

P029 Subcellular Targeting of Rab GTPases

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Small GTPases of the Rab family are key regulators of membrane trafficking. Each Rab shows a characteristic subcellular distribution, and may serve as an important determinant of organelle identity. The molecular mechanisms responsible for targeting Rabs to specific intracellular compartments, however, remain poorly understood. The divergent C-terminal hypervariable region was postulated to contain Rab targeting information. Here we generated a series of hybrid Rab proteins by exchanging the hypervariable domains of Rab1a, Rab2a, Rab5a, Rab7, and Rab27a, and analysed their subcellular localisations. We found that the various hybrid proteins retained their targeting to the parent organelle and were functionally active. We conclude that the hypervariable region does not contain a general Rab targeting signal. Furthermore, we identified other regions within the RabF and RabSF motifs that are required for specific targeting of Rab27a to secretory granules or melanosomes, and Rab5a to endosomes. We observed only partial overlap between targeting-determining regions in the Rab proteins examined, suggesting that Rab recruitment may be complex and at least partially Rab-specific. Mutations in these targeting-determining regions induced localisation to the ER, an observation which further strengthens our previous finding that ER/Golgi membranes serve as the default location for Rabs that have lost targeting information.