

**P034** Identification of a Ras effector associated exclusively with the early endosome.

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There is strong evidence that Ras proteins (H-Ras, N-Ras, K-Ras4A and 4B) traffic through the endosomal network. Ras can undergo rapid internalisation following receptor stimulation, and is present on clathrin-coated vesicles purified from PC12 cells and dorsal-root-ganglion neuronal cells, as well as endosomes isolated from rat liver and insulin-stimulated fibroblasts. When associated with endosomes Ras can be active, and signals through the ERK/MAPK cascade. Interestingly, Ras may also regulate endosomal membrane traffic. RIN1, a plasma membrane exchange factor for Rab5, has been identified as a Ras effector, which by allowing active Ras to induce the activation of Rab5 regulates the rate of endocytosis and early endosomal fusion. Although these data are consistent with a role for endosome associated Ras, a major conceptual problem is that of an "innocent bystander". As endosomes originate from the plasma membrane, one can argue that it is not surprising that the Ras machinery is also present on endosomes. This makes distinguishing the role of endosomes in Ras signalling from that of the plasma membrane extremely difficult. Recently we have identified a new Ras effector – this protein binds the GTP-bound but not GDP-bound form of Ras – that is localised exclusively to the early endosome. In cells suppressed for this protein growth factor signalling through the ERK/MAPK cascade is perturbed and the cells take on a transformed morphology. These data suggest that this protein may regulate Ras signalling, possibly through an ability to mediate the sorting of Ras through the endocytic pathway.