Transport of siderophore-drug conjugates in Gram-negative bacteria

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In Gram-negative bacteria, hydrophilic antibiotics cross the outer membrane by permeation through general or drug-specific porins. To overcome the particularly slow permeation of antibiotics in *P. aeruginosa and A. baumannii*, drugs can be conjugated to substrates which are taken up by dedicated active transport systems. A prominent example are siderophores, which are essential for iron acquisition in bacteria. Conjugation to drug molecules directs the uptake through siderophore specific TonB-dependent transport systems. Several siderophore drug conjugates have been developed recently, including BAL30072, a monosulfactam-siderophore conjugate active against problematic Gram-negative bacteria.

We have identified several TonB-dependent transporters involved in the uptake of siderophore drug conjugates in *E. coli*, *P. aeruginosa and A. baumannii*. PiuA, PiuD and PirA are the main TonB-dependent transporters for siderophore drug conjugates in *P. aeruginosa* [1.2] while orthologous transporters of PiuA and PirA were identified in *A. baumannii* [3]. The transport of siderophore-drug conjugates requires an inner membrane protein complex ExbB-ExbD-TonB. *P. aeruginosa* possess four TonB proteins. We showed that only TonB1 is involved in siderophore-drug uptake. Besides its own siderophores, pyoverdin and pyochelin, *P. aeruginosa* can also use xenosiderophores for acquiring iron. We will discuss how interactions with siderophores from *Azotobacter vinelandii* may influence the activity of siderophore-drug conjugates. These results should be useful for the development of novel Trojan Horse strategies.

References

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