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# Manganese: the battle of the two armies

David Lalaouna and Pascale Romby  
 Université de Strasbourg, CNRS – France

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 (Spaan et al., 2013; Flannagan et al., 2015). They deploy an arsenal of antimicrobial effectors like reactive oxygen species (ROS), real bullets damaging cellular components (i.e. nucleic acids, proteins and lipids). They also release chelating agents like calprotectin, which avidly sequester essential metals such as Mn to prevent growth of the invader. After engulfment by macrophages, *S. aureus* is also Mn-starved by Mn<sup>2+</sup> extrusion from the phagosomal compartment

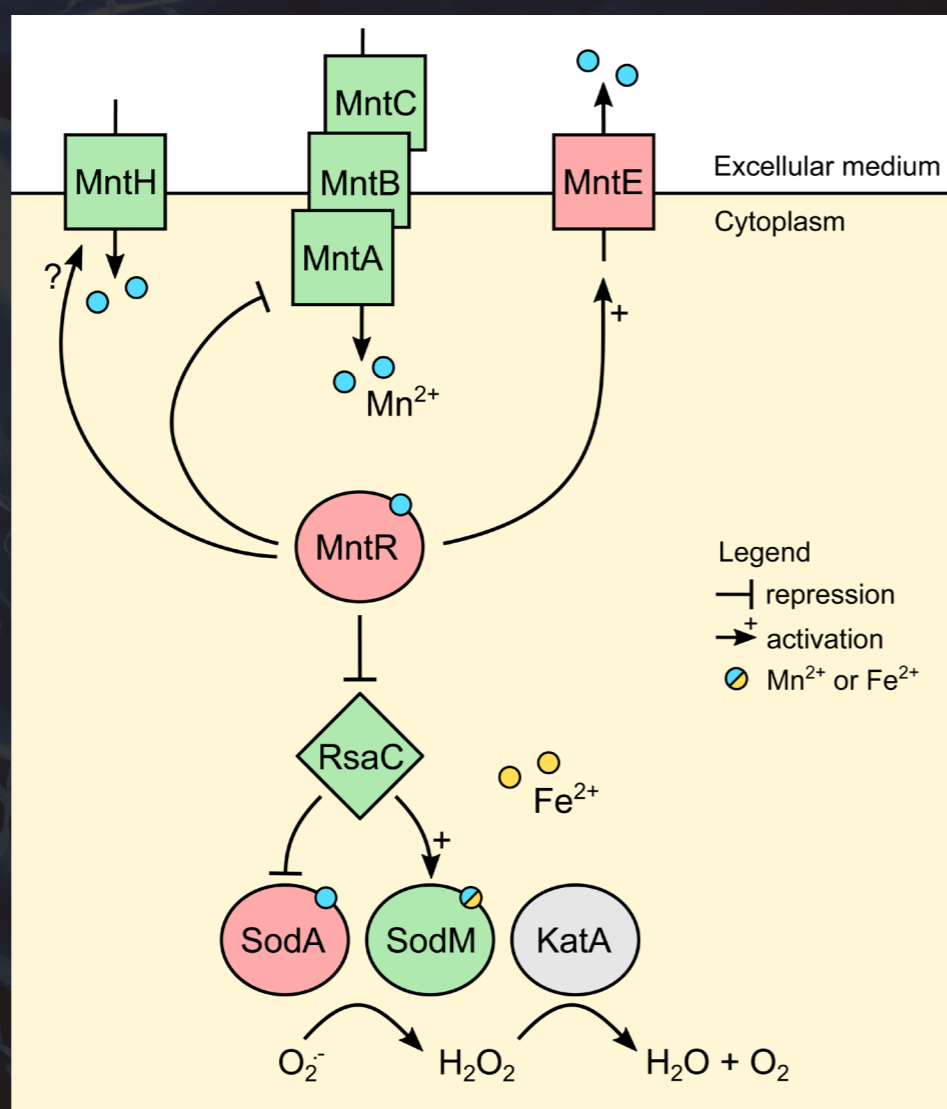


Figure 1: RsaC sRNA, a connection node between oxidative stress and metal homeostasis. In the presence of Mn<sup>2+</sup> (red), the transcriptional regulator MntR adjusts the cellular levels of Mn by controlling Mn import and export systems. In response to Mn starvation (green), RsaC acts primarily at the post-transcriptional level by targeting several mRNAs to favour the Mn-independent ROS detoxification pathways.

via the NRAMP-1 transporter (natural resistance-associated macrophage protein 1). Consequently, the battlefield is virtually devoid of this essential micronutrient. However, *S. aureus* is also well-equipped for this combat. Indeed, *S. aureus* genome encodes two Mn import systems, MntH and MntABC, to thwart these metal-based defensive strategies (Horsburgh et al., 2002).

Besides being an essential micronutrient, manganese is inherently toxic at high levels. Therefore, *S. aureus* also possesses a Mn efflux pump, MntE (Grunenwald, 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 Mn<sup>2+</sup>, MntR represses 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 *mntABC*. 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 Mn<sup>2+</sup> 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 SOD enzyme using either Mn<sup>2+</sup> or Fe<sup>2+</sup> 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 redirecting 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. schweitzeri*). 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 metallostatic systems.

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

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## SUMMARY

The aim of H2020-MSCA-IF project "Staphylococcus aureus sRNA targetomes 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 Lalaouna received a Marie Skłodowska-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 "mRNAs 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.

## CONTACT DETAILS

David Lalaouna  
 +33 3 88 41 70 51  
 d.lalaouna@ibmc-cnrs.unistra.fr  
 Pascale Romby  
 +33 3 88 41 70 68  
 p.romby@ibmc-cnrs.unistra.fr



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