

P028 A de-/re-acylation cycle regulates the compartmentalised localisation and activity of palmitoylated Ras isoforms **Oliver Rocks^{1,2}, Anna Peyker², Martin Kahms¹, Peter J. Verveer², Carolin Koerner¹, Maria Lumbierres³, Jürgen Kuhlmann¹, Herbert Waldmann³, Alfred Wittinghofer¹ and Philippe I.H. Bastiaens²**

*¹Department of Structural Biology and ³Department of Chemical Biology, Max-Planck-Institute for Molecular Physiology, Otto-Hahn-Straße 11, 44227 Dortmund, Germany
²European Molecular Biology Laboratory, Meyerhofstraße 1, 69117 Heidelberg, Germany*

The specific localisation of Hras and Nras and palmitoylated proteins in general is controlled by a constitutive de-/reacylation cycle that drives their rapid exchange between the PM and the Golgi. Depalmitoylation redistributes farnesylated Ras throughout the cell where it is in rapid equilibrium between the membranous and cytosolic phase. Membrane anchoring by repalmitoylation occurs at the Golgi from where Ras is redirected to the PM via the secretory pathway. This continuous cycle of membrane trapping and release in different subcellular localisations prevents PM Ras from spill-over to endomembranes, thus maintaining the specific PM/Golgi compartmentalisation. The stability of palmitoylation dictates both the speed of retrograde PM to Golgi trafficking and the steady-state distribution of palmitoylated proteins between these compartments. The de-/reacylation cycle also initiates Golgi Ras activation upon growth factor stimulus by transport of Ras-GTP from the PM: The speed of retrograde transport of different Ras proteins correlates with their respective Golgi activation kinetics and inhibition of palmitoylation and thus retrograde transport blocks Golgi Ras activation. Dual or monopalmitoylation of Hras or Nras result in different de-/reacylation kinetics, and this ultimately determines Ras isoform-specific activation responses in cells. Faster palmitate turnover of Nras result in a shorter PM dwell time, faster intercompartment exchange and more pronounced Golgi localisation. Dynamic palmitoylation thus both specifies the subcellular localisation and allows the spatio-temporal control of Ras activity patterns.