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

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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.

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Amer H. Asseri

Curriculum vitae

Amer Asseri was born on the 5th of May 1981 in Mahayl, Saudia Arabia. After finishing secondary education, he started his study in biochemistry at the Faculty of Science at King Abdulaziz University in Jeddah and graduated in 2004 with a Bachelor's degree. After graduation, he worked as a medical lab technician in the Saudi German Hospital in Jeddah for two years. From 2007 until 2013, he worked as an academic technician at King Abdulaziz University. During that period, he obtained his master's degree (2011), in technical anatomy and histology. He has published two scientific books and other scientific papers in the field of histology and biochemistry. In 2013 he became a lecturer in the Biochemistry Department – Faculty of Science at King Abdulaziz University. In the period between 2016-2020, he started a Ph.D. journey on Medical Biochemistry at the Department of Molecular Cell Biology at Vrije Universiteit Amsterdam, under the supervision of Dr. Dirk Bald and Prof. Holger Lill. Asseri's project at VU Amsterdam was embedded within the Amsterdam Institute of Molecular and Life Sciences (AIMMS), a research center that uniquely joins Molecular and Life Sciences and aims at the elucidation of molecular mechanisms of diseases and the development of novel therapeutics. There, his studies mainly focused on the biochemical characterization of bacterial membrane proteins and their role as novel drug targets. During his Ph.D., he was involved in a research collaboration with the Membrane Bioenergetics Group at Delft University of Technology (a top technology university in the Netherlands) headed by Dr. Duncan McMillan. After obtaining his Ph. D., Asseri will return to his country to start his career as an assistant professor and researcher at King Abdulaziz University.

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