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Rab 1

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Gene Symbols: Rab1a, Rab1b

1. General Function

Rab1 is a small GTP binding protein that is expressed in virtually all mammalian cells, fish, worms and flies and is homologous to the yeast protein Ypt1 (3). It is essential for ER to Golgi transport and has also been implicated in intra Golgi transport (22, 30). There are two isoforms Rab1a (205 aa) and Rab1b (201aa) which are 92% identical at the amino acid level with most differences in the carboxyl terminus (28). These two isoforms are generally localized in the same cellular regions and have similar biochemical properties and functions. Rab1a may also play a role in transcytosis (14). In addition to localization by immunoflourescence in tissue culture cells, Rab1a has been localized by immunogold labeling to vesicles between the ER and Golgi region and over Golgi stacks in NRK cells (23).

The vesicular transport activity of Rab1 is dependent on its GTPase activity as a GDP bound mutant form, Rab1aS25N and the nucleotide free mutant (N124I) block transport from ER to Golgi and lead in some cases to disruption of the Golgi (18, 27). Similar effects were seen with addition of Rab1b antibodies (19) and overexpression of Rab1b mutants with disruption of the Golgi structure and release of Beta-COP. This latter finding indicates a role for Rab1b in COP I coat assembly. Note COP II coat formation is not affected.

Regulation of Rab1 activity

Only a little is known of how Rab1 is regulated. Rab1, similar to other Rabs cycles between a membrane bound and cytosolic location with cytosolic Rab existing in the GDP-liganded state bound to Rab GDI as a 80 kDa complex (19). It is not clear how many GEFs are present and act on Rab1. The best known is TRAPP, a multimeric protein complex of which several subunits contribute to Rab1 GEF activity (5). A Rab1 GAP has been identified and is the Tbc1D20 protein (10, 25). Overexpression of Tbc1D20 blocked ER to Golgi transport of VSV-G protein and caused disruption of the Golgi. More is known of Rab1 effectors. The first identified effector was p115, a tethering factor that binds to the GTP-bound form of Rab1 (1). Rab1 recruits p115 to COP II vesicles and then p115 interacts with Golgi proteins. Subsequently Rab1 was shown to interact directly with the Golgi proteins GM130 (17) and giantin (7) as well as MICAL-1 a

scaffolding protein which links to the cytoskeleton (28) and Iporin which also links to GM130 (6). Golgi-specific brefeldin A resistance factor 1 (GBF1) is a new effector of Rab1 that modulates Arf activation (16).

Rab1 function in cells

Rab1 plays a role in the early steps of the protein secretory pathway. Early studies described this as vesicular transport from ER to Golgi (18, 27). More detailed later studies have shown the existence of specific ER exit sites where COPII coated vesicles form enclosing ER content proteins (4). The COPII complex is composed of the small GTPase Sar1, a inner Sec23/Sec24 complex and a outer Sec13/Sec31 complex (26). COPII recruits the TRAPP complex which among other things functions as a GEF for Rab1. The GTP liganded Rab1 binds to Sec23. Overexpression of dominant negative forms of Rab1, knockdown of Rab1 by siRNA, and antibodies to Rab1 all cause dissociation of COPII vesicles and Golgi proteins (18, 19, 27).

In mammalian cells, COPII vesicles fuse to form a intermediate compartment known as the Vesicular tubular complex or ERGIC (ER Golgi Intermediate Complex). COPII dissociates and is replaced by COPI. COPI vesicles are involved in sorting what goes on to the Golgi and what recycles back to the RER. COPI also redistributes through the cell when Rab1 function is inhibited (2).Thus Rab1 plays an important although not fully understood role in RER to Golgi transport. It is not clear whether there are any differences in function between Rab1A and Rab1B and different studies have used either protein usually without comparing the two forms.

Functional Rab1 is also important for biogenesis and maintenance of the Golgi (24). Overexpression of Rab1 increases Golgi size and modifies gene expression (21). In addition Rab1 has been shown to play an obligatory role in the trafficking of G protein coupled receptors to the cell surface (31, 32). In melanocytes, Rab1a is localized to the surface of melanosomes and is necessary for anterograde movement along microtubules (13). It has also recently been shown to be necessary for autophagosome formation (33). Finally, Rab 1 has been shown to be the target of the intracellular pathogen Legionella pneumophila which hijacks Rab1 to create a vacuole in which the bacteria replicates (12). Legionella LepB protein acts as a GAP to inactivate Rab1(15).

2. Rab1 in Pancreas

Surprisingly there has been little work evaluating the function of Rab1 in exocrine pancreatic cells. Rab1 was identified in rat pancreas microsomal subfractions by immunoblotting (23). Rab1 has also been observed in proteomic analysis of dog and rat pancreas RER (8, 29) and in isolated rat zmyogen granules where it was localized to the external face of the granule (9). It is not clear whether this presence in granules is due to a functional role, the fact that a fraction of Rab1 escapes recycling and moves down the secretory pathway or because it is present in contaminating ER or Golgi membranes. Because of the specialization of acinar cells for protein secretion it seems likely that Rab1 will play a similar role in ER to Golgi transport in acinar cells as observed in cultured cells. However, since many of these studies used the transport of VSV-G, a membrane protein as a marker, it would be interesting to see if similar effects were seen on digestive enzyme transport.

3. Tools for Study of Rab1

a. cDNA

cDNA clones for human Rab1a and HA tagged Rab1a in pcDNA 3.1 are available from the Missouri S & T cDNA Resource (www.cdna.org/). Several studies have been published using constitutively active (Rab1 Q67L) or dominant negative (Rab1a S25N; Rab1b S22N; Rab1b N121I) mutant plasmids based on mutating residues known to be

important in Ras (2, 18, 27). Note the residues mutated are slightly different for Rab1a and 1b.

b. Antibodies

Rabbit polyclonal and mouse monoclonal antibodies have been raised against both full length expressed protein and peptide sequences (20), Santa Cruz sells rabbit and goat poyclonal antibodies against Rab1. One of these, a rabbit antibody against the carboxyl terminal (sc-311) should be specific for Rab1a. However we have not tested any of them. See Ref (24) for other information on antibodies.

c. Mouse lines

None.

d. siRNA

Rab1B silencing using siRNA has been described as a method (11).

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