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**Escorting STAT5A**
Some transcription factors take a chaperone to the nuclear dance. On page 469, Williams et al. show that STAT5A gets this escort from the ERBB4 receptor tyrosine kinase.

ERBB4 becomes an escort upon activation by growth factors such as heregulin (HRG). The activated receptor is known to recruit and phosphorylate STAT5A and get cleaved, thus releasing ERBB4’s intracellular domain (4ICD). Williams et al. show that 4ICD remains associated with STAT5A in the cytoplasm. And rather than simply turning on a signal transduction pathway, 4ICD also physically transports STAT5A all the way to the nucleus. Mutation of the 4ICD nuclear localization signal blocked both 4ICD and STAT5A nuclear entry.

In the nucleus, the two remained associated at the promoter of H9252-casein, a STAT5A-regulated milk protein gene. β-Casein transcription was not stimulated unless both 4ICD and STAT5 were nuclear.

Late in pregnancy, ERBB4 replaces the prolactin receptor as the major STAT5A activator. The authors hypothesize that this switch, and STAT5A’s resulting interaction with 4ICD, may subtly alter STAT5A-mediated gene expression to bring about terminal differentiation of breast cells. Whether ERBB4 directly transactivates gene expression or can recruit other proteins to the regulated promoters, however, has not been formally tested.

**Expanded inclusions**
Like the better-known polyglutamine expansions, lengthy stretches of alanines create inclusion bodies that lead to death, as shown on page 411 by Nasrallah et al. Alanine expansions are found in several transcription factors that are associated with multiple disorders; thus, these maladies may all be rooted in inclusion body formation.

One alanine repeat–associated disorder, which causes neurological defects in infants, is caused by mutations in the ARX transcription factor. The new results show that 50% expansion of one of ARX’s alanine stretches leads to inclusion body formation in neurons. As with glutamine repeat-induced inclusions, the insoluble clumps of mutant ARX are tagged with ubiquitin, as though the cell is trying, yet failing, to degrade the misfolded proteins. Overexpressed Hsp70 chaperone cleared the inclusions.

**Patches ride cables**

In cell culture, expression of the mutant ARX increased cell death. Arrasate et al. (Nature. 431:805–810) recently reported that inclusion body formation was an effective coping mechanism by which polyglutamine-expanded proteins are kept from doing harm. But ARX inclusions may cause extra problems by removing both ARX and its interacting partners from the functional pool, thus disrupting transcription, altering cell physiology, and causing cell death. To confirm this theory, the authors plan to identify ARX’s gene targets and examine their expression levels in normal and inclusion-containing cells.

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