THE ROLE OF RAB PROTEINS IN VESICLE TRANSPORT AND FUSION

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The Ras-like Rab GTPases are low molecular weight GTP-binding proteins (20-40 kDa) that regulate vesicular transport between the compartments of endo- and exocytic pathways in eukaryotic cells, and are implicated in the control of vesicle docking and fusion. More than 60 mammalian Rab proteins have been identified. Different Rab proteins were localized in early (Rab 4, Rab5), late (Rab7, Rab9) and recycling endosomes (Rab4, Rab11), and also in TGN (Rab6, Rab11) [Somsel Rodman and Wandinger-Ness, J. Cell Sci. 113 (2000) 183, Pfeffer, Trends Cell Biol 11 (2001) 487]. The best known is the Rab5 protein and its effectors, which control early endocytic traffic [Somsel Rodman and Wandinger-Ness, J. Cell Sci. 113 (2000) 183]. A key regulator of late endocytic membrane transport leading from early endosomes to degradation pathways is Rab7 [Feng et al., J. Cell Biol. 131 (1995) 1435, Mukhopadhyay et al., J. Biol. Chem. 272 (1997) 13055]. Rab5 and Rab7 have also been implicated in the maturation processes of phagosomes containing intracellular pathogens including M. tuberculosis and L. pneumophila [Fratti et al., J. Cell Biol. 154 (2001) 631].

Rab GTPases cycle between an inactive, soluble GDP-bound form and an active, membrane-bound, GTP-bound form. This lecture will discuss the mechanisms by which vesicle docking and fusion occurs, including various factors such as tethering proteins (early endosome antigen 1), PI-3 kinases (hVPS34) and SNAREs [Waters and Pfeffer, Curr. Opin. Cell. Biol. 11 (1999) 453]. Rab association with membranes is mediated by prenyl (geranylgeranyl) post-translational modification. Deficiencies in the Rab prenylation machinery can lead to different diseases such as choroideremia and Hermansky-Pudlak syndrome [Pereira-Leal et al., FEBS Lett. 498 (2001) 197].


The phylogenetic tree of Rab will be extended by the Rab7 gene fragment recently identified by us in the unicellular Paramecium: the deduced amino acid sequence revealed a 79% identity to N-terminal region of human Rab 7. The cloned gene fragment encodes the conservative regions of the effector and nucleotide-binding domains, including so-called RabF motifs that cluster in and around the switch regions. Switch regions in Rab families are important in the determination of binding specificity to protein partners and are conserved across species [Pereira-Leal and Seabra, J. Mol. Biol. 313 (2001) 889].