42. THE SMALL GTP BINDING PROTEIN RalA MEDIATES SIGNALLING PATHWAYS IN BRAIN AND TESTIS VESICLE TRAFFICKING

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A major vesicle traffic pathway in cells is the secretory pathway, which targets proteins destined for secretion out of the cell or for integration into the plasma membrane. Newly synthesised proteins processed by the Golgi are incorporated into different secretory vesicles, which are targeted to the membrane or to various types of endosomes. Another major type of vesicle traffic is endocytosis, where surface receptors are internalised and sorted via the endosomal system for degradation or recycling. Vesicle traffic is tightly controlled by molecular mechanisms that are directed by small GTPases. RalA is a small GTPase involved in the regulation of vesicle trafficking events. It is abundant in brain, testes and platelets. RalA is activated by growth factors and is involved in cell proliferation, oncogenic transformation, filopodia formation, and vesicle trafficking events. We find Ral on at two types of intracellular vesicles: the recycling endosome and a new ring-shaped vesicle that may be involved in the secretory pathway. RalA cycles in a controlled manner between "active" GTP-bound and "inactive" GDP-bound forms. The active form binds to two specific proteins. The first is RalBP1, which has a role in endocytosis of activated receptors. The second is the exocyst complex, which is involved in targetting secretory vesicles to sites of secretion. Ral signalling via the exocyst is involved in the regulation of both exocytosis and filopodia formation. Although Ral has a number of activator proteins, it was thought not to have any inhibitory factors. Through mass spectrometry we have discovered that the protein ERp57 binds inactive Ral. ERp57 is a redox-regulated RalGDI, a type of inhibitory regulator that keeps Ral in its GDP-bound (inactive) state. ERp57 only inhibits RalA when it is in its oxidised form, a state that is generated by oxidative stress in cells. GDI proteins for other small GTPases are important in the regulation of vesicle traffic, so ERp57 is likely to play an important role in RalA-dependent vesicle traffic. Therefore Ral is at the centre of a signalling complex regulated by ERp57 and which signals to either the exocyst or RalBP1. This complex directs intracellular vesicle traffic from recycling endosomes to the plasma membrane and for the secretory pathway.

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