INSTITUTIONEN FÖR KEMI OCH MOLEKYLÄRBIOLOGI

Structural and Functional Studies of Membrane Proteins

For Future Development of Antimicrobial Drugs

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Akademisk avhandling för filosofie doktorsexamen i Naturvetenskap, med inriktning kemi, som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras fredagen den 1:e februari 2019 kl. 10:00 i Karl Isaksson, institutionen för kemi och molekylärbiologi, Medicinaregatan 16, Göteborg.

ISBN: 978-91-7833-292-2 (Tryckt version)
ISBN: 978-91-7833-293-9 (PDF)
Tillgänglig via http://hdl.handle.net/2077/58373

Abstract

Antibiotic resistance is a world-wide occurring problem which threatens human health. Without development of any new and effective antibiotics, the rapid growth of antibiotic-resistant bacterial infections could put society in a situation resembling the pre-antibiotic era when a simple lung infection could kill a human being. This thesis presents two venues for targeting antibiotic resistance.

Pathogenic bacteria present in mucus rich environments are able to utilize host-derived sialic acid either as an alternative food source or by incorporating sialic acid to their surface glycoconjugates as a way to evade the host´s immune system. Hence, molecular mimicry enables bacteria to secure an ecological niche for survival. Transport of scavenged sialic acid into the cytoplasm of bacteria occurs through specific membrane bound sialic acid transporters.

The cell wall is an essential protective barrier for bacteria. The membrane bound enzyme MraY catalyzes the synthesis of lipid I, an intermediate step in the biosynthesis of peptidoglycan, the cell wall of bacteria.

This thesis presents work aimed to structurally and functionally characterize sialic acid transporters and MraY for future development of antibacterial drugs. Starting with a broad approach for expression and purification of sialic acid transporters resulted in low-resolution diffracting crystals of the *Pasteurella multocida* sialic acid TRAP transporter. In addition the X-ray crystallography structure of the sialic acid transporter SiaT from *Proteus mirabilis* was determined at 1.95 Å resolution in a substrate-bound outward-open conformation revealing a new sodium site. Furthermore, SiaT transporters have been characterized *in vivo* and the sialic acid specificity has been characterized for SiaT from *Staphylococcus aureus*. Structural comparison between MraY and the human homologue GPT have highlighted regions where to modify the natural product inhibitor tunicamycin to selectively target MraY. Further characterization of tunicamycin analogues identified potent inhibitors with reduced eukaryotic toxicity.

Keywords: Sialic acid transporters, SiaT, MraY, Tunicamycin, Antibiotic resistance