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Review

Interplay between iron homeostasis and virulence: Fur and RyhB as major regulators of bacterial pathogenicity

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ABSTRACT

In bacteria–host interactions, competition for iron is critical for the outcome of the infection. As a result of its redox properties, this metal is essential for the growth and proliferation of most living organisms, including pathogenic bacteria. This metal is also potentially toxic, making the precise maintenance of iron homeostasis necessary for survival. Iron acquisition and storage control is mediated in most bacteria by the global ferric uptake regulator (Fur) and iron-responsive small regulatory non-coding RNAs (RyhB in the model organism *Escherichia coli*). While the role of these regulators in iron homeostasis is well documented in both pathogenic and non-pathogenic bacteria, many recent studies also demonstrate that these regulators are involved in the virulence of pathogenic bacteria. By sensing iron availability in the environment, Fur and RyhB are able to regulate, either directly or indirectly via other transcriptional regulators or modulation of intracellular iron concentration, many virulence determinants of pathogenic bacteria. Iron is thus both a nutritional and regulatory element, allowing bacteria to adapt to various host environments by adjusting expression of virulence factors. In this review, we present evidences that Fur and RyhB are the major regulators of this adaptation, as they are involved in diverse functions ranging from iron homeostasis to regulation of virulence by mediating key pathogen responses such as invasion of eukaryotic cells, toxin production, motility, quorum sensing, stress resistance or biofilm formation. Therefore, Fur and RyhB play a major role in regulating an adaptative response during bacterial infections, making them important targets in the fight against pathogenic bacteria.

Contents

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1. Introduction

Iron is the most abundant transition metal in the host, and this metal is an essential co-factor for many metabolic enzymes involved in biological reactions such as respiration, DNA biosynthesis, gene regulation and for tricarboxylic acid (TCA) cycle. Due to its poor solubility under aerobic conditions at neutral pH, iron is nearly inaccessible within animal hosts. Proteins such as ferritin, haemoglobin or transferrin chelate iron and thus can restrict the availability of this essential metal from invading pathogens. In addition to extracellular metal restriction mechanisms, host cells can also deplete metals from inside phagosomes. In order to acquire iron in iron-limiting environments, bacteria synthesize and secrete high-affinity iron chelating molecules, siderophores, which contribute to bacterial survival by sequestering iron from the host (Hood and Skaar, 2012; Porcheron et al., 2013). Although iron is detrimental for survival, it is also toxic under oxygen-rich conditions. Indeed, it is involved, through the Fenton reaction, in the production of highly reactive oxygen species (ROS) that damage nucleic acids, proteins and cellular membranes (Andrews et al., 2003). Iron is thus both essential and potentially toxic for most living organisms, making the precise maintenance of iron homeostasis necessary for survival. Many organisms have thus developed strong homeostatic systems that maintain intracellular iron concentration within a range that is not detrimental for the cell.

To respond to their environment, especially iron availability, response regulators alter expression of genes that promote bacterial survival. In the model organism *Escherichia coli*, iron acquisition and storage are controlled by the global ferric uptake regulator (Fur) protein and the small regulatory non-coding RNA (sRNA) RyhB. Under iron-rich conditions, Fe^{2+}-Fur acts as a negative regulator of *ryhB* and iron uptake genes by binding in a sequence-specific manner within the promoter region of target genes, efficiently preventing their expression (Fig. 1). The Fur-binding site of regulated promoters contains a consensus of three or four imperfect adjacent hexamers 5′-GATAAT-3′, although an alternative consensus sequence 5′-TGATAATNATTATCA-3′ has been proposed (Baichoo and Helmann, 2002). Fur-mediated sensing of iron availability is conserved across Gram-positive and Gram-negative bacteria (Andrews et al., 2003). When iron availability is limited [below 5–10 μM external iron concentration (Andrews et al., 2003)], Fur becomes inactive and subsequently the production of RyhB and iron acquisition systems is initiated in order to restore iron homeostasis (Fig. 1) (Massé and Gottesman, 2002). The RyhB-mediated regulation is initiated by the antisense pairing of the sRNA

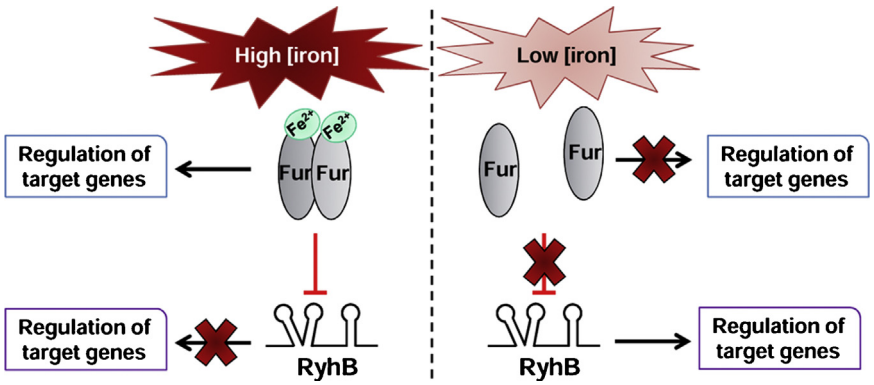

Fig. 1. Schematic representation of Fur and RyhB regulation. In iron-rich environments, the active Fur protein represses many genes as well as *ryhB*, resulting in deregulation of RyhB-specific target genes. In iron-poor conditions, Fur repression is relieved and *ryhB* is expressed, leading to regulation (activation or repression) of RyhB-specific target genes.