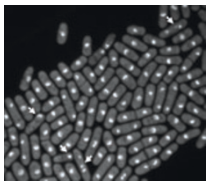
UV damage checkpoint



DNA damage caused by UV irradiation can be lethal to cells and can result in cancer, which is why we should slather ourselves in sunscreen. The cellular responses to UV-induced damage have been studied in several systems, and they involve DNA repair factors and proteins from cell-cycle checkpoints. When cells are exposed to high doses of UV, they delay entry into the next cell-cycle stage, which is thought to buy them time to repair the DNA damage. A recent report from Callegari and Kelly focuses on the responses of fission yeast to lower doses of UV, equivalent to sunlight exposure, and thus more akin to what organisms face in nature. Under these conditions, yeast cells did not delay the next division: instead, they went through the cell cycle and showed a delay only after they entered S phase and DNA was replicated. The postreplication delay presumably allows repair of DNA lesions, probably in the form of gaps left by the replication machinery across from the original UV-induced lesions. Thus, the cell cycle can continue in the presence of UV lesions, but after damaged DNA is replicated, postreplication repair processes must be completed before cells progress into mitosis. Mutants lacking the Chk1 kinase did not show the postreplication delay after UV damage, resulting in nuclear abnormalities and loss of cell viability. A similar postreplication checkpoint response was observed in budding yeast, and earlier reports suggest that the same might apply to mammalian cells, implying that the postreplication delay in response to damage by low doses of UV is conserved. Indeed, this novel mechanism might be the main response of these organisms to UV damage in the natural environment. (*Proc. Natl. Acad. Sci. USA* **103**, 15877–15882, 2006) *IC*

Not always 'one for all'

Most eukaryotic proteins have more than one independently folding domain. But do neighboring domains always cooperate, via their interaction surfaces, to facilitate formation of the native state? Batey and Clarke have used equilibrium denaturation studies to determine whether cooperativity is the norm for folding of multidomain proteins. Their model is the spectrin domain, which consists of a three-helix bundle. They measure *m*, a reflection of the change in solvent-accessible surface upon unfolding, for two paired spectrin domains (R1516 and R1617), compared with the individual R15, R16 and R17 domains. The folding pathways of the two paired domains are the same. However, whereas R1617 shows cooperativity (*m* of the paired domains is almost twice that of the individual domains), for R1516, *m* is approximately the same as for the single domains, indicating a lack of cooperativity. This is explained by the kinetics of the two paired domains. Folding of the two domains of R1516 occurs so that a substantial proportion of intermediate with one domain folded accumulates, but for R1617, this intermediate form does not accumulate. The unanticipated conclusion is that kinetic behavior contributes to *m*, and therefore equilibrium measurements alone do not provide enough information to understand how one domain affects its neighbors. Consequently, both equilibrium and kinetic studies need to be performed on individual domains and interacting paired domains to understand the basis of apparent cooperativity. (*Proc. Natl. Acad. Sci. USA*, advance online publication 15 November 2006, doi:10.1073/pnas.0604580103) *AKE*

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Reading OMP signatures

Outer membrane proteins (OMPs) are usually β-barrel proteins present in Gram-negative bacteria, mitochondria and chloroplasts. OMPs are assembled and inserted into the outer membrane by a dedicated multiprotein complex, containing the conserved protein Omp85. How the complex recognizes its OMP substrates was largely unknown. Tommassen and colleagues have shed some light on this process, reporting that purified *Escherichia coli* Omp85 forms oligomers that function as channels in planar lipid bilayers. The reconstituted Omp85 channels opened in the presence of denatured OMPs from *E. coli*, but not of PorA from *Neisseria meningitidis*. A signature motif at the C termini of OMPs determines the specificity for *E. coli* Omp85 interaction. A single-residue substitution at the C terminus of neisserial PorA, rendering it more similar to the *E. coli* OMP signature, was sufficient to allow PorA to interact with Omp85 and be correctly assembled by *E. coli*. The species specificity of the C-terminal signature explains the poor expression of heterologous OMPs in *E. coli* and demonstrates the evolutionary divergence in this conserved pathway. Interestingly, the same C-terminal sequence from OMPs has previously been found to signal cell-envelope stress, activating the protease DegS in *E. coli*. Thus, the C terminus of OMPs has a dual function: it identifies unfolded OMP precursors to Omp85, and it allows DegS to sense the accumulation of OMP assembly intermediates under membrane-stress conditions. Although it is clear that other regions of OMPs interact with Omp85 (and possibly with other members of the complex) during insertion into the outer membrane, this work is an important step toward understanding OMP biogenesis. (*PLoS Biol.* **4**, e377, 2006) *IC*

Methylation regulation on p53

The methylation status of particular histone lysines can be related to opposing states of promoter activity, with methylation at closely located lysines being associated with transcriptional activation and repression, respectively. Recent data from Berger and colleagues suggests that an analogous mechanism seems to regulate the tumor-suppressor protein p53: homologs of histone methyltransferases regulate p53 methylation at distinct residues, with opposing effects on p53 activity. Previously, it has been shown that the Set9 methyltransferase monomethylates p53 Lys372, increasing p53 activity. Berger and colleagues now show that, *in vitro* and *in vivo*, p53 Lys370 is also specifically monomethylated by a distinct methyltransferase called Smyd2. Smyd2-mediated Lys370 methylation decreases the abundances of p53 transcriptional targets such as *p21* and *mdm2*. Indeed, decreasing Smyd2 levels to prevent Lys370 methylation leads to increased apoptosis in cells with DNA damage, supporting the idea that methylation at this site normally represses p53 function. Intriguingly, methylation at Lys372, the mark that 'activates' p53, inhibits methylation at Lys370. This indicates cross-regulation of methylation at these sites. The study provides insight into the mechanism of this cross-talk, as increasing Lys372 methylation decreases the association of p53 with Smyd2. Further investigation will reveal how the two methyltransferase activities are coordinated and regulated by stress and DNA damage and why these modifications affect p53 activity. However, this study suggests that methylation at distinct lysines may be a broadly shared mechanism for coordinating activation and repression that extends beyond the histones. (*Nature*, advance online publication 15 November 2006, doi:10.1038/nature05287) *SL*