Agr/sarA: Molecular switches of biofilm regulation in Staphylococcus aureus

Abstract
Biofilms are commonly referred to as extra cellular matrices or extra polymeric structures composed of bio molecules and are known for their complexity. They confer the pathogen with a variety of functions that make them resilient and virulent. The current mini review attempts to highlight the significance of agr/sarA regulators and their role as molecular switches in the formation and dispersal of Staphylococcus biofilms.

Keywords: Agr pathway, sarA pathway, quorum sensing, auto inducing peptides

Introduction
It is a widely accepted fact that microscopic living organisms have their own significance in terms of challenging the scientific community through their ability to adapt and establish to a variety of environmental conditions. This in turn makes them a difficult competitor to contend. One such microscopic organism that has been threatening the human society for decades is Staphylococcus aureus. In fact, the organism is widely studied for its ability to cause hospitalized acquired infections also referred to as nosocomial infections. There are several reasons which include genetic and environmental factors that in turn favor the pathogen in causing the infection. The current mini review primarily focuses on genetic aspects of the pathogen which includes the Agr mechanism responsible for a variety of actions performed by the pathogen and highlights the significance of these genetic elements in biofilm formation.

Biofilms are vital structures of biological significance and have an important role in boosting the ability of the pathogen in conferring the infection. Research studies have described these biofilms as intricate biological complexes comprising of a variety of bio molecules. They are regarded as extra polymeric substances and play a vital role in offering the pathogen with a range of specialized functions that cannot be found in non biofilm forming microorganisms or the free floating planktonic microorganisms. They are self accumulated microbial constructions that are capable of optimizing their functions and are known to control a variety of metabolic activities in favor of the enclosed microbes. Organisms embedded within the biofilm matrix are arranged systematically and are regulated through a sequence of genes that result in the formation, multiplication and dispersal of the mature biofilms. Despite the fact that they are known as extra polymeric matrices, many scientific investigators have described them as an integral part of the microbes due to its role in assisting various regulatory and metabolic activities (Figure 1).

Figure 1 Various components of biofilms and their respective percentages.²,³

Agr/sarA regulation of biofilms
Several research studies and scientific demonstrations have validated the significance of Agr (accessory gene regulator) and sarA (Staphylococcus aureus regulator) in biofilm formation. In fact, these major global regulators have been the subject of research to enhance the understanding of the genes loci and specific genes associated with these pathways. Demonstrative studies have confirmed the importance of sarA/Agr loci in the regulation of gene locus encoded by arlRS gene which is a member of Omp-R Pho-B family.⁴ Activation of arlS gene hinders the biofilm formation as it intervene the attachment to the surface by influencing peptidoglycan hydrolase activity. Biofilm formation relies of the up-regulation of the sarA transcripts in contrast to planktonic cultures.⁵ Studies also reveal Himani Sharmalesser protease inhibitors result in the down regulation of protease activity which in turn prevents the degradation of the DNA and proteins that are vital for the formation of biofilms.
However, scientific investigators and their studies assert the affects between Agr and sarA to be mutual and claim a reciprocal relationship between these two pathways. Nevertheless, the consequence of Agr in vitro mutants is nominal. Though some research studies have claimed the mechanism of Agr independent pathway, other studies support its association with biofilms. Down regulation of genes responsible for cell wall adherence has been observed in Agr mediated quorum sensing. This in turn would result in reduced cell wall attachment which initially leads to the biofilm formation. Hence suppression of Agr has been shown to be beneficial for enhanced biofilm formation. Stimulation of Agr through auto inducing peptides (AIP) that are vital for quorum sensing system facilitates the dispersal of the mature biofilms. The repression of Agr occurs in a protease dependent manner which as a consequence enhances the dispersal of mature biofilms as protease inhibitors restrict the dispersal of the mature biofilms. Studies also emphasize the significance of Agr in the activation of peptides and nucleases which in turn enhances the process of biofilm detachment. For that reason, these major global regulators of Staphylococcus function in a complementary manner where sarA induces the formation of early biofilm adherence and Agr assists in the detachment of the mature biofilms. This subsequent relationship between these major global regulators is a consequence of a variety of factors which includes the expression of proteases and proteolytic enzymes for the formation of the desired population and later on results in the dispersal of the mature biofilms as a consequence of Agr expression.

Conclusion

Previous studies and ongoing research support that the biofilm regulation is enhanced by the Agr/sarA regulators. They work in tandem and share a mutual relation which allows the early biofilm formation and its dispersal after maturity in the later stages. The process is intricate and involves the activation and inactivation of different molecular facets in the regulation of biofilms in Staphylococcus aureus. Nevertheless, further research is necessary to explore the depths of the mechanism.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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