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New Transport Deals for Old Iron

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Abstract Maintaining iron homeostasis is a necessity for almost all organisms. Microorganisms such as *Escherichia coli* possess several systems for iron acquisition and storage. In recent years further systems have been discovered. These systems comprise the first characterized bacterial ZIP transporter, ZupT. ZupT is a transporter with broad substrate specificity and beside iron and zinc ZupT also transports cobalt or probably other divalent metal cations. Another novel bacterial iron transporter, EfeU, was recently found in *E. coli* and *Bacillus subtilis*. These EfeU permeases are the first characterized bacterial members of the OFeT-family of iron transporters that are well studied in yeast and in other lower eukaryotes.

Enterobactin, the primary catecholate-type siderophore from *E. coli* and other bacteria, is secreted from the cell in a two-step mechanism, functionally connecting the major facilitator protein EntS and an efflux-complex comprising the outer membrane exit channel protein TolC. Our knowledge of iron-transport systems was extended by the identification and characterization of an iron-efflux transporter, FieF, from *E. coli*. FieF is a member of the largest subfamily of cation diffusion facilitators (CDF). CDF proteins were previously known to be involved in detoxification of divalent transition metal cations such as Zn(II) or Cd(II) but probably participate in efflux of ferrous iron as well.

1 Introduction

For investigations on several general life processes the γ-proteobacterium *Escherichia coli* is broadly regarded as the primary prokaryotic model-

organism. Studies with *E. coli* also contributed significantly to our knowledge on homeostasis of essential transition metals. Interestingly, *E. coli* and other enteric bacteria possess most of the mechanisms of metal-homeostasis that can also be found in higher organisms. Yet, the advantage of the *E. coli* model is that it conjoins full genetic manipulability with simplicity of the experimental system, which is comprised of only two compartments confined by two membranes.

The plethora of systems for iron acquisition reflects the supreme importance of this element for almost all microorganisms. In *E. coli* there are, depending on the strain investigated, more than ten iron-uptake routes known. These encompass the siderophore pathways through the Fec, Fep, Cir, Fiu, Fhu, Ybt/Fyu, Iuc/Iut, or Iro proteins (reviewed by Braun 2003, also see Braun and Hantke, in this volume) or Chu for hemophore uptake (Torres and Payne 1997; also recently reviewed by Wandersman and Delepelaire 2004). In all these instances specific ferric-iron chelate-receptors of the outer membrane and ABC transporters for transport across the inner membrane are involved. Recently, an additional system of this composition, Fit, was identified in clinical *E. coli* isolate i484 (Ouyang and Isaacson 2006) but *fit* genes can be found in the genomes of other pathogenic strains as well.

While much work has been done on ferric-siderophore uptake into bacteria during the last few decades relatively little is known about how indigenous apo-siderophores leave the cell after biosynthesis. This piece of work is not devoted to ferric-siderophore uptake but it will briefly recapitulate what was elucidated for siderophore secretion within the last couple of years.

In addition to the ferric-siderophore transporters several proteins implicated in non-siderophore bound iron uptake were identified in *E. coli*. To differentiate these principal speciations of iron, a new terminology for the latter, elemental iron uptake, was introduced (Ollinger et al. 2006). A number of pathogenic *E. coli* strains take up elemental iron through ABC-transporters lacking an associated outer membrane receptor. These are the putative ferric-iron transporters AfuABC of enterohemorrhagic (EHEC) *E. coli* O157:H7 or the iron/manganese transporter SitABCD of uropathogenic (UPEC) *E. coli* CFT073 (Sabri et al. 2006). All known iron transport systems of *E. coli* and the chronology of their discovery are depicted in Fig. 1.

In contrast to the ATP-driven ferric-siderophore ABC-transporters another integral membrane protein involved in iron uptake, FeoB, possesses a N-terminal cytoplasmic domain that functions as GTPase (Marlovits et al. 2002). FeoB proteins are frequently found to be associated with iron uptake in different bacterial species (Kammler et al. 1993; Velayudhan et al. 2000; Robey and Cianciotto 2002). However, it is not known, whether GTP-hydrolysis actually drives iron transport or even whether FeoB is an iron transporter *per se* or not. Still, FeoB contributes to ferrous iron uptake in one way or another because *E. coli* strains expressing *feo* were shown to have increased cellular iron concentrations (Kammler et al. 1993; Grass et al. 2005a).