Non-canonical Ras output: RalGEF $\rightarrow$ Ral and segregating signals

Abstract:
We investigate novel components and organizational principles of signal transduction networks. EGF induces certain C. elegans epithelial cells to form the 3°-3°-2°-1°-2°-3° pattern of cell fates. Interpretation of a dose-sensitive EGF-EGFR gradient is mediated by LET-60/Ras switching effectors, from the canonical Raf-MEK-ERK MAP kinase cascade to promote 1° fate to the non-canonical RalGEF-Ral to promote 2° fate. We observe that Ras activates its two effectors in spatially segregated subcellular compartments: Raf is recruited basolaterally while RalGEF is recruited apically. We have also discovered that Ral signaling through Exo84 of the exocyst complex leads to activation of GCK-2, a CNH domain-containing MAP4 kinase, which in turn signals through a PMK-1/p38 MAP kinase cascade to promote 2° fate. RalGEF, an inessential component, orchestrates opposing signals; its deletion increases patterning errors by 15x, suggesting a role in mitigating signaling noise. Thus, we have found novel components and wiring mechanisms in signaling networks.