PTEN prevents junction instability

The spatial organization of epithelial cells is dependent on the length and stability of adherens junctions. Bellaïche and colleagues demonstrate that the lipid phosphatase and tumour suppressor PTEN, known to mediate cell packing through undefined mechanisms, is a critical regulator of junction length during *Drosophila melanogaster* wing development (*Dev. Cell* **25,** 534–546; 2013).

Expanding previous characterizations of *pten* mutants, the authors found defects in hexagonal cell packing that were independent of apical–basal polarity disruption. A theoretical model in combination with laser ablation of junctions predicted that the 'cobblestone' phenotype arises from a heterogeneity in junction adhesion and contractility. Indeed, analysis of myosin II localization and E-cadherin–GFP behaviour agreed with this idea. The analysis showed that PTEN loss prevents junction elongation, leading to short unstable junctions that continue rearranging — another prediction of the model.

Analysis of GFP-tagged proteins demonstrated that myosin II and its upstream regulator Rho kinase are enriched at newly formed junctions, and decrease during junction elongation in wild-type, but not in *pten* mutant, tissue. Furthermore, loss of Rho kinase suppressed the loss of cell packing in *pten* mutants, suggesting that PTEN reduces Rho-kinase-mediated myosin II contractility at junctions — most probably through PtdIns(3,4,5)P_3, given that PtdIns(3,4,5)P_3 junctional levels fail to decrease in the mutants. Further simulations suggested that local maintenance of tension is sufficient to cause the cell-packing phenotype of *pten* mutants. The authors also characterized the contribution of PTEN to the global tissue architecture of the *Drosophila* wing. CKR

Collagen keeps muscle stiff for regeneration

Adult muscle stem cells, or satellite cells, ensure muscle regeneration and are embedded in a niche that contains myofibres and extracellular matrix (ECM). Bonaldo and colleagues used a mouse model lacking the collagen VI protein to demonstrate that the ECM modulates myofibre stiffness to ensure optimal activity of the satellite cells (*Nat. Commun.* **4,** 1964; 2013).

The authors observed that collagen VI is expressed by satellite cells and deposited in the interstitial ECM in muscle, and found that its expression is induced by injury. They described a decrease in satellite cell numbers after injury as well as impaired satellite cell activity and muscle regeneration in the collagen VI knockout mice. *In vitro*, these mutant satellite cells were not able to differentiate to cardiomyocytes, and displayed poor survival properties. The authors also demonstrate that collagen-VI-deficient satellite cells transplanted alongside wild-type satellite cells, or fibroblasts (which can produce collagen VI), show restored regeneration capacity. It is known that physiological levels of muscle stiffness are required for optimal differentiation of stem cells into myoblasts. Mechanistically, the authors found that muscle isolated from the collagen VI knockout mice has lower stiffness properties than wild-type fibres following injury, and that growing wild-type satellite cells on these mutant fibres or transplanting these cells in a mutant animal decreases their regeneration properties. NLB

Replication origin regulation

Treslin (also known as TICRR; orthologue of yeast Sld3) is an essential replication protein regulated by cyclin-dependent kinases and DNA damage. Diffley and colleagues identify Mdm two binding protein (MTBP) as a crucial Treslin partner at replication origins (*Science* **340,** 981–984; 2013)

Using mass spectrometry, the authors identified MTBP as a Treslin binding partner. The authors confirmed the existence of a ternary complex that also contains the known Treslin-binding partner TopBP1 in cells. A Treslin mutant unable to interact with MTBP is unable to rescue DNA replication in Treslin-depleted cells. Time-lapse microscopy of cells expressing a GFP-tagged version of replication marker PCNA revealed that S phase is slowed down in MTBP-depleted cells. DNA fibre analysis showed that this is because of reduced origin firing rather than reduced replication fork speed. Origin licensing protein Mcm2 was efficiently recruited to chromatin in MTPB-depleted cells, but levels of PCNA and components of the CMG helicase, a complex involved in DNA unwinding at replication forks, were reduced.

These findings reveal a role for the Treslin–MTBP–TopBP1complex in origin firing. MTBP is amplified in some cancers, and it will be interesting to investigate whether its role in replication is relevant in this context. CKR

Macropinocytosis supports cancer cell proliferation

Cancer cells have a high and unique metabolic demand, and thus it is of interest to gain insights into the mechanisms that govern nutrient uptake. Overexpression of oncogenic Ras is known to stimulate macropinocytosis, an endocytic process whereby cells internalize extracellular fluid and its contents. Bar-Sagi and colleagues (*Nature* **497**, 633–637; 2013) have now demonstrated the functional importance of this process in Ras-transformed cancer cells. By studying these cells both *in vitro* and *in vivo*, the authors showed that they displayed increased levels of macropinocytosis, which enhanced albumin internalization and subsequently increased intracellular levels of glutamine and its downstream metabolite α-ketoglutarate. Furthermore, catabolized proteins entered the central metabolism, and protein-derived amino acids were metabolized through several pathways. The increased level of macropinocytosis translated into an increased proliferation of cells deprived of glutamine but supplemented with albumin. Increased protein uptake and proliferation could also be generalized to cells with enhanced levels of macropinocytosis regardless of Ras status. Interestingly, in mice, inhibition of macropinocytosis using a specific inhibitor of macropinosome formation resulted in attenuation or regression of tumour growth.

This shows that in cancer cells, increased levels of macropinocytosis can be a beneficial nutrient uptake mechanism to support proliferation. Therefore, inhibiting macropinocytosis could have potential therapeutic benefits. MT

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