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Membrane fusion: a riddle, wrapped in a mystery, inside an enigma

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Membrane fusion is a fundamentally important process required for transport of cellular cargo. It is essential - for example - in neurotransmission and blood glucose control.

The 2013 Nobel Prize in Medicine or Physiology was awarded to Rothman, Schekman and Südhof for their discovery of the molecular machinery supporting SNARE-mediated membrane fusion. This machinery is conserved from yeast to humans. Consequently, we know that two protein families are required for every membrane fusion event:
(i) SNARE proteins, and
(ii) Sec1/Munc18 (SM) proteins.

The SNARE proteins are located on different membranes and zip together in response to specific signals to bring the two membranes into close proximity. Formation of the SNARE protein complex is thought to be essential for providing the energy required for the two membranes to fuse.

The role of the SM proteins has proven much more difficult to define. Some reports describe a positive regulatory role for SM proteins on SNARE complex formation and membrane fusion. Other reports conclude a negative regulatory role.

This presentation explores the molecular basis of SNARE-mediated membrane fusion. A range of complementary biophysical methods were used including synchrotron MX and SAXS, as well as SANS with contrast-matching and chemical cross-linking with mass spectrometry. These technologies have allowed us to probe the atomic interactions and conformational changes that occur in these fascinating yet enigmatic nano-machines.

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