A giant that links microfilaments and the nucleus

Proteins related to α-actinin play multiple roles in organization of the actin cytoskeleton. α-actinin itself arranges actin filaments to form bundles, whereas relatives such as plakins and spectrins link the cytoplasmic actin network to the plasma membrane and organelles. Angelika Noegel and co-workers have now identified and characterized a giant spectrin-related protein, NUANCE, that could be the first that links the actin network to the nucleus (see p. 3207). Weighing in at 796 kDa, NUANCE is the largest known member of the α-actinin family. It contains 22 spectrin repeats and an actin-binding domain that binds to F-actin both in vitro and in vivo. The authors show that NUANCE resides both in the nucleoplasm and in the outer nuclear membrane (ONM) – its targeting to the ONM being mediated by a transmembrane domain at its C-terminus. Significantly, NUANCE shares sequence similarity in this region with two proteins implicated in nuclear migration: Drosophila Klarisicht and Syne-1. It might therefore have a dynamic role in nuclear migration as well as functioning as a cytolinker connecting microfilaments with the nucleus.

Tek kinases – calcium and beyond

Tek family kinases, such as Btk and Itk, are non-receptor tyrosine kinases related to the Src family. Initially shown to be important in immune cells for Ca2+ mobilization during antigen receptor signalling, Tek kinases function downstream of cell-surface receptors from Fc receptors to integrins. In a Commentary on p. 3039, Pamela Schwartzberg and co-workers review our understanding of the roles of these kinases in signalling. Tek kinases possess the SH1, SH2 and SH3 domains characteristic of Src kinases but contain additional, pleckstrin-homology (PH) and proline-rich (PR) domains. The PH domain regulates membrane targeting by binding to phospholipids such as the PI 3-kinase product PtdIns(3,4,5)P3. The PR domain appears to engage in inter- and intramolecular PR-SH3 interactions, disruption of which could activate the kinase. Once activated, Tek kinases regulate Ca2+ signalling by phosphorylating phospholipase Cγ. However, they also regulate signalling by MAP kinases and STATs, as well as by actin reorganization. Indeed interactions between Tek kinases and actin regulators such as WASP could be critical for formation of the immunological synapse required for sustained signalling by T-cell receptors.

mRNA surveillance: nonsense-mediated and non-stop

Inaccurate transcription, RNA-processing errors and lymphocyte gene rearrangements can all generate aberrant mRNAs whose translation would produce dominant negative proteins that disrupt cell function. Cells must detect and destroy such RNAs, but how do they discriminate them from normal mRNAs? In a Commentary on p. 3033, Eileen Wagner and Jens Lykke-Andersen discuss recent work that has identified two mRNA surveillance mechanisms that do this: nonsense-mediated decay (NMD) and non-stop decay. NMD destroys transcripts that contain premature termination codons (PTCs). The last exon-exon junction is marked with an exon junction complex (EJC), and if a PTC is present upstream, a group of ‘Upf’ proteins triggers degradation of the mRNA during translation. Non-stop decay, by contrast, targets RNAs that lack in-frame termination codons and does not involve Upf proteins. Instead it requires the GTPase Ski7. Ski7 binds to the empty A site in a ribosome that has reached the 3’ end of an mRNA and then recruits a multisubunit complex of exonucleases, termed the exosome, to degrade the transcript.

Regulation of PKC trafficking by synaptotagmin

Synaptotagmins play important roles in vesicle trafficking in neurons: they act as fusion clamps during synaptic vesicle (SV) exocytosis and as receptors for adaptor proteins during endocytosis of SV proteins. The proteins are also expressed in other cell types, but we know very little about their roles in non-neuronal cells. Ronit Sagi-Eisenberg and co-workers review new and emerging roles that synaptotagmins play in regulating PKC trafficking and degradation in mast cells (see p. 3083). After prolonged exposure of mast cells to phorbol ester, PKCα is transported to the plasma membrane and then to early/sorting endosomes, where it is targeted for degradation. The authors observe that overexpression of synaptotagmin II promotes PKCα degradation in mast cells, whereas transfection of antisense synaptotagmin II causes PKCα to be recycled. Using laser confocal microscopy and subcellular fractionation, they demonstrate that, when synaptotagmin II levels are low, PKCα is diverted through recycling endosomes back to the plasma membrane. Synaptotagmin II thus plays an active role in membrane trafficking in non-neuronal cells and could thereby regulate cell signalling.

Impaired p53 pathway in Alzheimer’s

Free radicals are often generated during normal metabolism and can cause oxidative stress and DNA damage. Cells respond by halting the cell cycle to allow DNA to be repaired or to undergo apoptosis. These free radicals appear to be risk factors in Alzheimer’s disease (AD) and might contribute to initiation and progression of neurodegeneration. To investigate this link, Maurizio Memo and co-workers have compared the effects of exposure to hydrogen peroxide on fibroblasts from sporadic AD patients and fibroblasts from individuals who do not have the disease (see p. 3131). They find that the AD fibroblasts exhibit reduced cell cycle arrest and re-enter the cell cycle more quickly in response to hydrogen peroxide – despite levels of DNA damage similar to those of non-AD fibroblasts. In addition, the AD fibroblasts are less likely to undergo apoptosis. The authors show that this is because peroxide-induced activation of the tumour suppressor p53 and its apoptotic target genes (e.g. Bax) is impaired in AD fibroblasts. Such an inability to respond correctly to free-radical-induced DNA damage could play an important role in neurodegeneration.

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