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Biochimica et Biophysica Acta 1610 (2003) 1
BIOCHIMICA ET BIOPHYSICA ACTA
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Editorial

# Preface: overexpression of integral membrane proteins

Membrane protein structure determination remains one of the great challenges in structural biology. Only 0.3% of the atomic resolution structures in the Protein Data Bank represent integral membrane proteins, yet about 30% of all genes encode membrane proteins. Knowing their structures will be essential to understand diverse biological systems such as energy production, signal transduction and intercellular communication; the pivotal role of membrane proteins in these processes makes them key targets for therapeutic intervention in both chronic and infectious diseases. However, each step on the road to determining the structure of a membrane protein can be a difficult and time-consuming exercise. The first step of heterologous overexpression can be especially challenging, particularly when the overexpression of mammalian integral membrane proteins is considered.

In compiling this selection of papers for this Special Issue on 'Overexpression of integral membrane proteins', we have tried to consider many aspects relating to this topic, both from the perspective of what can affect overexpression, and from the point of view of the subsequent purification, crystal formation and structural analysis.

Clearly, the mechanism of membrane protein insertion into the membrane and the subsequent folding steps are of paramount importance for the production of functional membrane proteins, although this has not been thoroughly studied in the context of heterologous overexpression. The lipid environment is also crucial for the functionality of membrane proteins, influenced both by the bulk effects of lipids and through extremely specific lipid–protein interactions. Refolding of membrane proteins is also a potential route to providing milligrams of protein for crystallisation, and this has the advantage of bypassing limitations in the insertion of the protein into the membrane; both empirical and rational refolding approaches are being applied to the production of membrane proteins. The choice of detergent, mimicking the lipid environment, is a key aspect of purification and crystallisation of membrane proteins. Likewise, crystallisation of membrane proteins is not only influenced by the detergent environment, but can be also improved by enlargement of the hydrophilic surface through co-crystallisation with antibody fragments. All of these aspects are covered by several contributions to this Special Issue.

The goal of publishing this collection of reviews on membrane protein expression is to aid researchers in the choice of a suitable expression system for their favourite proteins. This can still be a difficult task, but knowing that a related protein can be functionally expressed in a particular organism is always encouraging, despite not guaranteeing success in obtaining milligrams of the homologue. The shift towards 'genomic approaches' of expressing many related membrane proteins from different organisms in the same host is currently gaining popularity, not least because of the recent spectacular successes in producing structures of bacterial channels and transporters. The current challenge is to translate this strategy into successful determination of the structure of mammalian membrane proteins.

We hope that this compilation will provide a basis for choosing the best expression system for a given membrane protein. But we also hope that the related articles will provide some food for thought. How can we improve these expression systems? If we change the translocon in bacteria, can we improve the production of mammalian integral membrane proteins? Should we co-express particular molecular chaperones? Is the lipid environment optimal or should we engineer bacteria or yeast to synthesize specific mammalian sterols or lipids? The contributions to this Special Issue illustrate the substantial progress that has been made towards understanding which factors influence heterologous membrane protein expression, and in the subsequent steps involved in determining the structures. However, only once the overproduction of functional membrane proteins becomes easier, will we see exponential growth in the number of atomic resolution structures of integral membrane proteins.

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doi:10.1016/S0005-2736(02)00706-X