Phosphorylation for break repair

A constitutive, phosphate-based interaction between two repair proteins may help provide instant, well-coordinated repair of double-stranded DNA (dsDNA) breaks, according to two articles in this issue from Melander et al. and Sypcher et al.

Nearly every step in dsDNA break repair requires MRN, from recognizing the break to activating signaling pathways to the mechanics of repair—or apoptosis, if repair fails. MRN can bind directly to DNA, but past experiments revealed that it also associates with the histones wrapped around damaged sequences, through an adaptor protein called MDC1.

Both groups now dissect this chromatin association. The findings reveal that the connection depends on a heavily phosphorylated domain within MDC1, which docks to a subunit of MRN called NBS1. In both articles, MRN was displaced from dsDNA breaks in cells containing mutant versions of MDC1 that lacked the phosphorylation sites.

The link between MRN and MDC1 did not depend on the presence of damaged DNA, however; even undamaged cells had phosphorylated MDC1. This phosphorylation depended at least in part on the constitutive and ubiquitous kinase, casein kinase 2 (CK2). Depletion of CK2 blocked the interaction between the repair proteins.

Repair aficionados often think that events taking place on the DNA itself are more important. But cells spend a great deal of energy coordinating the comings and goings of repair proteins on the chromatin, suggesting that these events might have evolved to improve repair precision. MDC1 is one of the earliest proteins to recognize histones at damage sites; by forming a constitutive link with MDC1, MRN ensures a rapid arrival to those same sites.

Previous results showed that MDC1 stays on damaged chromatin longer than MRN, indicating that the MDC1-MRN link is dynamic. This freedom may allow MRN to travel from the damage to the sundry other sites where it is needed, including the broken ends of the DNA.

The groups now hope to uncouple MRN and MDC1 without interfering with MDC1’s other binding partners by mutating only its CK2 target sites. They can then determine which of MRN’s sundry repair duties rely on its association with chromatin.

Ramírez-Valle, F., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200710215.

An eIF for proliferation

Proliferation gets its own translation initiation factor, based on findings from Ramírez-Valle et al. The results help explain why that eIF is commonly overexpressed in breast cancers.

The same group previously showed that malignancy in human breast cancers is correlated with high levels of elf4GI, a scaffolding protein within the translation initiation complex. In the new work, the authors block production of this protein to understand its effects on cells. In its absence, overall protein synthesis rates in an epithelial cell line were only partially reduced, but the cells were small and replicated slowly, similar to cells undergoing nutrient starvation.

Like starved cells, those lacking elf4GI had lethargic mitochondria and thus low ATP levels. In an attempt to boost ATP levels, the cells began to cannibalize their own contents via autophagy.

Some mRNAs were affected more than others by the absence of elf4GI. By identifying transcripts on polysomes, the group showed that loss of elf4GI specifically blocked the translation of mRNAs necessary for proliferation and energy production. These transcript-specific effects might explain how cancer cells with extra elf4GI thrive in the dense tumor environment, where cells should be starved for oxygen and nutrients. The initiation factor might therefore be a good target for cancer therapeutics.

According to the authors, the findings suggest that translation initiation requires individualized factors for classes of transcripts, much as transcription factors differentially activate promoters. The molecular basis for elf4GI’s preference for certain mRNAs is unknown. Many of the transcripts that depended on elf4GI were in very low abundance or had additional upstream open reading frames. elf4GI is known to help load the extra ribosomes needed to translate downstream reading frames.

Ramírez-Valle, F., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200710215.