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Manganese: the battle of the two armies

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The battle for manganese (Mn) between host and pathogens like Staphylococcus aureus is critical to determine the outcome of the full-scale war (Juttukonda and Skaar, 2015; Kelliher and Kehl-Fie, 2016). Manganese is an essential metal for all living organisms, being notably required as a cofactor for multiple metalloenzymes to perform their functions. Given its importance in S. aureus cellular processes—e.g., carbohydrate and amino acid metabolism, oxidative stress response, DNA synthesis and repair—and virulence (Juttukonda and Skaar, 2015; Kelliher and Kehl-Fie, 2016), the host takes advantage of this dependency and captures Mn resources. This defensive metal-based tactic is termed nutritional immunity. Despite experiencing Mn starvation, S. aureus successfully causes a wide range of infections, indicating that S. aureus possesses efficient adaptative mechanisms to overcome the Mn-based nutritional immunity. Hence, the respective armies scramble for either Mn sequestration or acquisition.

Crucial components of the innate immunity, neutrophils and macrophages represent the first defensive trench. S. aureus, devoid of this essential micronutrient, is inherently toxic at high levels. Therefore, S. aureus also possesses a Mn efflux pump, MntE (Grunewald, 2019). To efficiently maintain the subtle balance between manganese starvation and toxicity, Mn transporters receive instructions from the main transcriptional regulator MntR. Upon interaction with Mn2+, MntEpresses or activates all aforementioned Mn import and export systems to set an adequate Mn intracellular level. Remarkably, MntR also gives orders to the regulatory RNA RsaC, which is strongly induced during manganese starvation. Indeed, RsaC is co-transcribed with mntR. After its release from its precursor by a ribonuclease-mediated cleavage, RsaC represses the translation of SodA, the main Mn-dependent superoxide dismutase involved in ROS detoxification (Figure 1). Hence, RsaC spares intracellular Mn2+ for essential Mn-containing proteins (e.g. involved in DNA synthesis and repair) by negatively regulating non-essential Mn-containing proteins and avoids the synthesis of non-functional enzymes. Concurrently, RsaC indirectly activates SodM synthesis, a MnO2-dependent Mn-containing superoxide dismutase as cofactor, which displaces SodA to re-establish ROS detoxification pathway and counteract the sequestration of Mn by host immune cells. Thus, RsaC plays a critical role in oxidative stress response by redireciting the needs for manganese to iron. Both rsaC and sodM genes have been acquired exclusively by S. aureus and closely related strains (S. argenteus and S. chweni). This genetic setup indicates that S. aureus has adapted its defence arsenal by the acquisition of a second SOD enzyme and a regulatory RNA, a clear advantage compared to other Staphylococcus spp. when facing host-imposed metal starvation.

RsaC might have a broader role in metal homeostasis via the regulation of iron (Fe) and zinc (Zn) transporters and the Zn-dependent transcriptional regulator Zur. As RsaC favours the Fe-dependent ROS detoxification pathway, it is easy to assume that RsaC should also control iron homeostasis. Interestingly, host immune cells use zinc as a chemical weapon by harnessing its toxic properties to poison S. aureus (Flannagan et al., 2015; Djoko et al., 2015). A Zn overload notably perturbs Mn homeostasis by inactivating crucial components such as MntC and MntR through mismetallation. Hence, RsaC protects S. aureus from host assaults by interconnecting all these metalloastas systems.

A better understanding of this ‘fight over metals’ might suggest new drug targets for antimicrobial therapy and tailored promising therapeutic alternatives (e.g. metal chelators or metal-based antimicrobials). This perfectly illustrates the importance of exploiting regulatory networks in the human pathogen S. aureus, the main objective of the SaRNAReg project.

Figure 1: RsaC, an RNA, is a connection node between oxidative stress and metal homeostasis. In the presence of Mn2+ (red), the transcriptional regulator MntR adjusts the cellular levels of Mn by controlling Mn import and export systems. In response to Mn starvation (green), RsaC acts primarily at the post-transcriptional level by targeting several mRNAs to benefit the Mn-independent ROS detoxification pathways.

References

SUMMARY
The aim of H2020-MSCA-IF project “Staphylococcus aureus sRNA targetomics and regulatory networks involved in fast adaptive responses: structure, mechanisms and dynamics (SaRNAReg)” was to deeply characterise sRNA-dependent regulatory networks and reveal their functional roles in S. aureus cell physiology and virulence.

PROJECT LEAD PROFILE
Dr David Laloua received a Marie Sklodowska-Curie Individual Fellowship in 2018 to unravel sRNA-based regulatory networks in S. aureus. He recently secured a CNRS researcher position (CRCN).
Dr Pascale Romby is Director of the CNRS research unit (UPR 9002) since 2016 and Head of the research team entitled “sRNAs and regulatory RNAs in bacteria”.

PROJECT PARTNERS
The SaRNAReg project is based at the CNRS research unit (UPR 9002) “Architecture and Reactivity of RNA” at the Institute of Molecular and Cellular Biology (IBMC), recognised as a leading national and international centre on RNA biology.

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