

Coordination Properties of the Zinc Domains of BigR4 and SmtB Proteins in Nickel Systems—Designation of Key Donors

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The increasing number of antibiotic-resistant pathogens has become one of the foremost health problems of modern times. One of the most lethal and multidrug-resistant bacteria is *Mycobacterium tuberculosis* (Mtb), which causes tuberculosis (TB). TB continues to engulf health systems due to the significant development of bacterial multidrug-resistant strains. Mammalian immune system response to mycobacterial infection includes, but is not limited to, increasing the concentration of zinc(II) and other divalent metal ions in phagosome vesicles up to toxic levels. Metal ions are necessary for the survival and virulence of bacteria but can be highly toxic to organisms if their concentrations are not strictly controlled. Therefore, understanding the mechanisms of how bacteria use metal ions to maintain their optimum concentrations and survive under lethal environmental conditions is essential. The mycobacterial SmtB protein, one of the metal-dependent transcription regulators of the ArsR/SmtB family, dissociates from DNA in the presence of high concentrations of metals, activating the expression of metal efflux proteins. In this work, we explore the properties of $\alpha 5$ metal-binding domains of SmtB/BigR4 proteins (the latter being the SmtB homolog from nonpathogenic *Mycobacterium smegmatis*), and two mutants of BigR4 as ligands for nickel(II) ions. The study focuses on the specificity of metal–ligand interactions and describes the effect of mutations on the coordination properties of the studied systems. The results of this research reveal that the Ni(II)-BigR4 $\alpha 5$ species are more stable than the Ni(II)-SmtB $\alpha 5$ complexes. His mutations, exchanging one of the histidines for alanine, cause a decrease in the stability of Ni(II) complexes. Surprisingly, the lack of His102 resulted also in increased involvement of acidic amino acids in the coordination. The results of this study may help to understand the role of critical mycobacterial virulence

factor—SmtB in metal homeostasis. Although SmtB prefers Zn(II) binding, it may also bind metal ions that prefer other coordination modes, for example, Ni(II). We characterized the properties of such complexes in order to understand the nature of mycobacterial SmtB when acting as a ligand for metal ions, given that nickel and zinc ArsR family proteins possess analogous metal-binding motifs. This may provide an introduction to the design of a new antimicrobial strategy against the pathogenic bacterium *M. tuberculosis*.

Słowa kluczowe

Ions, Ligands, Metals, Monomers, Peptides and proteins

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