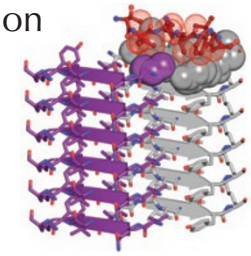
Inhibiting amyloid formation



Amyloid fibril deposits are associated with a number of neurodegenerative conditions. The relationship between the formation of such fibrils and the etiology of the diseases is not totally clear, but there has been considerable progress in understanding amyloid structures. This information comes mainly from X-ray crystallography of fibrils formed by short segments from the full-length proteins. Such fibrils have properties similar to those from amyloids formed with the full-length polypeptides. A common structural feature observed is the so-called steric zipper, in which β-sheets are held together by their interdigitated side chains; in the full-length amyloids, these short segments would stack to form the cross-β spine of the growing filament. Now Eisenberg and colleagues have used this detailed structural knowledge to design peptides that bind to the end of the fibrils and block them from further growth. The authors chose as targets the fibrils formed by peptides from tau protein and from prostatic acid phosphatase (PAP). Fibrils derived from these polypeptides have been respectively implicated in Alzheimer's disease and shown to increase infection by HIV-1. The inhibitory peptides were computationally designed to bind tightly to the ends of the steric zippers, with the interfaces maximized for hydrogen bonding and hydrophobic interactions. To achieve this, the authors used both D-amino acids and non-natural L-amino acids. They then found that the inhibitory peptides can efficiently block fibril formation by the full-length polypeptides *in vitro*. In addition, the inhibitor against PAP fibrils could also suppress the increase in HIV infectivity caused by the fibrils in human cells in culture. The predicted mode of interaction of the peptides with the fibrils was supported by electron microscopy imaging and by NMR spectroscopy. In addition to opening a new avenue for potential therapeutic intervention, the work supports the assertion that steric zippers are the structural spine of native amyloid fibrils. (*Nature* doi:10.1038/nature10154, published online 15 June 2011) *IC*

Nuclear membrane protein import

Nuclear pore complexes (NPCs) have a cylindrical central channel, in which nucleoporins (Nups) with disordered phenylalanine-glycine (FG)-rich regions provide the selectivity barrier. Some nuclear membrane proteins reach the inner nuclear membrane (INM) by diffusion through the pore membrane and adjacent lateral channels, and accumulate by binding nuclear structures. Other nuclear membrane proteins have a nuclear localization signal (NLS) and bind to transport factors karyopherin-α and karyopherin-β1 to pass the NPC and reach the INM. Veenhoff and colleagues now reveal new insights into the transport pathway of these NLS-containing nuclear membrane proteins. By using green fluorescent protein reporters of an integral INM protein from budding yeast in confocal fluorescence microscopy and immunoelectron microscopy analyses, the authors showed that the NLS-containing domain is sufficient for accumulation at the INM. The long linker region between the NLS and transmembrane domain is unstructured, as demonstrated by NMR analysis, and reporter proteins containing synthetic unfolded linker regions of sufficient length were efficiently transported to the INM. Remarkably, reporters containing a synthetic linker, an NLS and either one or all ten transmembrane segments of the endoplasmic reticulum protein Sec61 were efficiently imported to the INM. Transport of the reporters across the NPC was dependent on FG-rich regions of nucleoporins of the central channel, suggesting that nuclear membrane proteins pass through the central channel of the NPC. Trapping of reporter proteins at the Nup Nsp1–containing central channel of the NPC specifically blocked transport of membrane proteins but not soluble proteins. Together, these findings suggest a transport mechanism that is likely to exist in parallel with a previously proposed route based on diffusion and nuclear retention. (*Science* doi:10.1126/science.1205741, published online 9 June 2011) *AH*

Written by Inês Chen, Arianne Heinrichs & Steve Mason

Keep them separated

The transcriptional coactivator PGC-1α is known for its ability to regulate cellular metabolism in response to a variety of stimuli, and two of its best-characterized roles are the stimulation of mitochondrial biogenesis and gluconeogenesis. Separately controlling each of the many functions of PGC-1α would be advantageous to cells, but whereas mechanisms regulating overall PGC-1α activity are known, no pathway has been found that can differentially affect its actions. Spiegelman and colleagues now report that S6 kinase can regulate PGC-1α activity through phosphorylation of two serine residues in PGC-1α's arginine- and serine-rich domain. These modifications decreased the induction levels by PGC-1α of genes responsible for gluconeogenesis in both isolated hepatocytes and mouse livers but had no effect on the PGC-1α–mediated upregulation of genes promoting mitochondrial biogenesis. Rapamycin treatment or individual mutation of the phosphorylated residues in PGC1-α could block phosphorylation by S6K1 and therefore enhanced expression of gluconeogenic genes. Furthermore, phosphorylation of PGC-1α attenuated its ability to bind transcription factor HNF4, which activates gluconeogenesis. Conversely, the interactions between PGC-1α and FOXO1, PPARα and ERRα were unaltered by phosphorylation. It still remains to be seen whether other facets of PGC-1α activity can be regulated in similar fashion, and this will undoubtedly be an exciting area to explore now that this switch has been found. (*Genes Dev.* **25**, 1232–1244, 2011) *SM*

The heat is on

Hyperthermia therapy, in which the temperature in localized body tissues is raised to 41.0–42.5 °C, is used clinically to sensitize cancer cells to radiation or chemotherapy, but the mechanism behind this effect has remained unclear. Now Kanaar and colleagues show that hyperthermia inhibits homologous recombination, a major pathway to repair DNA double strand breaks (DSBs). Although the DNA damage response and early repair events (recruitment of MRE11, DNA end resection, RPA accumulation) seem unaltered by heat, the central step of homologous recombination—formation of a RAD51 nucleoprotein filament—is abrogated by incubation at higher temperatures. BRCA2 accumulation at DSB sites was also abolished, with cellular BRCA2 levels much reduced following heat treatment; similar observations were obtained from tumor biopsy tissues. BRCA2 deficiency makes cells more sensitive to PARP-1 inhibitors; here the authors found that cell lines and tumors showed higher sensitivity to PARP-1 deficiency when heated. This effect was also observed *in vivo*: rats and nude mice with implanted tumors were treated with PARP-1 inhibitors systemically and received local application of heat for 1 hour; the combined treatments resulted in a significant decrease in tumor growth. The mechanism by which BRCA2 gets degraded in response to heat remains to be determined, and hyperthermia may sensitize tumor cells through multiple mechanisms. Nevertheless, this work shows that locally inducing DNA repair deficiency in combination with genotoxic agent treatment can be a valuable therapeutic approach. (*Proc. Natl. Acad. Sci.* **108**, 9851–9856, 2011) *IC*