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Busy traveling Ras

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One of the best strategies for defining the function of a protein is to determine where it resides in the cell. The trouble is that many proteins are dynamic and mobile and found in many cell compartments. To further confound the problem, our tools of detecting protein localization can be inadequate in differentiating "noise" vs. patterns of localization that are truly physiologically relevant.

Ras GTPases function as molecular switches for signal transduction that controls a wide range of biological functions, the best known of which is tumorigenesis.[1] There are three *RAS* genes in mammals, *H-RAS*, *N-RAS* and *K-RAS*, and the latter can produce two proteins, K-Ras-4A and K-Ras-4B, due to alternative splicing. While these Ras proteins are highly similar at the N-terminus, they differ substantially in the C-terminus in a region called the hypervariable region (HVR). Ras proteins undergo several covalent modifications in the HVR, and these modifications clearly control how Ras proteins associate with cell membrane, which then in ways that are still mostly unclear, ultimately controls where in the cells Ras proteins function.[2]

For example, all Ras proteins have a CAAX motif in the C-terminus where the cysteine is farnesylated by farnesyl transferase in the cytoplasm. Farnesylation allows Ras proteins to associate with the membrane, such as endoplasmic reticulum (ER), where a protease, RCE1 (Ras converting enzyme 1), cleaves off the AAX motif. The newly formed terminal farnesylcysteine is then methylated by the ICMT (isoprenylcysteine carboxyl methyltransferase). To reach the plasma membrane, all Ras proteins required one additional mechanism. K-Ras4B appears to reach the plasma membrane by electrostatic interaction between a stretch of lysines in the HVR and phospholipids. In contrast, H-, N- and K-Ras4A Ras proteins are palmitoylated in Golgi at additional cysteines that are adjacent to the CAAX motif.[2]

It is now well established that Ras proteins must localize to the plasma membrane to transduce signals carried by proteins that bind receptors at the plasma membrane (e.g., growth factors in mammalian cells and mating pheromones in yeast). Intriguingly, in an early study by Hancock et al., while mutations abolishing farnesylation result in mutant Ras proteins that can no longer transform cells, mutations affecting palmitoylation (or lysines in K-Ras-4B), only partially do so.[3] These results suggest that Ras proteins in cytoplasm may also activate signaling pathways, some of which are important for transformation. Chiu et al. have later shown that in mammalian cells when Ras proteins are restricted in cytoplasmic membrane compartments, such as Golgi and ER, they can still transform cells.[4] In yeast, we and others have evidence that Ras proteins activate different effectors in different cell compartments in order to control different functions. For example, in fission yeast, we have shown that Ras1 stimulates Byr2 (a MEKK homolog) on the plasma membrane to control mating, and in endomembrane, Ras1 stimulates Scd1, a nucleotide exchange factor for Cdc42, to control cell polarity and morphogenesis.[5,6] In budding yeast, Ras2 activates adenylyl cyclase on the plasma membrane and Eri1 on the ER.[5,7]

To what extent is compartmentalized Ras signaling conserved in evolution? In a newly published paper, Cheng et al. have demonstrated that like in fission yeast, Ras proteins can also act via Cdc42 in the endomembrane (e.g., endosomes) and that this interaction is critical for transforming NIH3T3 cells.[8] Importantly, Ras proteins in mammalian cells also activate Cdc42 via its nucleotide exchange factors such as Dbl and ITSN1-L.[9] Thus the mode of Ras-GEF-Cdc42 interaction has been conserved during evolution. Despite the fact that Cdc42 is necessary for Ras-induced transformation, the presence of a constitutively active Cdc42, Cdc42(12V), does not detectably transform cells.[10] However, if Cdc42(12V) is combined with a constitutively active Ras protein that is restricted to the plasma membrane, which by itself can also only weakly transform cells, this combination transforms cells efficiently.[8] These observations suggest that in order for Ras proteins to fully transform cells, multiple compartment-specific Ras pathways need to be engaged.

In summary, the concept of compartmentalized Ras activities has by now been validated in many cell types across species. Therefore, the conventional view that Ras proteins solely act on the plasma membrane is evidently an oversimplification. In passing we wish to also point out that besides Ras, recent evidence indicates that even EGF receptors can act outside of the plasma membrane by entering the nucleus to directly control transcription.[11] Conversely, the estrogen receptors, which are best known for transcription control in the nucleus, may function at the plasma membrane and/or cytoplasm.[12] There seems to be a common theme that important regulatory proteins are "busy" and travel and work in many different places in the cell.

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