

The spatial organization of growth factor signaling systems in cells

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THE cell operates out of equilibrium to maintain its organization and counter the tendency to increase entropy. This also manifests in the spatial patterning of signaling molecules in cells that thereby can properly process extra-cellular information. As an example of this I will describe the dynamic cycles that maintain the spatial organization of the Ras proto-oncogene products. To sample both the diffusion and reaction dynamics of these spatially organizing systems, we have used a palette of advanced microscopic imaging approaches that quantitatively report on intracellular molecular dynamics and reactions. By combining this with chemical biological approaches we found that the maintenance of palmitoylated Ras isoform localization and signaling depends on kinetic trapping of the proteins at the Golgi by means of S-palmitoylation and distributed S-depalmitoylation. Interference with this dynamic Ras cycle with small molecules provides a means for affecting Ras localization and thereby its activity and coupling to effectors. Long-term inhibition of cellular thioesterase activity causes an entropy-driven loss of the precise steady-state localization of palmitoylated Ras proteins and as a consequence down-modulates oncogenic HRasG12V induced Erk signaling from the plasma membrane in transformed MDCK-f3 cells. This results in endothelial to mesenchymal back-transformation of these cells. This discussion will be extended to the spatial regulation of Ras family proteins, with an accent on the spatial regulation of non-palmitoylated KRas. From this I will argue that interference with spatial cycles may be a valuable strategy for the development of therapeutic modulators of pathological signaling via oncogenic Ras proteins.