

# Beyond clathrin: GRAF1-mediated endocytosis



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Cell migration requires the coordination of membrane and protein redistribution, cytoskeletal changes, and focal complex/adhesion turnover.

The mechanisms by which this coordination occurs are unclear. Rho family small G-proteins have been shown to be master regulators of cell migration.

Here we show that a Rho GAP domain-containing protein, GRAF1, regulates a major clathrin-independent endocytic pathway responsible for the internalisation of bacterial exotoxins, GPI-linked proteins, and extracellular fluid. We show that GRAF1 localises to PtdIns(4,5)P-2-enriched tubular and punctate lipid structures in vivo via its N-terminal BAR and PH domains, and that GRAF1 binds dynamin, GIT1, FAK, and PAK2. These latter proteins promote the disassembly of focal adhesions, placing GRAF1 in a position whereby it may coordinate cell migratory events. We show that GRAF1 is necessary for turnover of focal complexes/adhesions, that GRAF1-dependent endocytosis occurs from these sites in a small G-protein dependent manner, and that GRAF1 is necessary for cell migration. GRAF1 and its close homologue Oligophrenin are mutated in human diseases (Acute Myeloid Leukaemia and mental retardation respectively), and our results provide insight into the pathogenesis of these diseases. We have also shown how other BAR domain-containing proteins, and small G-proteins, may regulate endocytic pathways in other cell types through membrane curvature generation and stabilisation.



Department of Biological Sciences  
Seminar Announcement

**Date:** Tuesday, 8 July 2008  
**Time:** 11 am  
**Venue:** DBS Conference Room  
**Host:** A/P Low Boon Chuan