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Bacterial drug transporters

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Abstract

An expression study of prospective bacterial drug-transporter genes has extended the range of substrates known to be transported and has identified an ABC-family drug transporter in Gram-negative bacteria

Significance and context

Among the components of drug-resistance mechanisms in bacteria are transmembrane proteins that mediate the active efflux of antimicrobial compounds from the bacterial cell. These proteins are collectively referred to as drug-resistance translocases, and five families have been identified so far: major facilitator (MF) family, small multidrug resistance family (SMR), resistance nodulation cell division family (RND), the ATP-binding cassette (ABC) family and the multidrug and toxic compound extrusion (MATE) family.

Nishino and Yamaguchi have used the complete genome sequence of *Escherichia coli* to identify and clone 37 putative drug-transporter genes. These were introduced into an *E. coli* mutant that lacked the major drug-efflux system AcrAB, and their effect on the cell's ability to translocate 26 representative antimicrobial agents and chemical compounds (normally exported by AcrAB) was tested. As well as presenting this detailed study of drug-resistance mechanisms in *E. coli*, Nishino and Yamaguchi have also constructed a drug-exporter gene expression library that could also be used to study drug resistance in other bacteria.

Key results

In the first instance, genes encoding the putative drug transporters, cloned into multicopy plasmids, were expressed under the control of their native promoters. Of 37 genes expressed in this way, 16 conferred increased resistance to particular antimicrobial compounds and/or chemicals. Subsequently, putative genes were cloned downstream of the isopropyl-α-D-thiogalactopyranoside (IPTG)-inducible *trc* promoter. This revealed 10 additional drug-efflux systems. Some drug translocases showed a broader spectrum of substrates than originally thought. For example, the *bcr* and *acrD* genes have been reported to confer resistance to bicyclomycin and aminoglycosides, respectively, but Nishino and Yamaguchi show that they also confer resistance to tetracycline, kanamycin, fosfomycin and acriflavin (for *bcr*) and

kanamycin and novobiocin (for *acrD*). They also show that the YbjYZ ABC transport system could transport erythromycin in addition to macrolides composed of 14- and 15-membered lactones. According to the authors, YbjYZ is the first ABC-type drug-resistance complex described in Gram-negative bacteria.

Links

The sequences of all the drug-resistance translocase genes in *E. coli* are available in the TIGR microbial database, which presents the entire genomic sequence of the *E. coli* strain used in this study.

Conclusions

A valuable drug-exporter gene-expression library has been constructed, which will be useful for an in-depth study of the mechanisms that lead to clinical resistance of bacterial species to antimicrobial compounds. It may, in addition, also contribute to the development of future chemotherapies.

Reporter's comments

Nishino and Yamaguchi present a thorough analysis of the drug-transport systems present in *E. coli*. This should enable us to understand drug resistance in *E. coli*better, and could be used to tackle related questions in other pathogenic bacteria that are clinically drug-resistant. It illustrates the power of combining knowledge of a complete bacterial genomic sequence with comprehensive functional analysis. More research is needed to investigate those genes that encode putative drug-resistance translocases, but for which no activity could be demonstrated using the antimicrobial compounds tested in this study. It should be considered that resistance to antimicrobial agents and other chemical compounds is not only determined by the presence of a collection of drug-resistance translocases but also by the complexity of the bacterial surface, which consists of a multiplicity of complex surface polysaccharides. This bacterial envelope may simply prevent the entrance of particular drugs; this has been proposed to explain the lack of sensitivity of *Mycobacterium* species, such as *M. tuberculosis* and *M. leprae*, to many antibiotics.

Table of links

Journal of Bacteriology

TIGR microbial database

References

1. Nishino K, Yamaguchi A: Analysis of a complete library of putative drug transporter genes in *Escherichia coli*. J Bacteriol. 2001, 183: 5803-5812. 0021-9193