M09.0A Endocytosis and Exocytosis

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Attendance: 123

During the past two years, dramatic progress has been made to elucidate the structures of key components of the machinery's responsible for membrane vesicular traffic. The fusion machinery is responsible for diverse processes, such as calcium-triggered neurotransmitter release, protein secretion, and hormone release. Sutton presented the structures of the synaptic fusion complex (a SNARE complex prototype) and the calcium sensor synaptotagmin. The free energy released by the assembly of the SNAREs probably leads to close proximity and eventual fusion of the vesicle and target membrane. Synaptotagmin probably regulates the assembly of the synaptic fusion complex through interactions between its C2 domains, the SNARE complex and the vesicle membrane. Weis presented the structures of the D2 and N-terminal domains of N-ethylmalemide-sensitive factor (NSF) (these two domains were solved independently in the Weis and Brunger laboratories) and proposed a speculative mechanism for its function. NSF is an ATP-driven chaperon that dissociates the SNARE complex so that its components can engage into another fusion cycle. The D2 and N domain structures of NSF have similarities to domains of other ATP-driven molecular motors. Equally dramatic progress has been made to elucidate the structures of proteins involved in vesicle formation and cargo selection during clathrin-mediated endocytosis. Clathrin is recruited to the plasma membrane, where it forms the coat that drives vesiculation and recruitment of the adaptor molecules that capture transmembrane receptors for vesicular traffic. Ter Haar presented the peptide-in-groove model to describe the structure of complexes between the N-terminal domain of clathrin (a β-propeller) and the clathrin-box binding motifs responsible for the recruitment of the adaptors βarrestin2 and AP-3 to the clathrin coat. Hwang discussed the structure of a leg-segment of clathrin. Evans presented structures of several domains of the endocytic adaptor AP-2 complex, including the α-ear domain and part of the μ2 domain. The μ2 domain structure was solved in complex with peptides corresponding to the tyrosine-based sorting signals of a number of proteins and a general model for recognition was presented. The transferrin receptor is recruited by AP-2 adaptors and undergoes multiple rounds of clathrin-mediated endocytosis to import iron-loaded transferrin and is also a key component in human hereditary hemochromatosis, a prevalent genetic disease among caucasians. Lawrence concluded the session by presenting the structure of the complete ectodomain of human transferrin receptor and proposed a model to explain the recognition of transferrin by its receptor.

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