inside blood

Decay and antidecay in mammalian development: clues to transcript abundance in the RNA world?

In 1986, Gray Shaw and Robert Kamen described an elegant set of experiments that identified a functional element in the 3′ untranslated region of GM-CSF mRNA (Cell. 46:659-667), a region that Caput et al (Proc Natl Acad Sci U S A. 1986;91:1318-1322) identified as being highly conserved in transcripts that specified proteins involved in the inflammatory response. This AU-rich region (AURE) contained repeated clusters, sometimes concatenations, of the sequence AUUUA, and marked any transcript to which it was attached for rapid destruction in mammalian cells. Probably in part because these sequences are so highly conserved (in sea urchins, for example; Asson-Batres et al, Proc Natl Acad Sci U S A. 1994;91:1318-1322), Houzet and colleagues (page 1281) reasoned that there might exist regulatory mechanisms governing transcript abundance during development. The group observed that enforced expression of wild-type GM-CSF mRNA was tolerated by E14 embryos but enforcement of deletion mutants of GM-CSF transcripts that had no AURE was lethal at E14 (the lethality resulting from overproduction of phagocytes owing to accumulation of GM-CSF mRNA). Later, at E18, even the wild-type GM-CSF mRNA accumulated at high levels and was similarly lethal.

These important observations on the ontogeny of RNA degradation may be clues to the evolution of inducible responses in the RNA world. In projecting how this world worked, much attention has been paid to the function of catalytic RNA and less to mechanisms that might provide for dynamic fluctuations in transcript abundance (without transcriptional control to fall back on). Which came first? Did the AURE transcripts and ribonucleases evolve before the appearance of ribonuclease inhibitory factors? Probably, because in ontogeny some antidecay factor evolved only after an AURE-targeted ribonucleolytic mechanism had been well established for at least 4 days and probably more. No doubt these experiments will lead to others that will define the critical molecular events that evolve between days E14 and E18, events that may clarify some of the difficult questions we have struggled with for more than 15 years in the field of inflammation and granulopoiesis.

—Grover C. Bagby Jr
Oregon Health Sciences University
Cancer Institute

It's the proteases, stupid!

Despite its clinical importance, no intellectually satisfying mechanistic explanations have been provided for G-CSF–induced stem cell mobilization. Insights, however, from studies addressing the mechanism of IL-8–induced mobilization in normal or G-CSF–receptor deficient mice have been obtained. A pool of normal neutrophils and their liberated proteases are found to be critical both in G-CSF– and IL-8–induced mobilization, bolstering the concept that diffusible factors are responsible for mobilization. As a result of neutrophil activation by G-CSF, increases in circulating elastase (NE), cathepsin G (CG), and matrix metalloproteinase 9 (MMP9) have been documented after G-CSF mobilization (Van Os et al, Blood. 1999;94(suppl):637a). But the mode of action of these proteases in vivo, their specific substrates, and their interplay with other molecules was not previously addressed.

Lévesque and colleagues (page 1289) present compelling evidence that integrates the function of proteases and of adhesion molecules in G-CSF–induced mobilization. NE and CG can cleave vascular cell adhesion molecule-1 (VCAM-1) within the confines of bone marrow (BM). The sequestered BM microenvironment with its tight cell-cell and cell-matrix interactions and membrane presentation of proteases provides a favorable environment for effective proteolytic activity evading the action of inhibitors. A progressive decrease in bone marrow VCAM-1 levels and concomitant increases in sVCAM-1 in circulation, together with increases in serine proteases is corroborating evidence. The specificity of NE and CG on BM VCAM-1 cleavage, but not of other proteases tested, is of interest, especially when VCAM-1 in other tissues is cleaved by activated MMPs instead (Hummel et al, J Neuropathol Exp Neurol. 2001;60:320-327). Despite this enlightening scenario, lingering questions remain. To what extent do mice deficient in NE or CG or dipeptidyl peptidase I (DPPI) (Pham et al, Proc Natl Acad Sci U S A. 1999;96:8627-8632) mobilize in response to G-CSF? Are other targets besides VCAM-1 involved? Why is soluble VCAM-1 increased after SCF or IL-3 treatment? If VCAM-1 shedding occurs fairly quickly, why does progenitor mobilization lag for 2 or 3 days after G-CSF administration? Despite these caveats, the present data open a new window of observation and may eventually suggest new strategies to improve mobilization.

—Thalia Papayannopoulou
University of Washington