Integral membrane proteins: fundamental medical biochemistry studies towards novel antibiotic targets

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English Summary

Membrane proteins (MPs) are found in the cell membrane and act as a window to the outside world. With the help of MPs, the cell can see what is in the surrounding environment, take up the nutrients it needs for growth, and release toxins and waste products. Through the MPs, the cell can also communicate with other cells and defend itself against intruders.

About a third of all genes contain the code for MPs and half of all drugs on the market work by affecting these proteins' functions. Nevertheless, despite this importance, we know relatively little about MPs, at least compared to other proteins. For example, only a few of all known 3D protein structures are MPs. To accelerate drug discovery, we need a better understanding of how MPs work.

In this thesis, MPs in bacterial energy metabolism are investigated. This metabolic pathway has gained attention as a highly promising target pathway for next-generation antibacterials, in particular for combating Mycobacterium tuberculosis.

In the first part of this thesis, we show that targeting two MPs in the respiratory chain of this pathogen leads to a synergy that can be exploited for the design of a new anti-mycobacterial regimen. Based on this finding, a versatile phenotypic assay is utilized to evaluate the mechanism of action of individual inhibitors targeting the respiratory chain or their combinations. As the use of drug combinations rather than single drugs is essential for avoiding the rapid emergence of resistance, these results can contribute to improving tuberculosis chemotherapy.

In the second part of this thesis, MPs from energy metabolic pathways are purified and biochemically characterized. For these experiments, *Escherichia*

coli is used as a model. In particular, the importance of the detergent employed to isolate the MP, and the role of the lipid environment is investigated. In this regard, a new method to investigate purified MPs in an optimally active state is described. Insights gained here can be utilized for the biochemical characterization of MPs from pathogenic bacteria and may open up new opportunities for the discovery of drugs that are urgently needed to combat drug-resistant bacteria.