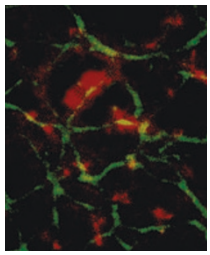
Cytoskeletal RNAs



Both mRNAs and noncoding RNAs are localized to specific regions of a variety of developing and differentiated polarized cells where they can specify cell lineages, pattern the embryo and create gradients of proteins. Some localized RNAs cofractionate and coimmunoprecipitate with cytoskeletal elements, such as cytokeratin and actin, that transport RNAs and anchor them to a specific area of the cell. Now, Kloc *et al.* show that VegT mRNA, which encodes a transcription factor, as well as Xlsirts, a noncoding RNA, are integrated into the cytokeratin network and may be involved in the structural organization of the vegetal cortex of the *Xenopus* oocyte. They show that depletion of VegT or Xlsirts RNA using antisense deoxyoligonucleotides reduces the integrity of the cytokeratin filaments, but not the actin cytoskeleton, in a transcript-specific manner. This results in premature aggregation of germinal granules, changes in the appearance and behavior of the germplasm in the oocyte and defects of germline development. Addition of exogenous VegT RNA can reconstitute and rescue the cytokeratin network in oocytes, indicating that it is the RNA and not the protein it encodes that is essential for structural integrity of the filaments. In live oocytes, VegT and Xlsirts RNA are located in the cytokeratin filaments, but further studies are needed to determine whether the RNA interacts directly with cytokeratin or whether it requires an RNA-binding protein to mediate the interaction. The data from Kloc *et al.* suggest that coding and noncoding RNAs could function in the cytoskeletal network of polarized cells. (*Development* **132**, 3445–3457, 2005) *EJ*

Stacking the G deck

Although DNA is best known in its double helical conformation, it can adopt other structures such as the four-stranded guanine (G) quadruplex that forms with G-rich DNA sequences. The G quadruplex can form most readily from single-stranded DNA such as that found at the 3′ ends of telomeric DNA or they can also be extruded from duplex DNA. Recently a parallel G quadruplex structure was identified in the promoter region of the *c-myc* oncogene. Human *c-myc* is a transcription factor that is involved in diverse cellular processes such as cell growth, cell proliferation, apoptosis and cellular metabolism. In normal cells the expression of *c-myc* is tightly regulated, whereas it is deregulated in many human cancers. Support for the biological relevance of the G quadruplex structure(s) in the *c-myc* promoter was recently strengthened by showing that mutations that destabilize the structure increase *c-myc* expression and the addition of ligands that stabilize the structure decrease *c-myc* expression. Now, Phan *et al.* have determined the NMR structure of a five guanine tracts sequence from the G-rich strand of the *c-myc* promoter. The structure reveals an unusual G quadruplex involving three stacked G tetrads formed by four parallel G tracts and a G at the 3′ end that folds back into the core. The interactions of this structure with four different small-molecule ligands show that they all stack on top of the G tetrad core and that this stacking, along with electrostatic interactions, contributes to the stability of the complexes. These results should aid in the design of anticancer drugs that target G-rich sequences with the potential to form G quadruplex structures, including telomeres, whose maintenance is required for the proliferation of cancerous cells. (*Nat. Chem. Biol.* advance online publication, 17 July 2005 doi:10.1038/nchembio723) *BK*

Research highlights written by Hwa-ping Feng, Evelyn Jabri, Boyana Konforti and Michelle Montoya.

A molecular bouncer

Vascular cell adhesion molecule-1 (VCAM-1) is a cell surface glycoprotein and a potential drug target for a variety of chronic inflammatory conditions, such as inflammatory bowl syndrome and Crohn disease. Like most proteins targeted for secretion to cellular membranes and compartments, one of the early events during VCAM-1 biogenesis is cotranslational translocation across the ER membrane. In general, this translocation step is directed by the highly variable signal sequences, which are recognized and interpreted by the ER translocation machinery. How such machinery discerns the various signals encoded in the sequences has not been determined. Previous studies have identified a fungal cyclopeptide that selectively inhibits the expression of VCAM-1 on the cell surface. Using different compounds derived from the fungal peptide, two independent studies—from Garrison *et al.* and from Besemer *et al.*—report that the cyclopeptides selectively inhibit VCAM-1 translocation into the ER. Both studies show that, although the signal sequence of VCAM-1 is important for selective inhibition, the cyclopeptides do not block VCAM-1 targeting to the translocation channel but rather prevent transport of nascent VCAM-1 into the ER lumen. Garrison *et al.* further show that the Sec61 complex, the core of the translocation machinery, is necessary for selective inhibition. Cross-linking experiments demonstrate that the cyclopeptides may affect the selectivity of the translocation channel by altering the conformation of the Sec61 complex. Although the detailed mechanism of this selective inhibition will require additional studies, these results provide evidence that low molecular weight natural compounds can modulate the biogenesis of certain proteins by changing the specificity of the translocation channel. (*Nature* **436**, 285–289 and 290–293, 2005). *HPF*

Surviving the interferon way

The transcription factor NF-κB regulates the expression of genes involved in cell survival as well as inflammatory and immune responses. In mammals, NF-κB exists as homo- or heterodimers that include NF-κB1, NF-κB2 or Rel proteins bound and inhibited by IκB. Recently, NF-κB activation was shown to be induced by type I interferons (IFNs), antiviral cytokines that regulate cell survival and inflammatory response. In this pathway, IFN promotes dissociation of the inactive NF-κB–IκB complex via activation of phosphatidylinositol-3 kinase (PI-3K) and Akt. These proteins are involved in the degradation of IκB, which allows NF-κB to translocate to the nucleus and bind DNA. Now, Yang *et al.* have identified an alternative pathway whereby IFN promotes NF-κB activation. They find that TRAF2, an adaptor molecule of the tumor necrosis factor receptor, and its downstream signaling partner, NF-κB–interacting kinase (NIK), are able to mediate IFN-induced NF-κB activation without causing IκB degradation. Additional studies indicate that IFN can induce processing of NF-κB2 from p100 to p52, and that this processing requires NIK and TRAF2, but not PI-3K. Furthermore, cells expressing dominant negative NIK are sensitive to IFN-induced cell death, suggesting that IFN is able to generate a survival signal through this second NF-κB pathway. Further studies will be needed to understand how TRAF2 and NIK are facilitating NF-κB2 processing. Nevertheless, the use of multiple NF-κB pathways in cytokine signaling underscores the importance of the different NF-κB protein dimers in gene expression and survival. (*J. Biol. Chem.* Published online, 11 July 2005, doi:10.1074/jbc.M503120200) *MM*