Proceedings of the ASME 2008 Summer Bioengineering Conference (SBC2008)
June 25-29, Marriott Resort, Marco Island, Florida, USA

SBC2008- 192724

LIPID PHASE BEHAVIOR. DATABASES, RATIONAL DESIGN AND MEMBRANE PROTEIN CRYSTALLIZATION

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INTRODUCTION

The relationship that exists between structure and function is a unifying theme in my varied biomembrane-based research activities. It applies equally well to the lipid as to the protein component of membranes. With a view to exploiting information that has been and that is currently being generated in my laboratory, as well as that which exists in the literature, a number of web-accessible, relational databases have been established over the years. These include databases dealing with lipids, detergents and membrane proteins. Those catering to lipids include i) LIPIDAT, a database of thermodynamic information on lipid phases and phase transitions, ii) LIPIDAG, a database of phase diagrams concerning lipid miscibility, and iii) LMSD, a lipid molecular structures database. CMCD is the detergent-based database. It houses critical micelle concentration information on a wide assortment of surfactants under different conditions. The membrane protein data bank (MPDB) was established to provide convenient access to the 3-D structure and related properties of membrane proteins and peptides. The utility and current status of these assorted databases will be described and recommendations will be made for extending their range and usefulness.

Much of our lipid structure-function work focuses on the monoacylglycerols (MAGs), chosen because of their chemical simplicity and the wealth of liquid crystalline states, or mesophases, they form as a function of temperature and composition. A range of *cis*-monounsaturated MAGs have been synthesized in the lab where the chain length and position of unsaturation along the chain have been modified systematically. Phase diagrams for each have been constructed using small-angle X-ray diffraction which provides definitive phase identification and microstructure characterization. The information content of this collection of phase diagrams has been mined and used to rationally design new MAGs with desired mesophase properties for application in membrane protein crystallization. Successes we have had with this approach will be described.

Our latest work addresses membrane protein structure and function where structure determination is done crystallographically. For this purpose, diffraction-quality crystals of the target membrane protein must be procured. This represents a major, rate-limiting step on the route that leads to structure with the inevitable insights into function that structure provides. We have made important contributions toward developing and understanding the molecular basis for membrane protein crystallogenesis using lipidic mesophases by what is referred to as the *in meso* method. This bilayer-based method accounts for over 10% of the membrane protein structures in the Protein Data Bank and received notoriety recently having being used in the high-resolution structure determination of a human engineered β2-adrenergic G protein-coupled receptor. *In meso* crystallogenesis involves an initial reconstitution of the purified protein into a bicontinuous mesophase followed by nucleation and crystal growth triggered by changes to the chemical composition of the bathing lyotrope. Material transport dictates whether or not crystallization occurs and, eventually crystal quality. Our current understanding of and attempts to control the fascinatingly complex physical chemistry governing *in meso* crystallogenesis will be described.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Institutes of Health (GM75915), the National Science Foundation (IIS-0308078) and Science Foundation Ireland (02-IN1-B266).