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Mini Review

Inhibition of *Staphylococcus aureus* by *Corynebacterium* Species: A Mini-Review

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ABSTRACT

Staphylococcus aureus is a colonizer of human skin and nose. This asymptomatic carriage is an important risk factor of infection ranging from polymicrobial diabetic foot infection to monomicrobial bacteremia. Emergence of resistant bacteria, in particular, methicillin resistant *S. aureus* strains is a major health care problem worldwide. Looking for alternative ways to prevent *S. aureus* carriage and autoinfection is crucial. Some researchers focused on the study of the elimination of *S. aureus* by the implantation of nonpathogenic microorganisms. *Corynebacterium* spp., a common constituent of the human skin and mucosa, showed a potency to inhibit and decrease the virulence of *S. aureus*. In this mini-review, we will focus on the role of *Corynebacterium* species in the regulation of the virulence of *S. aureus*.

Keywords: *Staphylococcus aureus*; *Corynebacterium*; Inhibition

INTRODUCTION

Staphylococcus aureus is a common colonizer of human nose and skin. This carriage increased the risk of autoinfection. Indeed, the emergence of *S. aureus* resistant to multiple antibiotics, in particular, Methicillin-Resistant *S. aureus* (MRSA) is a serious problem worldwide. It becomes crucial to look for alternative methods to prevent the nasal chronic colonization of *S. aureus*. The use of the symbiotic microbiota may be a good approach. Recently, *C. accolans* was suggested as a promotor probiotic to ameliorate the health of patients with chronic rhinosinusitis [1].

Corynebacterium spp. constitutes a major compound of the normal microbiota. The coexistence of *Corynebacterium* spp. with *S. aureus* in the skin and the nasal cavities leads to an interaction between them. Some researchers demonstrated that *S. aureus* is inhibited by *Corynebacterium* spp. Here, we summarized the main results of researchers studying the interaction between these two microorganisms.

Corynebacterium spp. inhibits the growth of *S. aureus*

Since 1987, studies focusing in the interaction between *Corynebacterium* species and *S. aureus* have been started. Hogan et al (1987) reported that the coculture of *C. bovis* and *S. aureus* inhibited the growth of this last in comparison with a monoculture.

In 2016, Ramsey et al (2016) studied *in vitro* the interaction between *S. aureus* and *Corynebacterium* spp. They showed that the coculture of *C. striatum* and *S. aureus* inhibited the growth of *S. aureus* on agar plates. The number of CFUs of *S. aureus* in a co-infection is lower in a mono-infection, whereas CFUs of *C. striatum* increased [2].

This same observation was recently confirmed when *S. aureus* was co-incubated with *C. pseudodiphtheriticum* (2020). Hardy et al (2020) found that the strain obtained from the nose of a healthy volunteer exhibited a larger inhibition zone than a lab-adapted strain. This species exhibited a selective bactericidal activity against *S. aureus* strains [3].

It collectively suggests that certain species of *Corynebacterium*, such as *C. bovis*, *C. striatum*, and *C. pseudodiphtheriticum*, possess the ability to inhibit the growth of *S. aureus*. This inhibition may be mediated through mechanisms such as the production of antimicrobial substances or competition for nutrients and resources. It is needed to understand the specific mechanisms involved in this interaction and explore its potential applications in combating *S. aureus* infections.

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Corynebacterium inhibits the adherence of *S. aureus* to epithelial cells

The binding of *S. aureus* to nasal epithelial cells is a crucial step in the process of infection [4,5].

The relationship between *S. aureus* nasal carriage and the development of serious infections has been established in immune-depressed patients [6]. The elimination of nasal carriage may be done by the administration of antibiotics (local or systemic). The use of bacteria instead of antibiotics may be a potential strategy is to decrease *S. aureus* nasal carriage [6].

In 2000, Uehara et al (2000) evaluated the role of the normal nasal microbiota in the elimination of *Staphylococcus* spp. They found that the implantation of a *Corynebacterium* strain (Co304) leaded to the eradication of *S. aureus* from the nares of 71% of the 17 volunteers. However, this strain didn't exhibit a bacteriocin-like activity against *S. aureus* in solid and liquid culture media [7].

The authors suggested that there is a competition for survival between these species [7]. This hypothesis was previously established by Wickham et al (1978) who supposed that initial bacterial colonizers could block later establishment of *S. aureus*.

This observation was confirmed by testing bacterial adherence to epithelial cells in nasal cavities. *Corynebacterium* spp. strain showed higher affinity to nasal mucus than *S. aureus* [7].

In 2013, a study yielded in USA showed the effectiveness of a bacterial solution of *C. pseudodiphtheriticum* to shift the nasal community. The administration of this solution to volunteers with chronic staphylococci nasal carriage exhibited a notable reduction in the number of CFU of *S. aureus versus* an augmentation in *C. striatum* CFUs. This solution eradicated *S. aureus* after 2 to 3 weeks of spraying. Observations with Transmission Electron Microscopy (TEM) showed that the presence of *C. pseudodiphtheriticum* altered the cell wall of *S. aureus* which causes the cell lysis [8].

The authors suggested that this method could be useful for the prophylaxis and the treatment of the nasal carriage by *S. aureus*, potentially providing an alternative strategy to antibiotics to reduce *S. aureus* nasal carriage and associated infections [9].

Corynebacterium spp. regulated the expression of *agr* QS system

Ramsey et al (2016) investigated the molecular mechanism of the inhibition of *S. aureus* by *C. striatum*. They found that the co-incubation of *S. aureus* with *C. striatum* in a solid media inhibits the transcription and the expression of genes implicated the colonization and the virulence.

The expression of more than 460 genes was different in the co-culture compared to the monoculture. *C. striatum* regulated the transcription of *agr* operon which results in the decrease of *psmb1* gene. Also, *C. striatum* deceased the expression of *agr* Quorum Sensing (*agr* QS) system [10].

In *S. aureus*, the *agr* QS system controls the expression of many virulence factors [11]. As a consequence, *C. striatum* inhibited the expression of virulence genes involved in the invasive infection and increased the expression of the factors implicated in cell-adhesion and host colonization. It indirectly influenced the expression of other *agr*-dependant genes [10].

In the same study, results showed that, in addition to *C. striatum*, other *Corynebacterium* species including *C. amycolatum*, *C. accolans*, *C. pseudodiphtheriticum* and *C. glutamicum*, also altered the expression of the *agr* QS system in *S. aureus*. This suggests that the regulation of *agr* QS by *Corynebacterium* species may be a common mechanism among different strains [10].

Results of an investigation conducted by Hardy et al (2020) joined this study. They reported that the target of *C. pseudodiphtheriticum* is the *agrBDCA* gene. Resistance of *S. aureus* to *C. pseudodiphtheriticum* was induced by the absence or the diminution in the expression of *agrBDCA* [3].

This team studied the link between the *agr* QS system and *C. pseudodiphtheriticum*-mediated bactericidal activity. Their experiments showed that the expression of alpha-*psm* reduced the sensitivity of *S. aureus* strains to *C. pseudodiphtheriticum*-mediated bactericidal activity [10].

These findings indicate that *Corynebacterium* species, including *C. striatum* and *C. pseudodiphtheriticum*, have the ability to regulate the *agr* QS system in *S. aureus*, leading to alterations in gene expression and modulation of virulence factors. This is to fully understand the underlying mechanisms and implications of this regulatory interaction.

Corynebacterium spp. regulated the expression of the *Spa* gene

Staphylococcal protein A (*Spa*) is an important virulence factor of *S. aureus* which is expressed during the exponential phase of growth and then is transcriptionally down-regulated during the post-exponential phase of growth [12]. It enables *S. aureus* to evade hosting immune response [13].

In a co-culture of *S. aureus* and *C. striatum*, researchers observed an alteration in the expression of the gene encoding the surface protein of *Staphylococci* (*Spa*), which is implicated in its protection from the opsonization and phagocytosis, and during nasal colonization. However, the exposure of *S. aureus* to *C. striatum* increased its adhesion to human epithelial cells [10].

Corynebacterium spp. reduces the hemolytic activity of *S. aureus*

Hemolysin is one of the important virulence factors for *S. aureus* and causes the typical β-hemolytic. Recently, clinical isolates showed a new profile characterized by an incomplete hemolytic phenotype. The hemolytic activity of *S. aureus* facilitates the damage the red cell membrane, alters the phagocytosis, induces toxic shock syndrome, and participates in the biofilm formation [14].

The hemolytic activity of *S. aureus* clearly decreased in the presence of *C. striatum* which confirms that *S. aureus* shifts its virulence factors when exposed to *C. striatum* [10,15].

Corynebacterium spp. compete for iron uptake

Iron is a vital factor for the growth and proliferation of pathogenic bacteria. Iron acquisition is required for *S. aureus* in colonization and subsequent pathogenesis. The functional redundancy built into staphylococcal iron acquisition systems guarantees the pathogen obtains enough iron to successfully colonize a variety of diverse niches within the host. A restriction of iron amount in the environment during infection affects directly the survival of *S. aureus* and may be alternative strategies to combat this pathogen [16].

Recently, Stubbendieck et al (2016) focused on the bacterial interaction in the human nasal cavity. They isolated three *C. propinquum* isolates that strongly inhibited coagulase negative *Staphylococcus*. The genome sequencing of these strains revealed that it was rich in genes implicated in the iron acquisition. The biosynthetic gene cluster implicated in siderophore production was identified in the inhibitor strains and absent in the non-inhibitor strains [17,18].

CONCLUSION

In conclusion, *Corynebacterium* spp. have a negative effect on *S. aureus*. The presence of this microorganism induced the repression of genes encoding virulence factors in particular the *agr* system and its related genes. *Corynebacterium* spp. caused also a decrease in the hemolytic activity and was responsible for harmful damages in the wall *of S. aureus*. Therefore, the use of *Corynebacterium* spp. strains may be a good alternative to eradicate *S. aureus* in particular with the emergence of MRSA strains. However, it is important to note that further in-depth studies are needed to fully understand the mechanisms involved and to explore the feasibility and efficacy of using *Corynebacterium* spp. strains as a therapeutic approach against *S. aureus* infections.

Overall, these findings suggest that the interactions between *Corynebacterium* spp. and *S. aureus* hold promise for the development of novel strategies to combat *S. aureus* infections, but more research is required before such approaches can be implemented clinically.

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