Translation turns on dendritic cells

Peaks and valleys in protein translation prepare one set of immune cells for duty, according to findings from Lelouard et al. With the ebb and flow of translation, antigen-presenting dendritic cells (DCs) adjust the origin of their antigens. DCs are professional immunity activators that alert T cells to the presence of invaders by displaying antigens on their surface. This display is ramped up by a maturation program initiated when a DC encounters inflammatory stimuli such as pathogenic components. Scientists have identified an abundance of transcriptional changes that take place during maturation. The new results show that a boost in translation is necessary to put the new transcripts into action.

Translation peaked in DCs about 4 hours after their activation. During this stretch, translation—and the PI3K/AKT/mTOR signaling pathway that activated it—was needed for maturation-associated changes in the DCs. These changes include producing T cell-activating cytokines and activating the antigen-presenting machinery.

After 4 to 8 hours, protein synthesis levels declined, due at least in part to proteasome-mediated cleavage of the eIF4GI translation initiation factor. At 16 hours, overall translation levels were even lower than they were before activation.

Some transcripts, however, escaped the translation shutdown. As also occurs during stress conditions, eIF4GI cleavage initiated an unusual translation pathway that bypasses the need for a 5’ cap on transcripts. Cap-independent translation, which favors the synthesis of anti-apoptotic proteins, made mature DCs resistant to apoptosis-inducing drugs. This pathway might thus help activated DCs survive the stress of their heavy new transcription and translation loads while they search for and then activate T cells.

As DCs switched translation pathways, they also changed the source of antigens presented on MHC class I molecules. During the early, translation-heavy stage, antigens were derived from pieces of newly synthesized proteins; when the authors blocked translation, antigen presentation was limited. But later on, translation inhibitors did not interfere with MHC class I presentation.

The authors speculate that once DCs have matured, their antigens are mainly derived from exogenous sources, such as pathogens. Although normally presented on MHC class II molecules, exogenous peptides can also crossover to the class I pathway. An alternative possibility is that late antigens come from a pool of stored, presynthesized self-peptides. JCB Reference: Lelouard, H., et al. 2007. J. Cell Biol. 179:1427–1439.

Motility without invasion

Breast cancer cells dance around the subject before becoming invasive, if results from Pearson and Hunter are any indication. The findings show that mammary epithelial cells can become motile within their environment without being invasive. Their motility, however, places them one step closer to metastasis.

Many breast cancers are hallmarked by the unchecked activity of the ERK1/2 MAP kinase pathway. Pearson and Hunter investigated the mechanism by which these kinases, which are normally activated by extracellular growth factors, lead to tumorigenesis. They imaged breast epithelial cells in a 3D model that mimics their in vivo environment. In this model, the cells polarize on a basement membrane to form hollow spheres called acini.

Within mature acini, the provoked action of ERK1/2 encouraged cells to leave their appointed locations. They glided along the basement membrane (underneath other cells) or within the lumen of the acini (on top of the other cells). Motility required the activation of a myosin motor by a kinase that is a known target of ERK1/2.

The movements resembled those that occur in developmental contexts, such as in the forming kidney or salivary gland. These programs are shut down when cells differentiate but might be wrongly reactivated in cancers.

DANGEROUSLY Invasive cells are characterized by their ability to break through the basement membrane, but this escape was not seen in the ERK-activated acini. The cells did not display the usual set of molecular changes, including increases in N-cadherin and vimentin, that accompany the epithelial–mesenchymal transition. Nonetheless, the movements disrupted the architecture of the acini, as the wandering cells squeezed between more well-behaved stationary cells.

Although not yet invasive, motile breast cells might suggest that a more aggressive form of cancer is brewing. With the ability to flee already in place, these cells would require fewer mutations to become fully invasive. The authors hope to identify molecular markers of this motility that will help physicians diagnose those patients who are at a higher risk for metastases. Motile but noninvasive cells might also permeate other epithelial cancers, including lung and bladder cancers. JCB Reference: Pearson, G.W., and T. Hunter. 2007. J. Cell Biol. 179:1555–1567.