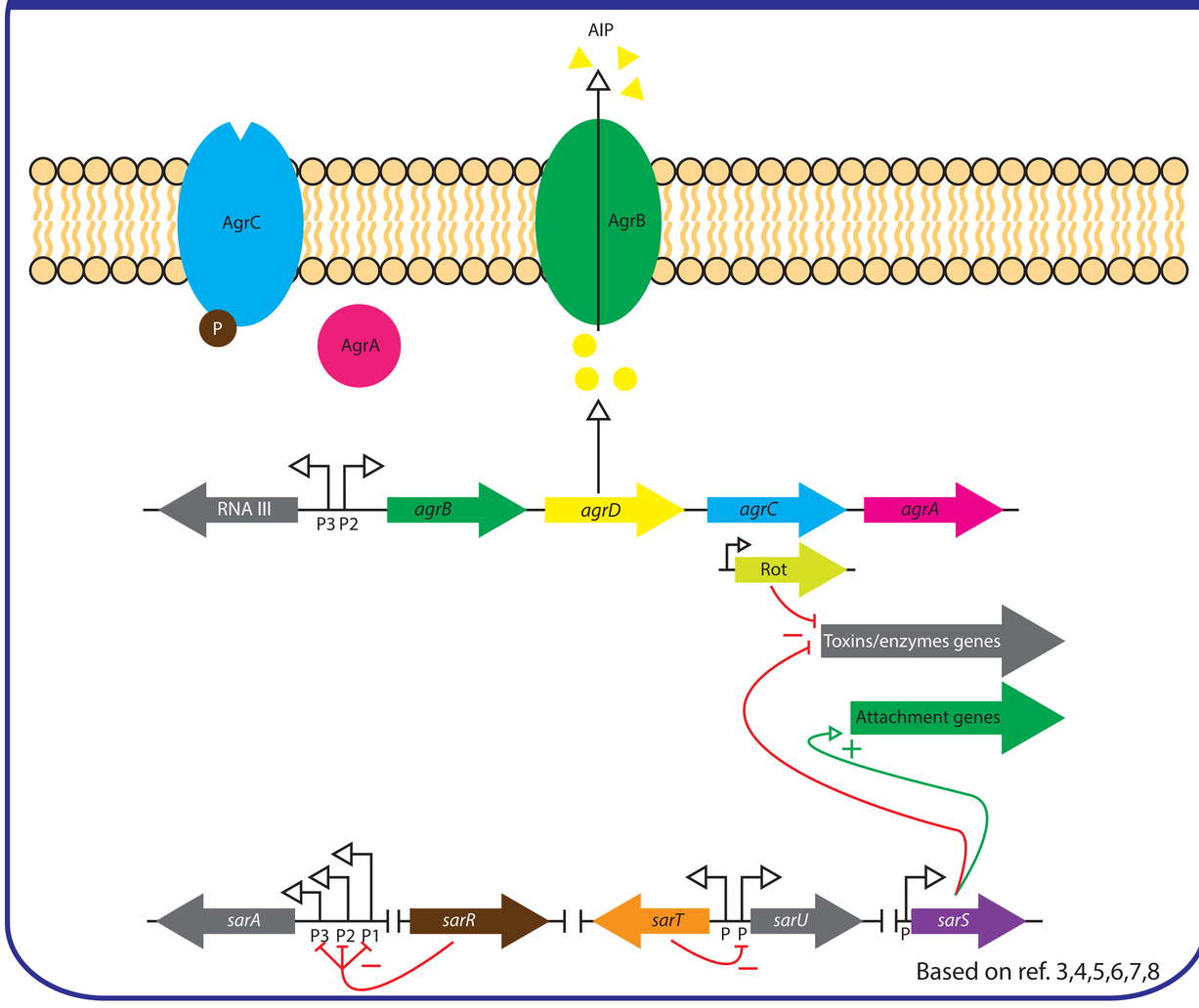
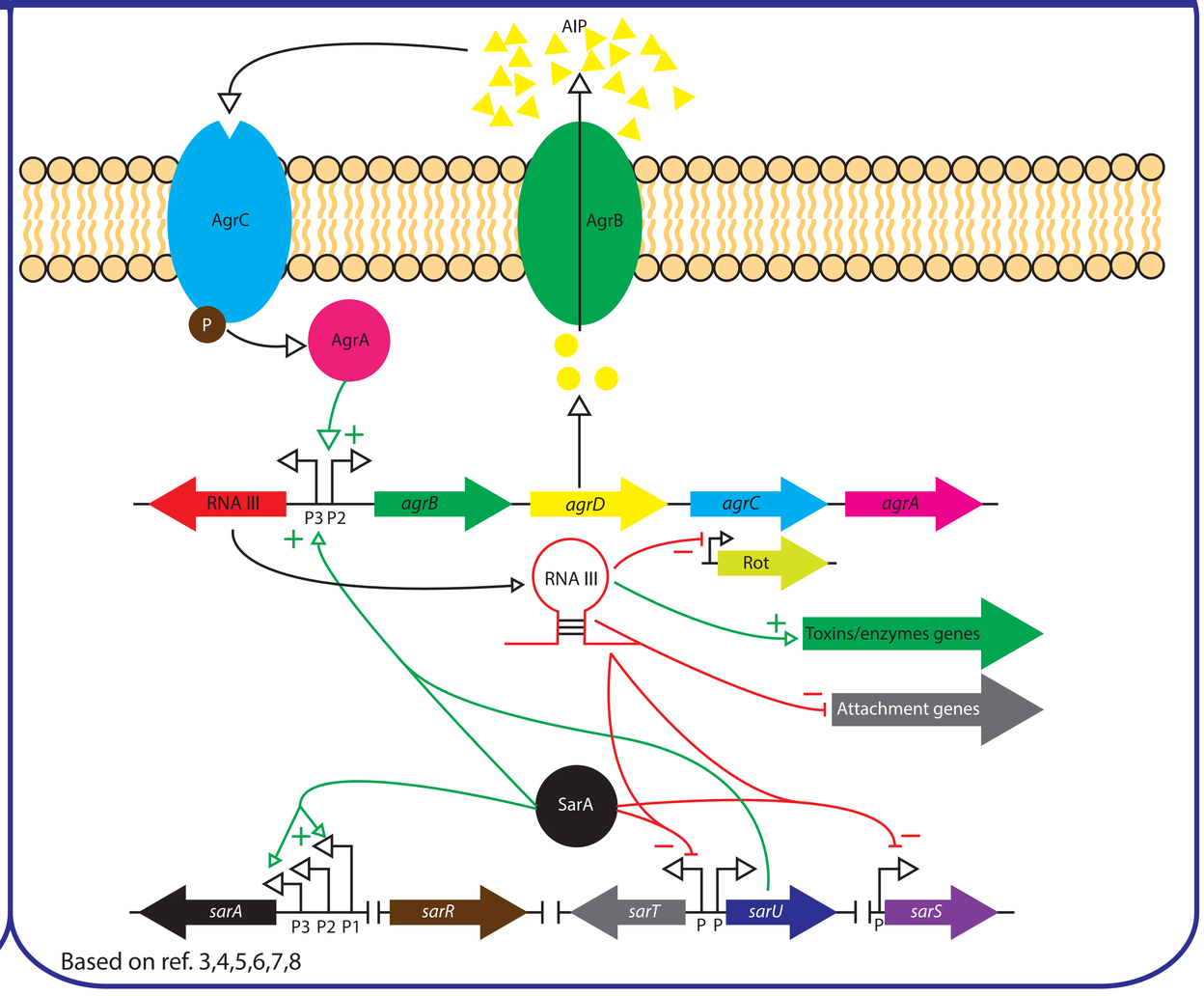


Fig. 4. Regulatory mechanisms during post-exponential phase



Virulence regulation

Depending on the moment of the infection process, *S. aureus* expresses different groups of genes with a simillar pathogenic function. These are the attachment genes (i. e. *cna*, Fig. 1A) and the toxins/enzymes genes (i. e. *hla*, Fig. 1A). In the first steps of the infection (correlated with lag phase, Fig. 2), the microorganisms are able to attach themselves to a cellular surface thanks to the expression of the first group of genes. However, when the bacterial population reaches a specific density level (post-exponential phase, Fig. 2), *S. aureus* switch its gene expression by repressing the attachment genes and activating the second ones, which are responsible of damaging the host tissues and the spreading of them to another site of the human body. Figures 4 and 5 represent this switching, based on the action of the *agr* and *sar* systems that are activated when the molecule AIP (autoinducing peptide) reaches a limit (high population density). The main effector molecules are RNAIII and SarA, and their coordinated action implies a radical change on the expression of the virulence genes (1, 2).

Concluding remarks

S. aureus presents a tremendous ability to adapt its biological functions in every step of the infection process, thanks to the regulation mechanisms that had been evolving for hundreds of millions of years. The strong control of the antimicrobial resistance that MRSA and VRSA strains present provides them the capability of being resistant without diminishing their biological efficiency, a huge advantage respect non-resistant *S. aureus* strains. Although considerable studies demonstrate that the main virulence regulators of *S. aureus*, described above, are growth-dependent because all of them are related to the *agr* locus, the importance of these genetic systems is not completely studied *in vivo*.

The complex biology of the pathogens is directly reflected in the regulation of their molecular processes, and so in its capacity to overcome new fight strategies that we develope against them. To understand their molecular mechanisms is a big challenge, but it is basic if we want to reduce their prevalence on a global scale.

References

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