Ras nanoclusters: lipid-based assemblies for signal processing

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My lab studies the plasma membrane nanoscale organization of Ras proteins using quantitative electron microscopy and FLIM-FRET microscopy. We have shown that the ubiquitously expressed Ras isoforms, H-Ras, K-Ras and N-Ras operate in spatially non-overlapping, transient nanoclusters. Approximately 40% of each Ras protein assembles into nanoclusters of ~6 proteins, with radii of ~9nm and lifetimes of <1s. Furthermore H-, K- and N-Ras all undergo GTP-regulated segregation, such that GTP- and GDP-nanoclusters of each isoform are also spatially segregated. Since Ras effector activation is restricted to Ras-GTP nanoclusters interesting emergent properties flow from the imposition of nanocluster spatiotemporal dynamics on Ras signal transmission. On one level the system operates as an analog-digital-analog converter to deliver high fidelity signal transmission in the Raf-MAPK circuit with signal gain being controlled by the Ras nanocluster fraction. Lipid mapping experiments also show that different Ras nanoclusters have distinct compositions revealing isoform-selective lipid sorting. The anionic phospholipid phosphatidylserine (PS) is an obligate structural component of K-Ras nanoclusters. Our most recent experiments now reveal that PS spatial organization, and thereby K-Ras nanoclustering, are sensitive to transmembrane potential, revealing a previously unsuspected mechanism whereby electrical signals can control the gain in K-Ras signaling circuits.