Acetylate to kill or save

Mammalian p53 can kill, or it can save. The end result, according to Knights et al. (page 533), depends on opposing acetylation events that send p53 down disparate paths. The stabilization of p53 following cellular damage can trigger either apoptosis or a reversible cell cycle checkpoint that probably gives cells time to recover. As either savior or killer, p53 is subject to a battery of posttranslational modifications, including phosphorylation and acetylation. One such acetylation event (on K373) is now shown to trigger apoptosis, whereas another (on K320) works against death.

To understand how, the authors expressed mutant versions of p53 that mimic the acetylation events. After a brief treatment with a mild DNA-damaging agent, only cells with K320-modified p53 resumed proliferation; the rest died. The promoters bound, and genes activated, by the two p53 mimics correlated with their outcomes.

Many proapoptotic genes have promoters that might be too low in affinity for K320-acetylated p53. This form of p53 was in a slightly denatured state with less intrinsic DNA-binding ability. It was also more readily exported from the nucleus due to a block in serine-15 phosphorylation. The K320 site is not conserved in fly and worm p53, which are solely death-inducing proteins. Mammalian tissues lacking regenerative abilities might have evolved the survival effect as a way to help maintain their numbers. Indeed, the group recently found that only K320 is acetylated during the neuronal maturation and neurite outgrowth that accompany regeneration.

Titinless mice

Titin needs no kinase activity to assemble sarcomeres, the building blocks of muscle tissue, according to Weinert et al. (page 559).

The giant protein called titin is a major component of muscles. Its COOH terminus, also known as the M-line region, includes a kinase-like domain. In yeast two-hybrid assays, titin’s M-line interacts with proteins that shuttle to and from the nucleus, leading scientists to believe that it might initiate sarcomere assembly via signaling pathways.

A mouse strain lacking the kinase-like domain and nearby regions, however, reveals that the domain is not necessary for sarcomere assembly. These mice died during embryogenesis, but histological images revealed that sarcomere assembly and heart formation were initially normal. The lethal defect was heart failure due to a lack of sarcomere thickening—the addition of more actin and myosin filaments.

Recently identified signaling proteins that control muscle gene expression, and protein turnover via the kinase domain were not expressed during embryogenesis in wild-type or mutant mice. The effects thus seem to be mostly structural, unless as-yet unidentified kinase targets are required. In the deletion strain muscles, titin tails failed to overlap with neighboring molecules and were swinging freely, locked down on only one end.

Myomesin, a protein that links actin filaments, also binds to a titin region lost in the deletion. Weinert believes its lost binding site may lead to loosely packed filaments that impair the stability of the sarcomere.