

MEMBRANES & MOLECULES

ATTENTION : date et horaire exceptionnels !

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**Solve the "ESKAPE game" to combat antibiotic resistance:
CryoEM studies of a tripartite assembly of RND multidrug efflux pumps**

Abstract

The dangerous increase of resistant pathogenic bacteria (including *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), to most of available antibiotics emerges as a worldwide public health concern. It is urgent to develop original solution and focus on unconventional targets. Active efflux is one of the four main mechanisms by which bacteria exhibit resistance to antibiotic.

In Gram-negative bacteria, tripartite efflux pumps spanning the cell envelope can mediate the efflux of a wide variety of antimicrobial compounds, and participate to the antibiotic resistance. These efflux systems share a similar structural architecture composed of an inner membrane transporter and an outer membrane channel bridged by a periplasmic adaptor protein. The prototypical and clinically relevant efflux pump from *Pseudomonas aeruginosa*, MexAB-OprM is involved in the transport of drugs from the periplasm to the extracellular medium through the use of the proton gradient.

We have developed a method to reconstitute a tripartite assembly from native components using lipid nanodiscs. MexB and OprM inserted in lipid nanodisc self-assembled in the presence of MexA. The structure of tripartite system has been studied by electron microscopy [1]. The 3D structure analyzed by single particle cryoEM of the tripartite efflux pump at less than 4 Å resolution reveals a hexamer of MexA anchored in the lipid membrane, wrapping the periplasmic domains of MexB and interacting with OprM building a sealed channel suited for expelling drug out the cell. Structural details on the protein-protein will be detailed and the key parameters governing the assembly process will be discussed.

[1] Daury L, Orange F, Taveau JC, Verchère A, Monlezun L, Gounou C, Marreddy RK, Picard M, Broutin I, Pos KM, Lambert O (2016). Tripartite assembly of RND multidrug efflux pumps. *Nat Commun.* 7:10731.

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