Unspliced regulator

Although most RNA splicing occurs in the nucleus, HAC1 and XBP1 mRNAs are spliced in the cytoplasm during ER stress. On page 565, Yoshida et al. demonstrate that in the case of XBP1 both the unspliced and spliced RNAs produce functional proteins and together the proteins form a feedback system that controls the duration of the stress response.

When unfolded proteins accumulate in the ER, sensor proteins trigger expression of chaperones. One sensor, IRE1, is a membrane-bound RNase located in the ER membrane. IRE1 cleaves XBP1 RNA to produce an mRNA encoding a transcription factor. Although unspliced XBP1, (XBP1[U]), is translated, it is degraded immediately and previously had no known function.

With improved extraction techniques, Yoshida et al. found that XBP1(U) does accumulate in cells and shuttles between the nucleus and cytoplasm. Moreover, XBP1(U) bound to the spliced form of the protein, XBP1(S), and the binding appeared to accelerate degradation of XBP1(S).

During the initial phase of the stress response, IRE1 was highly active, and most of the XBP1 RNA was spliced, allowing XBP1(S) to stimulate transcription of chaperones. As the amount of unfolded protein decreased, so did IRE1 activity, and the amount of XBP1(U) increased relative to XBP1(S). With more XBP1(U) available to sop up the spliced protein, activation of chaperone transcription was rapidly reduced.

This system should respond rapidly as it is acting on a pool of preformed cytoplasmic RNA; by contrast, any change in nuclear splicing patterns must wait for new transcription to supply a substrate. With that advantage in mind, and noting the elaborate machinery used by the IRE1 system, the team speculates that there must be other RNA templates that use the system. Already, the HAC1 RNA is known to have similar regulation, but the team is on the hunt for more. JCB

Making γ-tubulin ring

γ-tubulin is required at the centrosome for the formation of bipolar spindles and arrives in the form of a large complex, γTuRC. Vérollet et al. (page 517) and Haren et al. (page 505) find that a recently identified member of γTuRC, Dgp71WD in Drosophila and its mammalian homologue NEDD1, is necessary for proper spindle formation. However, the protein functions are not fully conserved between the two species.

Two complexes in cells contain γ-tubulin. The smaller complex is γTuSC, which contains γ-tubulin and two other proteins (GCP2 [Dgrip84] and GCP3 [Dgrip91]). γTuRC is composed of γTuSC, NEDD1/Dgp71WD, and three additional proteins (GCPs 4, 5, and 6).

Vérollet et al. found that depletion of any one of three γTuRC-specific proteins (Drosophila homologues of GCP4, 5, or 6) disrupted the γTuRC complex. Dgp71WD depletion did not affect complex formation, but frequently disrupted mitotic spindles. Most embryos lacking Dgp71WD were viable and appeared to survive by accumulating γ-tubulin at the centrosomes in the form of γTuSC.

Meanwhile, Haren et al. showed that NEDD1 is absolutely required for centrosomal function and for accumulation of γ-tubulin at the centrosome in mammalian cells, but not for the assembly of γTuRC. NEDD1-depleted cells resembled γ-tubulin mutants, with monopolar spindles forming in a large percentage of cells. These data agree with and extend recent work published by Lüders et al. (Nat. Cell Biol. 2005. doi:10.1038/NCB1349). Further analysis by Haren et al. demonstrated that NEDD1 is also required for duplication of the centrioles, which form the heart of the centrosome.

Why NEDD1 is essential in vertebrate cells, whereas flies can survive in the absence of Dgp71WD, may have to do with the abundance or functionality of the smaller γTuSC in flies. Despite the apparent differences, the researchers expect that ultimately the main processes involving NEDD1/Dgp71WD and γTuRC are likely to be similar between the organisms. The differences, they are finding now, may help them sort out possible models of centrosome assembly and function. JCB