Methionine sulfoxide reductase enzymes: a possible virulence factor for the management of antibiotic resistance crisis in the climate change era

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ABSTRACT

The problem of antibiotic resistance develops when bacteria are able to grow in the presence of conventional antimicrobial drugs and today represents a serious public health issue. The environmental effects of global warming, by unknown genomic mechanisms of adaption, could dramatically increase this phenomenon and support a more rapid progression to "post-antibiotic era", in which common infections will be untreatable. Alternative approaches toward drug-resistant bacterial infections need to be explored to ensure effective therapies. Bacterial pathogens produce virulence factors that allow them to invade and to damage host cells. Methionine sulfoxide reductase (Msr) enzymes (MsrAs and MsrBs) are important, but poor studied, virulence factors for many bacterial strains. A deeper insight into their mechanism of action and regulation could help in developing novel therapeutic strategies toward drug-resistant bacteria, in order to overcome the antibiotic resistance crisis.

Keywords: Antibiotic crisis; Bacterial infection, Global warming, Methionine sulfoxide reductase; MsrA, MsrB, Public health, Virulence factor

1. BACKGROUND

The first documented antibiotic resistance concerned the penicillin, that was discovered by Alexander Fleming in 1928, and dates back to the 1940s, well before the use on a large scale that began in the second half of the past century. The proportions of antibiotic resistance have grown exponentially over the past few years, leading to reduced therapeutic efficacy, and increased mortality rates [1]. This emergency is recognized by the World Health Organization as one of the most important public health threats affecting humans worldwide in this century. Current estimates suggest that by 2050 ten million of premature deaths annually will be caused by resistant infections [2].

Antibiotic resistance is amplified by overuse or inappropriate prescription of antibiotics, the extensive use of them as growth supplements in livestock, and the stall in development of new antibiotics by the pharmaceutical industry [1]. Climate change has been identified by the World Health Organization as a major factor in the spread of emerging infectious disease worldwide. Climatic factors such as temperature, precipitation, and humidity modulate many biological aspects concerning the transmission of pathogens [3]. More recently, a relationship between increased antibiotic resistance of certain bacterial strains and global warming was observed [4]. The mechanism behind the phenomenon is still unknown and, in view of this scenario, the impact of antibiotic resistance on global hearth could be dramatically underestimated [5].

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Bacterial adaptive response to antibiotics originates from the massive genetic plasticity of prokaryotic cells, based on processes such as acquisition of genetic material through horizontal gene transfer, and alteration of gene expression. These mechanisms of mutational adaption, an example of Darwinian principle of evolution, can confer to the pathogen resistance to virtually all drugs currently available in clinical practice [6]. This aspect is so important that the term "resistome" has been coined to define the set of genes that provide bacteria with an arsenal of weapons to resist antibiotics. Furthermore, an open source database has been implemented (Comprehensive Antibiotic Resistance Database, http://arpcard.mcmaster.ca), containing high quality reference data on the molecular basis of antimicrobial resistance [7].

2. NEW PERSPECTIVES

The knowledge of the biochemical and genetic basis of this phenomenon is fundamental to design novel therapeutic strategies against antibiotic-resistant microorganisms. The discovery of new virulence factors (proteinaceous or non-proteinaceous molecules produced by the bacteria and that assist them during the colonization of host cells) is one of the strategies adopted in pursuing this goal. Along this line, over the past years methionine sulfoxide reductase (Msr) enzymes have gained significance as contributors of virulence for several bacterial strains. Msrs perform the reconversion of methionine sulfoxide to methionine in proteins, and are classified on the basis of their stereoselectivity toward the two diastereoisomers of methionine sulfoxide: MsrA isoforms reduce methionine-*S*-sulfoxide, whereas MsrB isoforms reduce methionine-*R*-sulfoxide [8]. The ubiquitous distribution of Msrs, from prokaryotes to eukaryotes, highlights the strategic role they play against oxidative stress, by repairing the oxidative damage inflicted to sensitive protein-bound methionines, and by participating in a cyclic oxidation/reduction mechanism in which methionines, free or bound in proteins, act as scavengers of oxidants [8]. Several studies shown that MsrA enzymes play a role in the virulence of *Staphylococcus aureus*, *Salmonella typhimurium*, *Streptococcus gordonii*, *Mycobacterium smegmatis* and *Mycobacterium genitalium* [9]. Furthermore, evidence suggested that MsrA could be involved in the transition of *Staphylococcus epidermidis* from commensalism to pathogenicity [9]. MsrA knock-out strains of these microorganisms showed reduced virulence with respect to wild-type strains, in properties such as the ability to survive inside phagocytic cells, the defense against oxidative attack by neutrophils, the colonization of host tissue, and cytotoxicity and adhesion to host cells [9]. MsrB enzymes do not confer significant contribution to virulence in these bacterial strains. Conversely, in *Francisella tularensis* MsrB, but not MsrA, appears to be a key determinant for virulence [9]. Furthermore, in *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Helicobacter pylori* and *Escherichia coli* both MsrA and MsrB enzymes are engaged in the promotion of virulence, in the resistance to phagocytosis by macrophages and in contrasting the oxidative insult by neutrophils [9]. Finally, upregulation of msrA gene in *Streptococcus aureus* appears to occur in response to cell wall-active antibiotics, indicating a possible role of MsrA in antibiotic resistance [10].

3. CONCLUSION

While most literature proposes MsrA as a very important virulence factor in some bacterial strains, little is still known about MsrB [9]. More detailed studies are needed to understand the exact function of these intriguing proteins and their mechanism of regulation in prokaryotes. A deeper insight into these aspects could help in stimulating the development of innovative and effective antimicrobial therapies based on the targeting/blocking of bacterial virulence factors, an alternative solution of growing interest for the management of a wide range of infectious diseases that are not amenable to standard clinical approaches [11]. This could circumvent the planetary plague of antibiotic resistance and mitigate the deleterious effects of climate change on human health, in view of the ineluctable further increase of global mean temperature by the end of this century and that could be more severe respect the optimistic scenario prefigured by the Paris Climate Agreement in 2015 [12].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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