Enterobactin-dependent iron uptake pathway as a gate for antibiotic Trojan horse strategies against *P. aeruginosa*

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Pseudomonas aeruginosa is a pathogenic bacterium responsible of severe infections affecting cystic fibrosis patients and immuno-compromised patients. This bacterium is naturally resistant to many antibiotics due to the low permeability of the envelope. In this context, siderophore-dependent iron uptake systems could be used as gates to deliver antibiotics into the bacterial inner space using a Trojan Horse strategy.[1]

P. aeruginosa excrete the siderophores pyochelin (Pch) and pyoverdin, however this bacterium proceeds also to "iron piracy" by expressing OMTs able to transport siderophores produced by other bacteria. The expression of proteins involved in the uptake of an exogenous siderophore is induced by the presence of the corresponding siderophore in the bacterial environment. In this context, enterobactin (Ent) is a siderophore produced by *Escherichia coli* but useable by *P. aeruginosa*. The Ent-dependent iron uptake pathway was well described in *E. coli* but was never exhaustively studied in *P. aeruginosa* so far. In this bacterium, ferric-Ent is assimilated by the OMT PfeA. We reported recently the synthesis of catechol siderophores azotochelin (BCS) and protochelin (TCS), secreted by *Azotobacter vinelandii* and the development of synthetic siderophore BCV and TCV mimicking respectively BCS and TCS.[2] Using RT-qPCR and proteomic approaches, we showed that P. aeruginosa sense the presence of Ent, BCS, BCV, TCS and TCV in the medium, leading to strong activation of the transcription and expression of PfeA. ^{55}Fe uptake assays confirmed that Ent, BCS, BCV, TCS and TCV imported iron(III) into P. aeruginosa via PfeA. In iron-restricted medium, uptake rates between 3.10^2 and 2.10^3 iron(III) atoms/bacterium/min were observed. This switching "ON" of the PfeA expression is associated with a repression of the Pch pathway genes.[3] This switch "ON" of PfeA expression and switch "OFF" of the Pch-dependent iron uptake pathway open new perspectives for antibiotic Trojan Horse strategies using catechol siderophores as vectors and the Ent-dependent iron uptake system as a transmembrane gate.

References

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