The Ferric uptake regulator (Fur) and iron availability control the production and maturation of the antibacterial peptide microcin E492

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Microcin E492 is a pore-forming bacteriocin with toxic activity against Enterobacteriaceae, which undergoes amyloid aggregation as a mechanism to regulate its toxicity. To be active, it requires the posttranslational attachment to the C-terminus of a glycosylated enterochelin derivative (salmochelin), a process carried out by the proteins MceC, MceI and MceJ encoded in the MccE492 gene cluster. Both microcin E492 and salmochelin have a proposed role in the virulence of the bacterial pathogen Klebsiella pneumoniae. Besides, enterochelin is produced as a response to low iron availability and its synthesis is controlled by the global iron regulator Fur. Since the production of active microcin E492 depends on enterochelin biosynthesis, both processes could be coordinately regulated. In this work, we investigated the role of Fur in the expression of the microcin E492 maturation genes mceCJI. mceC was not regulated by Fur as it occurs with its homolog iroB in Salmonella enterica. We demonstrated that mceJI along with the previously uncharacterized gene mceX are transcribed as a single mRNA, and that Fur binds in vivo to a Fur box located upstream of the mceX-mceJI unit. Also, we established that the expression of these genes decreased in a condition of high iron availability, while this effect is abrogated in a ?fur background. Furthermore, our results indicated that MceX acts as a negative regulator of microcin E492 structural gene expression, coupling its synthesis to the iron-dependent regulatory circuit. Consequently, fur or mceX overexpression led to a significant decrease in the antibacterial activity of cells producing

microcin E492. Altogether these results show that both the expression of microcin E492 maturation genes mceJI, and MceX the negative regulator of microcin E492 synthesis, are coordinated with the enterochelin production by Fur, depending on the iron levels in the medium.