

Título: INSIGHTS INTO IRON AND ZINC UPTAKE SYSTEMS IN COAGULASE-NEGATIVE STAPHYLOCOCCI

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Abstract:

Coagulase-negative staphylococci (CoNS) have emerged as an important cause of human infections, mainly in immunosuppressed patients or indwelling medical device. For that reason, studies aiming to unravel the virulence mechanisms involved in CoNS pathogenesis are essential in the search for new drug targets. An important part of the arsenal of bacterial virulence factors comprises the strategies to overcome the nutritional immunity, including trace elements such as metals. The mechanisms related to metal scavenging has been extensively studied in microorganisms such as *Staphylococcus aureus* and *Bacillus subtilis*. Therefore, an outspreading search for genes related to the main iron and zinc scavenging systems was conducted using these two species. A total of 41 iron-related genes and 15 zinc-related genes were selected. The search for homologous genes in CoNS was based on the sequence similarity using *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, and *Staphylococcus haemolyticus* genomes. *S. aureus* produces two main polycarboxylate-type siderophores, staphyloferrin A (*sfa*ABCD) and staphyloferrin B (*sbn*ABCDEFGHI). Upon binding iron, both siderophores are internalized by two distinct ABC transporters, HtsABC and SirABC. Homologous sequences of the genes coding staphyloferrin A biosynthesis and transporting systems were found in CoNS. A divergent response was observed for genes belonging to operon Sbn and Sir, related to staphyloferrin B biosynthesis and internalization. Also, *S. aureus* is able to acquire iron ions from hemoglobin, heme groups and hemoglobin-haptoglobin complex via *Isd* system. The absence of *Isd* homologous in CoNS suggested a different mechanism for heme acquiring. In agreement, it were observed genes homologous to *oppA-F* in *S. epidermidis*, and *fepABC* in *S. haemolyticus*. In *B. subtilis*, the zinc acquisition is mediated by three different systems: YcdHI-yceA, YciABC and ZosA. The ABC transporter, encoded by *ycdHI-yceA*, belongs to the high-affinity zinc acquiring system and no homologous genes were found in CoNS. The second zinc uptake system is mediated by YciABC, also not present in CoNS. Previous studies have shown that under metal starvation, adequate zinc recruitment is ensured by the high-affinity Zn uptake system encoded by the *znuABC* genes in *S. aureus*, which is also present in CoNS. Genetic comparisons revealed a putative difference among CoNS and *S. aureus* metal acquisition mechanisms.

Key-words: metal acquisition; Coagulase-negative staphylococci; nutritional immunity; virulence; host-interaction

Acknowledgements: Programa de Apoio a Iniciação Científica no Amazonas (PAIC/FAPEAM 2014-2015), Fundação de Amparo à Pesquisa do Estado do Amazonas (FAPEAM), Fundação de Hematologia e Hemoterapia do Amazonas (FHEMOAM).