STRUCTURE WATCH

A common fold

Telomeric DNA terminates in a single-stranded overhang, and several proteins bind these overhangs to protect them from degradation and fusion. Such proteins include the *Oxytricha nova* telomere-end-binding protein (TEBP), *Schizosaccharomyces pombe* protection of telomeres 1 (Pot1), human Pot1 and *Saccharomyces cerevisiae* Cdc13. The Pot proteins were identified on the basis of weak sequence similarity to TEBP, but no similarity between any of these proteins and Cdc13 was found. Now, however, Wuttke and colleagues report in *Science* that Cdc13 and TEBP use a common fold for telomeric-DNA interactions.

The authors determined the solution structure of the Cdc13 DNA-binding domain bound to telomeric single-stranded DNA, and found that Cdc13 is a member of the oligonucleotide-binding superfamily of OB-fold proteins. The OB motif — a β barrel composed of two, three-stranded antiparallel β sheets packed orthogonally — is used to bind oligonucleotides, oligosaccharides and oligopeptides, and, at present, it cannot be predicted using sequence comparisons. So, despite the lack of sequence similarity, Wuttke and co-workers showed that the Cdc13 OB fold is highly similar to that of *O. nova* TEBP, and conclude that structure-based comparisons should be used to assess homology in divergent proteins. They also conclude that the structural and functional similarities between Cdc13 and the other telomere-end-binding proteins indicate the evolutionary conservation of telomeric-end-protection mechanisms.

REFERENCE Mitton-Fry, R. M. *et al*. Conserved structure for single-stranded telomeric DNA recognition. *Science* **296**, 145–147 (2002)

A new folding machine

Molecular chaperones and proteases monitor protein folding, and distinguish misfolded proteins that can be correctly refolded from those that should be degraded. Unique insights into one such protease–chaperone machine — DegP (HtrA) from *Escherichia coli* — have now come from Clausen and co-workers, who describe its crystal structure in *Nature*.

The authors found that each DegP monomer has three domains — a protease domain and two PDZ domains. The functional DegP hexamer is formed by the staggered association of two rings, each comprising three DegP monomers. The protease domains form the 'top' and 'bottom' of the structure, and the PDZ domains make up the side walls. Clausen and colleagues observed two states for the hexamer. One state is 'open', with a wide lateral cavity through the oligomer, whereas the other state is 'closed' — a change that is mediated by the mobile PDZ domains.

Clausen and co-workers found that the proteolytic sites are situated in the cavity, which is only accessible laterally. They propose that the PDZ domains are involved in initial substrate interactions, and that hydrophobic patches in the cavity might subsequently bind unfolded proteins. The structure of the DegP hexamer is different from other cage-forming proteins, in which substrates enter a central cavity through narrow axial or lateral pores, so these authors have provided the structural basis to further understand the mechanism of this new type of protease–chaperone machine.

REFERENCE Krojer, T. *et al*. Crystal structure of DegP (HtrA) reveals a new protease–chaperone machine. *Nature* **416**, 455–459 (2002)

BONE HOMEOSTASIS

Control yourself!

Considering its 'static' structure, it's hard to believe that bone is being constantly remodelled by a dynamic equilibrium of deposition and resorption. To prevent matrix-degrading osteoclasts from getting over-zealous, bone-depositing osteoblasts keep them in check, but Taniguchi's group now reports that osteoclasts also exert a considerable amount of self-control.

Osteoclastogenesis — the process by which cells of macrophage/monocyte origin differentiate into functional osteoclasts — requires signalling downstream of RANK (receptor activator of NFκB ligand), which induces expression of the transcription factor c-Fos. Taniguchi and colleagues were looking to see which genes were induced when RANK is activated by its ligand — RANKL — and found that several of them required interferon (IFN)-α/β signalling. As mice with a defective IFN-α/β receptor system show enhanced signs of osteoporosis, the authors suspected that IFN-α/β signalling negatively regulates osteoclast activity.

Further analysis showed that IFN-β — not IFN-α — was responsible for this negative regulation. But how does IFN-β inhibit c-Fos? As c-Fos transcripts weren't downregulated, the authors carried out pulse-chase experiments to establish that protein synthesis was inhibited, and proposed that the double-stranded-RNA-activated protein kinase PKR was involved. This was not a wild guess — it is well known that PKR is induced by IFN-β through the heterotrimeric transcription factor complex ISGF3 (IFN-stimulated gene factor 3), and the authors showed that the inhibitory action of IFN-β was indeed mediated by ISGF3. Furthermore, PKR inhibits protein synthesis by phosphorylating eIF2α — a protein that has an important function in messenger RNA translation. As IFN-β could not fully inhibit osteoclast differentiation in *PKR*$^{-/-}$ mice, the authors propose that PKR is a target, probably among several others, that prevents osteoclastogenesis by inhibiting c-Fos.

Digging slightly deeper, Taniguchi and colleagues found that c-Fos itself was responsible for the RANKL-mediated induction of IFN-β, probably by directly binding to the *IFN-β* promoter. So, RANKL induces c-Fos, which induces IFN-β and then, in turn, IFN-β inhibits c-Fos expression. c-Fos, therefore, signals its own inhibition. The authors also showed that applying IFN-β to the site of bone destruction in an *in vivo* model inhibited bone resorption, causing excitement among clinicians, too.

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References and links

ORIGINAL RESEARCH PAPER Takayanagi, H. *et al.* RANKL maintains bone homeostasis through c-Fos-dependent induction of interferon-β. *Nature* **416**, 744–749 (2002)