species, and ablating Ero1p function rescues premature lethality in worms with a defective UPR.

The work presented by Harding and colleagues highlights the way in which multiple stresses are interrelated and the conservation of a generalized stress response for adapting to these stresses. Questions, of course, remain. Are there other proteins that are upregulated specifically as a consequence of eIF2α phosphorylation, and what role would such proteins play in mediating adaptation to multiple stressors? What is the mechanism by which Ero1p generates reactive oxygen species? What fraction of cellular oxidative stress is attributed to ER function? Are there additional pathways through which stress in one location (e.g., the ER) is communicated to other organelles, enabling a cell-wide response to specific stressors? Unlocking the cellular response to stress may turn out to be a stressful exercise.

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Selected Reading

Frand, A.R., and Kaiser, C.A. (1999). Mol. Cell *4*, 469–477.

Harding, H.P., Novoa, I., Zhang, Y., Zeng, H., Wek, R., Schapira, M., and Ron, D. (2000). Mol. Cell *6*, 1099–1108.

Harding, H.P., Zhang, Y., Zeng, H., Novoa, I., Lu, P.D., Calfon, M., Sadri, N., Yun, C., Popko, B., Paules, R., et al. (2003). Mol. Cell *11*, 619–633.

Hinnebusch, A.G., and Natarajan, K. (2002). Eukaryot. Cell. *1*, 22–32.

Pollard, M.G., Travers, K.J., and Weissman, J.S. (1998). Mol. Cell *1*, 171–182.

Scheuner, D., Song, B., McEwen, E., Gillespie, P., Saunders, T., Bonner-Weir, S., and Kaufman, R.J. (2001). Mol. Cell *7*, 1165–1176.

Travers, K.J., Patil, C.K., Wodicka, L., Lockhart, D.J., Weissman, J.S., and Walter, P. (2000). Cell *101*, 249–258.

Tu, B.P., and Weissman, J.S. (2002). Mol. Cell *10*, 983–994.

Filling Gaps in Signaling to Actin Cytoskeletal Remodeling

A recent publication in the April 4 issue of *Cell* advances our understanding of stimulus response coupling leading to actin remodeling. It describes the identification of a novel membrane component Mig-2 that engages filamin A through a new intermediary, migfilin, to stimulate actin assembly and cell spreading on a substrate of extracellular matrix.

Diverse stimuli induce cells to remodel their actin cytoskeletons. Depending on the agonist and the signal intermediates it sets into motion, actin remodeling builds different structures. For example, TNFα activates the Rho GTPase Cdc42 to induce extension of linear actin bundles that project hair-like protrusions called filopodia. In contrast, extracellular matrices activate Rho GTPases, Rac and Rho, to cause circumferential actin assembly and cell spreading (Etienne-Manneville and Hall, 2002). Our challenge is to understand how hundreds of actin binding proteins that actually do the work of actin remodeling respond to upstream signals in a coordinated manner to shorten, lengthen, and organize the three-dimensional organization of actin filaments and control the reversible linkage of actin filaments to extracellular matrices (Pollard and Borisy, 2003).

From the starting point of cloning a previously uncharacterized gene, Mig-2, Tu et al. (2003) have added substantively to this understanding. They identified Mig-2 as a component of adhesion complexes where cells attach to the extracellular matrix. They then discovered a novel Mig-2 binding partner they named migfilin and demonstrated that Mig-2 recruits migfilin to adhesion complexes. Using RNA interference to downregulate protein expression, they showed that cell spreading requires both Mig-2 and migfilin. In addition, they identified filamin A (FLNa) as a ligand of migfilin and that the interaction of migfilin and FLNa is necessary for matrix- and Mig-2-induced cell spreading. The Fil-2, migfilin, and FLNa interaction is not merely a static chain of physical connections, because it promotes net actin assembly as cell spreading occurs.

Bringing FLNa into this story is a big step, because FLNa is the first-recognized non-muscle cell actin binding protein and has therefore been under investigation for over 25 years (Stossel et al., 2001). Originally defined as a potent actin filament gelation factor that promotes orthogonal branching and crosslinking of actin filaments, FLNa binds over 30 proteins of great functional diversity. These include membrane receptors for extracellular matrix components, receptors for various cell activating ligands, and even nuclear factors. Of greatest importance for signaling to actin remodeling, however, is the fact that FLNa binds intracellular signaling intermediates, including the Rho GTPases and Rho GTPase regulating proteins implicated in actin remodeling. Normal FLNa expression is a prerequisite for mammalian cellular locomotion.

FLNa is a large dimeric protein with filamentous subunits. Twenty-three repeating units of amino acid sequence and two short runs of unique sequence, termed “hinges,” separate an amino-terminal actin binding domain from a carboxy-terminal repeat number 24, which is the dimerization site (Figure 1; Stossel et al., 2001).

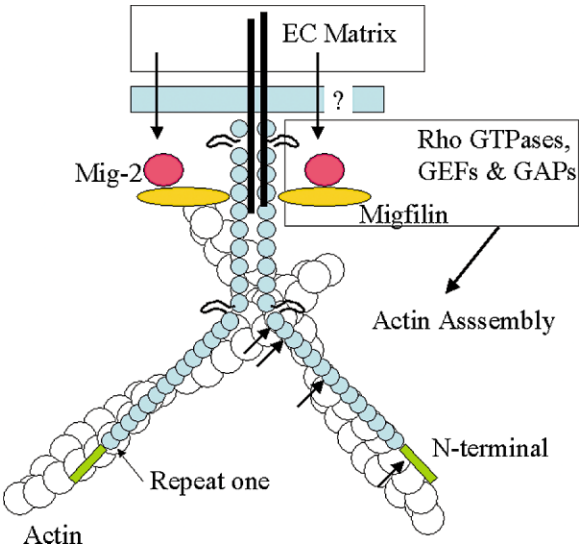

Figure 1. Scheme Depicting Possible Connections on a Filamin A Scaffolding Leading from Mig-2 to Actin Remodeling

FLNa (shown in blue) orients with its carboxy-terminal dimerization domain toward the plasma membrane, because transmembrane matrix receptors, such as integrins, bind in that region. Rho GTPases and their regulatory components also bind FLNa near that site. Receptor engagement by extracellular (EC) matrix components somehow localizes Mig-2, which in turn recruits migfilin, leading to activation of Rho GTPases and actin assembly. Small arrows indicate sites of point mutations responsible for diverse human congenital anomalies.

The FLNa binding partners other than actin interact with the carboxy-terminal end of the FLNa subunits, and Tu et al. show that migfilin is no exception, binding to FLNa repeat 21. With the information from the work of Tu et al., it is possible to construct a model of actin remodeling that produces cell spreading on an extracellular matrix (Figure 1). By bringing together matrix receptors such as integrins, activating intermediates like Mig-2 and migfilin, Rho GTPase regulators, and Rho GTPases, FLNa programs the spatial and temporal coordination of actin filament remodeling. Whether Mig-2 and migfilin activate GTPases directly or indirectly is not yet clear, but pathways from activated GTPases to actin assembly are well known. Rho GTPases stimulate phosphoinositide kinase activities, and the resulting phosphoinositide accumulation promotes actin polymerization by removing capping proteins from the fast-growing (barbed) ends of actin filaments and by activating WASP family proteins that stimulate the branching polymerization of actin filaments at free barbed ends by the Arp2/3 complex (Pantaloni et al., 2001; Pollard and Borisy, 2003). Rho GTPases also activate PAK, leading in turn to the phosphorylation and inactivation of the actin-depolymerizing factor, ADF/cofilin (Chen et al., 2000).

Robertson et al. recently reported that point mutations on FLNa are responsible for congenital malformations affecting multiple human organ systems, presumably due to defective cell migration during embryonal development (Robertson et al., 2003). This indicates that we are barely scratching the surface about FLNa's role as a scaffold for signaling to actin assembly. Most of the mutations in the Robertson et al. study reside at positions in the FLNa sequence not yet implicated in binding of specific partners. Future research will undoubtedly define such partners. It will also increasingly define how localized actin remodeling occurs, specifically revealing the details of how particular actin structures arise.

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Selected Reading

Chen, H., Bernstein, B.W., and Bamburg, J.R. (2000). Trends Biochem. Sci. *25*, 19–23.

Etienne-Manneville, S., and Hall, A. (2002). Nature *420*, 629–635.

Pantaloni, D., Le Clainche, C., and Carlier, M.-F. (2001). Science *292*, 1502–1506.

Pollard, T., and Borisy, G. (2003). Cell *112*, 453–465.

Robertson, S.P., Twigg, S.R., Sutherland-Smith, A.J., Biancalana, V., Gorlin, R.J., Horn, D., Kenwrick, S.J., Kim, C.A., Morava, E., Newbury-Ecob, R., Ørstavik, K.H., et al. (2003). Nat. Genet., in press. Published online March 3, 2003. doi: 10.1038/ng1119.

Stossel, T.P., Condeelis, J., Cooley, L., Hartwig, J.H., Noegel, A., Schleicher, M., and Shapiro, S.S. (2001). Nat. Rev. Mol. Cell Biol. *2*, 138–145.

Tu, Y., Wu, S., Shi, X., Chen, K., and Wu, C. (2003). Cell *113*, 37–47.

SETting the Stage: Eed-Enx1 Leaves an Epigenetic Signature on the Inactive X Chromosome

Despite evidence implicating the Polycomb group protein, Eed (embryonic ectoderm development protein) in imprinted X inactivation, a similar role in random X inactivation in the embryo has remained an open question. Brockdorff and colleagues now report that Eed, along with its binding partner Enx1, transiently associates with the inactive X chromosome (Xi) and likely contributes to the epigenetic signature and long-term stability of the Xi heterochromatin.

In spite of unequal X chromosome copy number between the sexes, gene expression levels are largely comparable as a result of dosage compensation mechanisms. In mammals, this is achieved by rendering most