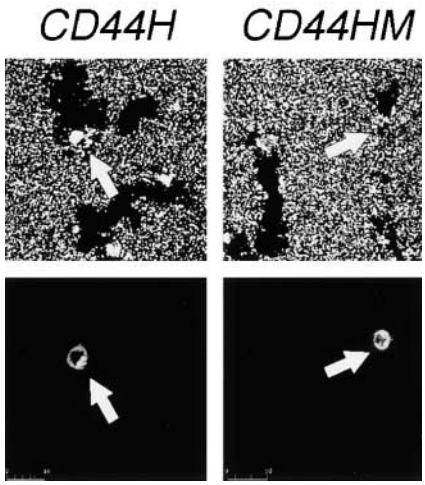
Releasing Anchors

The degradation of extracellular matrix by membrane-type 1 matrix metalloproteinase (MT1-MMP) clears the way for invasive cancer cells, allowing them to migrate. But, on page 893, Kajita et al. propose that MT1-MMP has another function in getting cells moving: it may cleave anchoring proteins that would otherwise hold the cell in place.

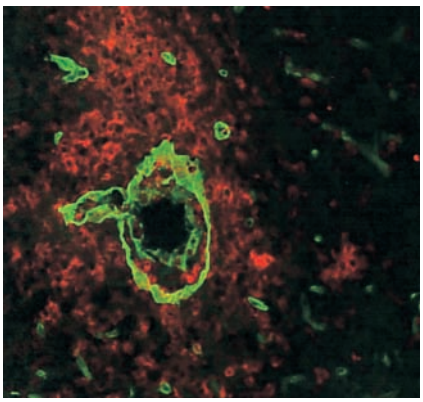


Kajita et al. look in particular at CD44, an abundant cell–cell and cell–matrix adhesion molecule. CD44 promotes migration, presumably via binding to extracellular molecules such as hyaluronic acid (HA), which activates intracellular signaling. But CD44 binding to HA might also be expected to physically retard the cell.

This is apparently where MT1-MMP comes in. Kajita et al. find that cotransfection of CD44 and MT1-MMP stimulates motility. The motility of these transfected cells and of a pancreatic tumor cell line is inhibited by both MMP inhibitors and a dominant-negative CD44 mutant that lacks MMP cleavage sites. In the latter experiment, the cells that do not receive the mutant construct are motile and shed soluble CD44, and yet the surrounding transfected cells are not motile. This suggests that the important event is the processing itself, rather than the binding of the product of processing. Kajita et al. therefore suggest that the cleavage of CD44 by MT1-MMP allows cells to detach once CD44 has provided its positive signal.

Breaking into the Brain

Immune cells seeking to enter the brain encounter two basement-membrane obstacles—the endothelial and parenchymal basement membranes. On page 933, Sixt et al. describe some of the extracellular matrix molecules that make these layers distinct, and suggest a model for the multi-step entry of cells into the brain.



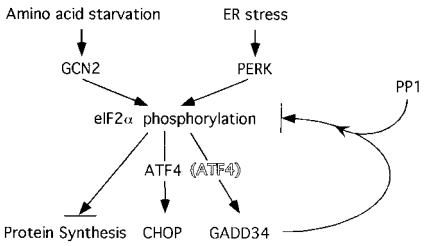
Sixt et al. induce brain inflammation by immunizing with myelin. During the resultant experimental autoimmune encephalomyelitis (EAE, a model for multiple sclerosis), some of the invading cells get stuck between the two layers. This allows Sixt et al. to differentiate between the inner parenchymal layer, containing laminins 1 and 2, and the outer endothelial layer, containing laminins 8 and 10. Laminin 10 is noticeably absent from areas of infiltration.

In vitro adhesion assays demonstrate that activated T cells adhere far more strongly to laminin 10 than 8, and not at all to laminins 1 and 2. Sixt et al. suggest that high affinity of infiltrating leukocytes for laminin 10 may prevent migration, whereas three factors (increased turnover of laminin 8 in the endothelial cell basement membrane, a decrease in the amount of laminin 8 ligand on the endothelial cell surface, plus low affinity adhesion of infiltrating leukocytes for laminin 8) may increase penetrability of the endothelial monolayer in areas lacking laminin 10. Previous work is also consistent with laminin 8 providing a direct pro-migratory signal to attract cells.

Work by others has shown that metalloproteinases are necessary only for the second step, in which invading cells break through the remaining barrier of the parenchymal basement membrane. The metalloproteinases may degrade obstructing matrix, liberate adhesion molecules or chemoattractants, or both.

Feedback on Stress

Many different stresses cause cells to reduce translation rates drastically by phosphorylating the alpha subunit of translation initiation factor-2 (eIF2α). On page 1011, Novoa et al. report that the stress-induced protein GADD34 is a feedback inhibitor of this response, allowing cells to recover from the stress-induced shutdown.

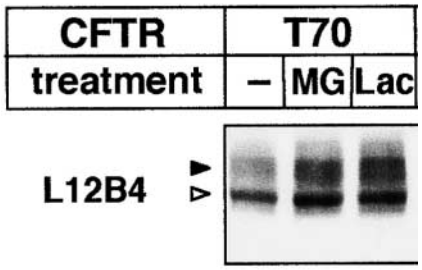


Novoa et al. isolate the COOH terminus of GADD34 in a screen for proteins that prevent accumulation of a stress-induced transcript. Lysates from cells overproducing GADD34 have increased dephosphorylating activity specifically against eIF2α, and this activity remains in GADD34 immunoprecipitates. This suggests a parallel with the $\gamma_1$34.5 protein from herpes simplex virus (HSV), which was previously noted by Bernard Roizman and co-workers to share a region of similarity with GADD34 and to bind the catalytic subunit of protein phosphatase 1 (PP1c). Indeed, GADD34 mutants that do not bind PP1c no

longer shut down the stress response. Novoa et al. now want to test whether GADD34 is, as they suspect, necessary for attenuation of the stress response in normal cells.

Proteasome Action, Post-ER

For secreted or plasma membrane proteins, most quality control comes at the level of the endoplasmic reticulum (ER). On page 957, however, Benharouga et al. report that COOH-terminal truncations of the cystic fibrosis transmembrane conductance regulator (CFTR) are degraded largely after the ER in a process that is initiated by proteasomes, not lysosomes.

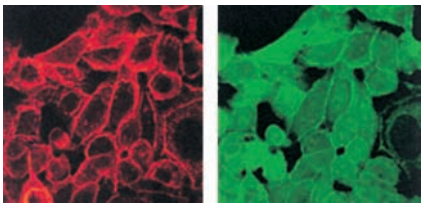


Wild-type CFTR is a complex, multidomain protein, 70% of which never gets past the proteasome-dependent degradation pathway at the level of the ER. But the T70 truncation studied by Benharouga et al. is also unstable after it passes through the ER quality-control apparatus. Delivery from the Golgi to the plasma membrane is normal, and inhibition of lysosomal proteases does not prevent continued degradation of T70. Proteasome inhibitors do, however, increase the survival time of surface-biotinylated T70.

Lysosomal protease inhibitors cause the accumulation of protein fragments, suggesting that initial proteasome-dependent fragmentation is followed by more complete degradation of these fragments in lysosomes. T70 may be susceptible to proteasome degradation because of its reduced stability, which Benharouga et al. detect as an increase in protease sensitivity in vitro, and a temperature dependence of protein instability.

Signaling Not Sticking for Tumor Suppression

As a tumor suppressor, the cell–cell adhesion protein E-cadherin could work one of two ways. Earlier work suggested that increased adhesion can inhibit cell movement, and thus metastasis. But, on page 1049, Gottardi et al. show that, at least in their colorectal carcinoma cell line, cadherin expression also results in a direct suppression of proliferation, via E-cadherin's binding of the signaling protein β-catenin.



Gottardi et al. find that E-cadherin–mediated inhibition of anchorage-independent growth can be achieved with a construct that lacks adhesive properties (due to a foreign extracellular domain) but retains the ability to bind β-catenin. Growth inhibition can be reversed by adding an activated version of β-catenin's target (the transcription factor TCF), or by deleting the β-catenin–binding domain in E-cadherin.

Despite this evidence for its mechanism of action, E-cadherin does not appear to be sequestering the majority of β-catenin. Instead, Gottardi et al. report that E-cadherin binds only the subset of β-catenin that is capable of binding to TCF. Future work will focus on identifying what distinguishes this pool of β-catenin and on determining whether the adhesion-promoting activity of E-cadherin is more important later in cancer progression, when tumors become invasive.

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