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Manganese: Uptake, Biological Function, and Role in Virulence

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Abstract Recent data have demonstrated that bacterial homologs of eukaryotic Nramp transporters as well as members of the LraI family of proteins are both highly selective Mn^{2+} transporters. Mutation of these transporters in several pathogenic bacterial species causes decreased virulence in a variety of model systems. This implies that the Mn^{2+} ions are required for one or more processes essential for bacterial virulence. However, Mn^{2+}

has few known enzymatic roles compared to other divalent cations. This review will describe what is currently known about the two classes of prokaryotic Mn^{2+} transporters, how each is regulated and the virulence deficits that arise when they are mutated. Finally, possible enzymatic roles for Mn^{2+} will be outlined, and their potential for a role in virulence discussed.

1 Introduction

Manganese is transported by biological systems solely as the divalent cation. Virtually all bacteria express one or both of two major classes of Mn^{2+} transport systems: the MntH (Nramp) H^+-divalent cation transporters and ABC ATPase Mn^{2+} transporters (in Gram-positive organisms, the ABC ATPases belong to the lipoprotein receptor antigen (LraI) class of cell surface proteins). A much smaller number of bacterial species such as *Lactobacillus* appear to carry a Mn^{2+}-transporting P-type ATPase. Eukaryotes also appear to have both Nramp and ABC ATPase class Mn^{2+} transporters though the latter class has not been characterized extensively. Although both types of transporters can mediate flux of multiple transition metal divalent cations, most of the bacterial Nramp transporters and many of the ABC transporters are highly selective for Mn^{2+} over other cations. Mutation of these selective Mn^{2+} transporters in several bacterial species causes decreased virulence in a variety of models of infection. The obvious conclusion is that Mn^{2+} ion is required for one or more processes essential for bacterial virulence. This review describes the properties of prokaryotic Mn^{2+} transporters, their cation selectivity and the regulation of their expression. After a discussion of the virulence deficits that arise when the transporters are mutated, possible enzymatic roles for Mn^{2+} relevant to pathogenesis will be outlined.

2 Mn^{2+} Transport Systems

Transport systems for manganese belong to several protein families, Nramp-, ABC-transporters and P-type ATPases.

2.1 MntH (Nramp) Mn^{2+} Transporters

The Nramp (**n**atural **r**esistance **a**ssociated **m**acrophage **p**rotein) transporter is a broad spectrum H^+-coupled transition metal divalent cation antiporter, transporting Fe^{2+}, Mn^{2+}, and Zn^{2+}, initially described in macrophages of