IN BRIEF

TELOMERES

Shelterin fends off six repair pathways

Telomeres have to be protected from being recognized as DNA damage by the repair machinery (the so-called 'end-protection problem'). This is mediated by the shelterin complex, and deletion of individual shelterin subunits has revealed that end-protection involves repression of signalling by ataxia telangiectasia mutated (ATM) and ATR, as well as inhibition of repair mediated by the non-homologous end-joining (NHEJ) and homology-directed repair (HDR) pathways. To definitively pin-point all pathways that are repressed by the shelterin complex, Sfeir and de Lange generated mouse telomeres lacking all shelterin proteins and associated factors. They identified two additional pathways: alternative NHEJ (which was activated when Ku70–Ku80 was also absent) and nucleolytic degradation (which was activated when p53-binding protein 1 (53BP1) was also absent). So, telomeres are protected from six DNA repair pathways by the shelterin complex, which functions together with DNA repair proteins.

ORIGINAL RESEARCH PAPER Sfeir, A. & de Lange, T. Removal of shelterin reveals the telomere end-protection problem. *Science* **336**, 593–597 (2012)

NUCLEAR TRANSPORT

Hikeshi 'puts out the fire' in the nucleus

During heat shock, the chaperone HSP70s translocates to the nucleus, although its exact nuclear functions are not well understood. Moreover, the mechanism of translocation was unknown, but Kose *et al.* now identify an evolutionarily conserved protein that acts as a protein carrier for HSP70s. This protein, which does not seem to belong to the importin-β family, was shown to preferentially bind to the ATP-bound form of HSP70s and to interact with FG repeat-containing nucleoporins, thereby translocating HSP70s through the nuclear pore complex. Importantly, the authors find that depletion of the protein, which they term Hikeshi (Japanese for firefighter), inhibits HSP70s import and reduces cell viability following heat shock.

ORIGINAL RESEARCH PAPER Kose, S, Furuta, M. & Imamoto, N. Hikeshi, a nuclear import carrier for HSP70s, protects cells from heat shock-induced nuclear damage. *Cell* **149**, 578–589 (2012)

POST-TRANSLATIONAL MODIFICATION

Keeping cell cycle progression in check

Retinoblastoma protein (RB) prevents cell cycle progression by binding to and inhibiting E2F transcription factors. This interaction is regulated by cyclin-dependent kinase (CDK), which phosphorylates RB, thereby inactivating it. RB phosphorylation at Thr373 and Ser608 has previously been shown to inhibit the association of the RB pocket domain with the E2F transactivation domain (TD). This study elucidates the mechanism by which this occurs by delineating the structural changes induced by Ser608 and Thr373 phosphorylation. Although both phosphorylation events ultimately prevent the association of the RB pocket domain with E2F, they stimulate distinct structural changes: Ser608 phosphorylation induces a conformational change in the large loop within the RB pocket domain that blocks binding of E2F TD; and Thr373 phosphorylation triggers a conformational change that results in docking of the RB pocket and the RB amino-terminal domain.

ORIGINAL RESEARCH PAPER Burke, J. R., Hura, G. L. & Rubin, S. M. Structures of inactive retinoblastoma protein reveal multiple mechanisms for cell cycle control. *Genes Dev.* 8 May 2012 (doi:10.1101/gad.189837.112)