The Role of FilGAP–Filamin A Interactions in Mechanoprotection

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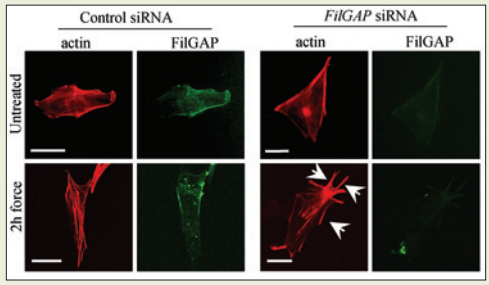
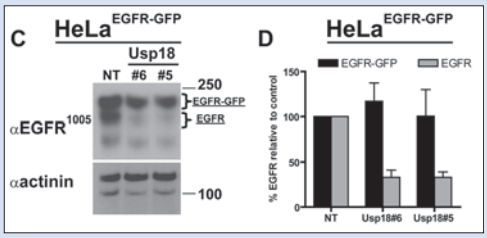


Cells in mechanically active environments are subjected to high-amplitude exogenous forces that can lead to cell death. Filamin A, an actin cross-linking protein, has been implicated in protecting cells from mechanically induced death, but the means by which this mechanoprotection is achieved is not known. In addition to binding and cross-linking actin filaments, filamin A interacts with a diverse array of proteins, including filamin A–binding RhoGTPase-activating protein (FilGAP). The authors found that FilGAP is targeted to sites of force transfer by filamin A. This force-induced redistribution of FilGAP is essential for the suppression of Rac activity and lamella formation in cells subjected to tensile forces. Depletion of FilGAP by siRNA, inhibition of FilGAP activity by dominant-negative mutation, or deletion of the FilGAP filamin A–binding domain each resulted in a dramatic force-induced increase in the percentage of apoptotic cells. FilGAP therefore plays a role in protecting cells against force-induced apoptosis, and this function is mediated by filamin A.



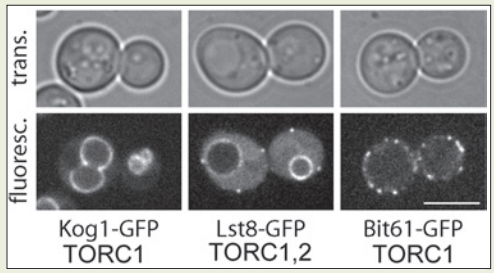
RNA Interference Screen Identifies Usp18 as a Regulator of EGF Receptor Synthesis

Jason E. Duex and Alexander Sorkin

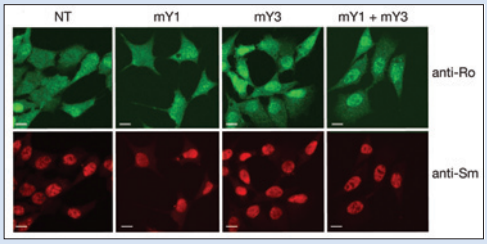
To identify novel regulators of oncogenic EGF receptor (EGFR), the authors developed a high-throughput RNAi screen. This screen revealed that the ubiquitin-specific protease Usp18 is a regulator of EGFR. Depletion of Usp18 by RNAi results in a 50%–80% decrease in the steady-state levels of EGFR in several cell lines, including squamous cell carcinoma. Conversely, overexpression of Usp18 increased EGFR levels. Interestingly, Usp18 does not function by controlling EGFR ubiquitination and subsequent degradation. Rather, Usp18 depletion leads to a dramatic decrease in the rate of EGFR protein synthesis. Further studies demonstrated that Usp18 regulates EGFR protein synthesis by controlling EGFR mRNA translation. Such regulation is dependent upon native 5' and 3' UTR sequences. Taken together, these studies demonstrate a unique role for Usp18 in controlling the levels of EGFR protein. Furthermore, inhibiting Usp18 activity has potential as a novel therapeutic approach to reducing EGFR levels and activity in tumor cells.

TORC2 Plasma Membrane Localization Is Essential for Cell Viability and Restricted to a Distinct Domain

Doris Berchtold and Tobias C. Walther



The conserved **t**arget **o**f **r**apamycin (TOR) kinase regulates cell growth and homeostasis and exists in two functionally distinct complexes, TORC1 and TORC2. The authors explored the spatial organization of the two TOR complexes in yeast and found them in distinct places: TORC2 localizes to the plasma membrane, whereas TORC1 localizes to the vacuolar membrane. TORC2 exists in small dynamic foci akin to signaling nanoclusters like those observed for Ras proteins. These clusters occupy a distinct membrane compartment. Avo1, a subunit of TORC2, binds the plasma membrane lipid $PI(4,5)P_2$ via a PH-like domain that is required for TORC2 function and localization. However, this region of the protein can be replaced by a short heterologous sequence tag that directs protein lipidation and targeting to the plasma membrane without loss of function, arguing that plasma membrane localization of TORC2 is essential. The spatial separation of TOR complexes suggests that cells employ compartmentalization to process distinct information using the same kinase in different locations.



The Subcellular Distribution of an RNA Quality Control Protein, the Ro Autoantigen, Is Regulated by Noncoding Y RNA Binding

Soyeong Sim, David E. Weinberg, Gabriele Fuchs, Keum Choi, Jina Chung, and Sandra L. Wolin

Noncoding RNAs are critical participants in diverse cellular processes. This study shows how a noncoding RNA can regulate the subcellular distribution of a protein. The Ro autoantigen is a ring-shaped protein that binds misfolded RNAs in nuclei and likely functions in RNA quality control. In the cytoplasm, Ro binds noncoding RNAs called Y RNAs that block access by Ro to other RNAs. In addition to its quality control function, Ro assists cell survival following ultraviolet irradiation. Following irradiation, an unknown signal causes Ro to change from mostly cytoplasmic to largely nuclear. The authors found that in the absence of bound Y RNAs, Ro accumulates in nuclei. Moreover, nuclear accumulation of Ro following ultraviolet irradiation requires sequences that overlap the Y RNA binding site. Ro also accumulates in nuclei during oxidative stress and similar sequences are required. These findings suggest that Y RNAs mask a signal for Ro nuclear accumulation that becomes accessible following environmental stress. ■