In This Issue

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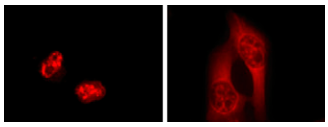
A pyrimidine scheme to restore mRNA export



mRNAs (red) are trapped in the nuclei of cells expressing NS1 (left), but export to the cytoplasm is restored when pyrimidine synthesis is inhibited (right).

Inhibitors of pyrimidine synthesis can stop the influenza virus from trapping host cell mRNAs in the nucleus, Zhang et al. report.

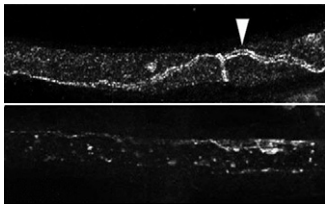
Many viruses switch off the expression of host cell genes in order to survive and replicate. The influenza virus, for example, produces a factor called NS1 that blocks the export of host mRNAs from the nucleus, in part by binding to the mRNA export factor NXF1. By screening a library of small molecules, Zhang et al. found that mRNA export was restored in NS1-expressing cells by inhibitors of dihydroorotate dehydrogenase (DHODH), a cellular enzyme required for the de novo synthesis of pyrimidines like cytosine, thymine, and uracil.

Restoring mRNA export allowed cells to express antiviral factors including the transcription factor HIF1-α. DHODH inhibitors rescued mRNA export in influenza virus–infected cells and blocked viral replication, effects that were mitigated if the cells were supplemented with extra pyrimidines. DHODH inhibitors also reversed the ability of the vesicular stomatitis virus M protein to block mRNA export, the researchers found.

NXF1 levels rose when pyrimidine synthesis was blocked, and DHODH inhibitors couldn't restore mRNA export to cells lacking this mRNA export factor. Zhang et al. don't yet know how pyrimidine levels influence NXF1 expression. Senior author Beatriz Fontoura speculates that pyrimidine synthesis may also be linked to mRNA export because many nuclear transport proteins are modified with *N*-acetylglucosamine, a process that requires the pyrimidine-based nucleotides UDP and UTP.

Zhang, L., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201107058.

Myelinated axons need a 4.1G connection



In wild-type axons (top), potassium channels (white) localize along the juxtamesaxonal line (arrowhead), but this organization is lost when Schwann cells lack 4.1G (bottom).

Ivanovic et al. report that a glial cytoskeletal adaptor protein organizes the membranes of Schwann cells and the axons they ensheath.

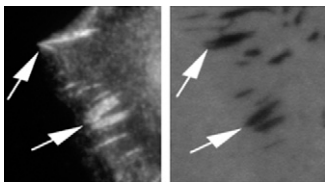
The speed of myelinated nerve conduction is boosted by the precise accumulation of ion channels in distinct membrane domains along the axon. Sodium channels, for example, accumulate in the nodes of Ranvier between neighboring Schwann cells, whereas potassium channels cluster on either side of the node, as well as between the nodes in a region of the axonal membrane adjacent to a seam in the surrounding myelin sheath termed the juxtamesaxonal line. Domain formation is dictated by distinct adhesion molecules in the membranes of both Schwann cells and axons, though how potassium channels localize to the juxtamesaxonal line is unknown.

Ivanovic et al. analyzed mice lacking 4.1G, an adaptor protein expressed in Schwann cells that links membrane proteins to the actin and spectrin cytoskeleton. In the absence of 4.1G, Schwann cell adhesion molecules such as Necl4 and NF155 were lost from the membrane contacting the underlying axon. As a result, several axonal membrane proteins were also mislocalized, including potassium channels, which aggregated and piled up near the nodes of Ranvier instead of stretching out along the juxtamesaxonal line.

Thus, in myelinating Schwann cells, 4.1G is required for the polarized distribution of proteins that in turn control the molecular organization of the internodal axonal membrane. Senior author Elior Peles now wants to investigate how the adaptor protein controls the expression levels and localization of Schwann cell adhesion molecules.

Ivanovic, A., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201111127.

Focal adhesions degrade the ECM



Arrows indicate where focal adhesions marked by vinculin (left) overlap with sites of ECM degradation (right).

Wang and McNiven reveal how a matrix metalloproteinase (MMP) is recruited to focal adhesions, where it degrades the extracellular matrix (ECM) to promote tumor cell invasion.

Cancer cells are thought to invade through tissues by forming invadopodia—actin-rich membrane protrusions that project from the base of the cell and contain MMPs that degrade the surrounding ECM. Invadopodia are formed by many of the same proteins that assemble into focal adhesions, which attach to the ECM and aid cell migration but aren't thought to function in matrix degradation. Wang and McNiven, however, noticed that many tumor cell lines degraded the matrix underlying both their invadopodia and their focal adhesions.

Matrix degradation by focal adhesions depended on a transmembrane MMP called MT1. This protease was recruited to focal adhesions because its cytoplasmic tail—when phosphorylated by the tyrosine kinase Src—bound to a protein called p130Cas, which bound, in turn, to the focal adhesion kinase (FAK). Cells lacking p130Cas or FAK couldn't degrade the matrix around their focal adhesions and invaded through ECM more slowly than control tumor cells, even though they still formed invadopodia.

Senior author Mark McNiven thinks that this degradative function for focal adhesions makes sense as they could cluster at the leading edge of invading cells to clear a path through the ECM. He thinks that researchers should continue to observe the invasive structures formed by tumor cells in vivo, where focal adhesions and invadopodia may interconvert due to the large number of components they have in common.

Wang, Y., and M.A. McNiven. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201105153.