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Acquisition of Iron by Bacteria

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Abstract Bacteria have evolved multiple mechanisms to cope with the extreme iron limitations in their natural environments. Fe^{3+} forms insoluble hydroxy aquo complexes. The free Fe^{3+} concentration lies orders of magnitude below the concentration required for microbial growth (0.1 μM). Bacteria synthesize and secrete low-molecular-weight compounds, called siderophores, which bind Fe^{3+} with very high affinity and specificity, and host organisms of bacteria bind Fe^{3+} to proteins that serve as iron sources for bacteria. Energy-coupled transport systems bring Fe^{3+}, Fe^{3+}-siderophores, and heme across the outer membrane, the periplasm, and the cytoplasmic membrane into the bacterial cytoplasm. There, iron is released from the carrier molecules and incorporated mostly into heme and iron-sulfur proteins. Intracellular iron metabolism is poorly understood. The transport systems and the biosynthesis of the siderophores are regulated by pro-

teins, usually by Fur in Gram-negative bacteria, and DtxR and IdeR in Gram-positive bacteria. These proteins act as transcriptional repressors when loaded with Fe^{2+}. Additional regulatory devices control siderophore biosynthesis and transport. The Fec-type of regulation is of particular interest because it involves a novel mechanism in which the ferric siderophore binds to the outer membrane transport protein and from there induces transcription of the transport and biosynthesis genes in the cytoplasm. Another recently detected device is the regulation of genes positively regulated by Fur via RhyB, a small regulatory RNA. RhyB facilitates degradation of positively regulated mRNAs, which does not occur when Fe^{2+}-Fur represses RhyB synthesis.

1 Introduction

The insolubility of Fe^{3+} and the solubility of Fe^{2+} requires different modes of iron acquisition by bacteria. The insoluble Fe^{3+} hydroxide polymer must be solubilized by iron-complexing compounds, called siderophores, which are synthesized and secreted by bacteria and fungi. In eukaryotic hosts, iron is incorporated into heme or carried by proteins, in particular hemoglobin, hemopexin, transferrin, lactoferrin, and ferritin. Bacteria have developed specific mechanisms to mobilize heme released from the heme proteins and iron released from transferrin and lactoferrin. When Fe^{3+} is provided by transferrin and lactoferrin, ionic Fe^{3+} is transported across the cytoplasmic membrane. The Fe^{3+}-siderophore complexes are transported into the bacterial cytoplasm where iron is released from the siderophores and incorporated into iron proteins, such as iron-sulfur proteins and cytochromes. The number of different siderophores a bacterial species synthesizes is lower than the number of different Fe^{3+} siderophores it takes up (it is more economical to synthesize only a few siderophores and use siderophores from other bacteria and fungi than to synthesize all siderophores for every available type of transport system). If a bacterial cell is unable to transport the siderophores secreted by other competing microbes, iron deprivation could result; therefore, the bacteria require a broad spectrum of Fe^{3+}-siderophore transport systems. These systems consist of specific outer-membrane transport proteins that are necessary because of the low concentration of Fe^{3+}-siderophores and their size, which may exceed the diameter of the pores formed by the outer-membrane porins. Synthesis of siderophores and Fe^{3+}-siderophore transport systems are regulated. Transcription of siderophore synthesis genes and Fe^{3+}-siderophore transport genes is repressed when cells contain enough iron. Transport of Fe^{3+}, Fe^{3+}-siderophores, and heme across the cytoplasmic membrane of Gram-positive and Gram-negative bacteria is catalyzed by ABC transporters, which involve a binding protein and one or two transmembrane proteins linked to a membrane-associated ATPase. Fe^{2+}, in contrast, diffuses across the outer membrane and is transported across the cytoplasmic membrane by a mechanism that differs from that of Fe^{3+} and Fe^{3+}-siderophores.