Grow old with me

Proteostasis—the ability of a cell or organism to control the amounts, conformations and locations of proteins—is influenced by many cellular processes, including translation, protein folding and degradation. A reduction in proteostasis capacity has been associated with ageing. Hoppe and colleagues now reveal a relationship between ubiquitin-mediated proteolysis and regulation of longevity. Working with the nematode *Caenorhabditis elegans*, the authors found that combined mutation of two factors involved in the ubiquitin-proteasome system, the chaperone-like ATPase CDC-48 (also known as p97 in mammals) and the deubiquitinase ATX-3, resulted in a considerable increase in worm lifespan (25.5 days on average, compared to 17.5 days in the wild-type parental strain). The physical interaction between CDC-48/p97 and the human Machado-Joseph disease related ATX-3 was previously known, though its functional relevance was unclear. The increased longevity of the *cdc-48 atx-3* mutant occurs via the insulin–IGF-1 signaling pathway and depends on the FOXO transcription factor DAF-16. A model substrate was found to be stabilized in the *cdc-48 atx-3* mutant, with an increase in polyubiquitinated forms enriched in non-K48 linkages. However, the overall levels of ubiquitinated proteins were no different in the double mutant than in wild-type cells, indicating that only specific endogenous substrates are targeted. The authors propose that CDC-48 and ATX-3 work together to edit ubiquitin chains on specific substrates and coordinate the formation of chains that are appropriate for proteasomal degradation. In the *cdc-48 atx-3* mutant, proteins involved in the insulin–IGF-1 signaling pathway might have abnormal ubiquitin chains and not be efficiently targeted to or degraded by the proteasome, resulting in longer lifespan; in support of this model, overexpression of CDC-48 (which could also result in abnormal ubiquitin chain editing) also increased longevity. The authors excluded DAF-16 as a direct target of CDC-48 and ATX-3, as its levels and cellular localization were not affected in the double mutant. Uncovering the identities of the relevant substrates will provide further insight into longevity regulation and also open avenues for therapeutic interventions. (*Nat. Cell Biol.* doi:10.1038/ncb2200, published online 13 Feb 2011) *IC*

Self-assembling cartwheels

Centrioles are important for the assembly of cilia, flagella and centrosomes and are characterized by a ninefold symmetrical structure resembling a cartwheel, with a central ring-like hub from which nine spokes radiate outwards. This cartwheel structure is thought to act as a scaffold onto which centriolar microtubules assemble, and it is the subject of two recent studies. Reporting in *Cell*, the groups of Gönczy and Steinmetz show, using structural analyses, that the centriolar protein SAS-6 from the nematode *Caenorhabditis elegans* forms rod-shaped homodimers through a strong interaction between their central coiled-coil domains. Analytical ultracentrifugation reveals the formation of higher-order oligomers in solution, which is mediated by the interaction between the N-terminal globular domains from adjacent homodimers. Experiments with transgenic worms and human cells confirm the physiological significance of SAS-6 oligomerization for centriole formation. Additional X-ray structures of the N-terminal domain and part of the coiled-coil domain of the related protein Bld12p from the green alga *Chlamydomonas reinhardtii* were used to generate a structural model in which nine homodimers assemble into a ring-like structure from which nine spokes corresponding to the coiled-coil domains emanate. In fact, recombinant Bld12p self-assembles into remarkably similar structures, as shown by EM. In *Science*, van Breugel *et al.* report the X-ray structure of the N-terminal domain of SAS-6 from zebrafish, which forms a head-to-head dimer. A crucial point mutation that prevents dimerization *in vitro* was validated *in vivo*, as the corresponding mutant failed to rescue aberrant flagellar formation in a Bld12p null mutant. The authors postulated that SAS-6 could also dimerize through its coiled-coil domain, a prediction that was confirmed through structural and genetic analysis. In fact, an SAS-6 mutant in which the coiled-coil domain and its packing against the N-terminal head domain are disturbed is unable to rescue the null phenotype, indicating that both dimerization interfaces have functional significance. An SAS-6 construct containing the two interfaces forms higher-order oligomers in solution, and cryo-EM images show a ring-like architecture with radially projecting spokes. Among structural models of SAS-6 rings with different symmetries, a nine-fold symmetric ring matches the diameter of cartwheel hubs observed in procentrioles by cryo-EM. Combined, these findings provide a structural basis for centriole formation that is evolutionarily conserved. (*Science* doi:10.1126/science.1199325, published online 27 Jan 2011; *Cell* **144**, 364–375, 2011) *AH*

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AKTing up

Although gene expression can vary from cell to cell, what this may mean in terms of functionality—or whether such differences are random fluctuations—is unclear. Using flow cytometry, Cantley and colleagues have now examined cell-to-cell variation in the PI3K-AKT signaling pathway in mammary epithelial cells. Upon saturating EGF treatment, AKT activation, as measured by AKT phosphorylation (pAKT), showed a distinct bimodal distribution rather than one indicating more random population fluctuations. The authors examined hemagglutinin-tagged p110α to see if variation was due to PI3K complex levels, and found that both this and the endogenous p85 subunit were quite dynamic, with distinct subpopulations of cells being classifiable by low, medium or high PI3K levels. The highest-p110α state was found by the authors to be stabilized when particular oncogenic mutants were expressed. The expression variation could also be correlated with particular phenotypes: cells about to undergo senescence tend to be p110α high, as do cells that initiate colony formation, and cells making multiple neighbor contacts tend to be p110α low. Even though the distribution of p110α levels are linked in the study through drug-based inhibition to synthesis and proteasome-mediated degradation, the mechanism by which this could maintain a bimodal distribution remains an interesting question for further pursuit, as does whether such control confers a selective advantage to the population by keeping most cells away from a state where tumorigenesis might arise. (*Curr. Biol.* **21**, 173–183, 2011) *SL*