mTOR regulates pyrimidine synthesis

The mammalian target of rapamycin (mTOR) regulates cell metabolism and proliferation, and deregulation of the mTOR signalling network is associated with several diseases. mTOR forms two distinct complexes, C1 and C2 — the C1 complex can be inhibited by rapamycin. Although direct substrates and downstream effectors of mTOR, such as S6 kinase, are well studied, the broad physiological role of mTOR implies that there are still downstream pathways to be identified.

Now, Hall and colleagues (*Science* http://doi.org/krg; 2013) and Manning and colleagues (*Science* http://doi.org/krh; 2013) have identified another target of mTORC1, the pyrimidine synthesis pathway. Hall and colleagues used a phosphoproteomics approach to identify unknown mTOR effectors, whereas Manning and colleagues screened for metabolites regulated by mTORC1. Both studies showed that mTORC1, through S6 kinase, phosphorylates CAD (carbamoyl-phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase), an enzyme that catalyses the three first steps of pyrimidine synthesis. mTORC1 activation led to an increase in *de novo* pyrimidine synthesis, but nutrient deprivation or inhibition of mTORC1 showed the opposite effect.

Furthermore, Hall and colleagues revealed that phosphorylation of CAD leads to oligomerization of the CAD proteins and cell cycle progression through S phase. These articles provide evidence of a further role for mTOR in orchestrating anabolic cell growth by stimulating nucleotide synthesis. MT

A jagged road to cancer stem cells

The tumour microenvironment has been shown to influence cancer stem cell properties. Ellis and colleagues now report that endothelial cells promote cancer stem cell properties in colorectal cancer cells, through the action of a secreted form of Jagged-1 (*Cancer Cell* **23,** 171–185; 2013).

The authors used cell co-culture experiments and treatment of colorectal carcinoma cells with endothelial-cell-derived conditioned media to show that endothelial cells could promote the de-differentiation of non-stem cancer cells towards a cancer stem cell phenotype. These endothelial-cell-influenced colorectal cancer stem cells exhibited increased tumorigenicity and metastatic colonization ability *in vivo* and chemoresistance *in vitro*.

Induction of cancer stem cell properties by endothelial cells depended on the activation of Notch signalling in colorectal cancer cells through the paracrine action of an endothelial-cell-produced factor, which was identified as the Notch ligand Jagged-1. Although Jagged-1 is usually membrane-associated, the authors demonstrated that in this setting, endothelial cells produced a soluble form through the action of the ADAM17 protease, and further showed that Jagged-1 cleavage by ADAM17 was necessary for promoting the cancer stem cell properties of colorectal cancer cells. Colorectal cancer stem cells with activated Notch signalling were also observed adjacent to endothelial cells in human primary and metastatic colon cancer samples, indicating that endothelial cells are important in establishing a perivascular niche for colorectal cancer stem cells. AIZ

A STUbL in telomere protection

Chromosome ends must be protected from repair machineries to avoid genomic instability. In yeast, the shelterin component Rap1 inhibits repair by non-homologous end-joining (NHEJ) at telomeres. Marcand and colleagues (*EMBO J.* http://doi.org/krj; 2013) have identified the SUMO-targeted ubiquitin ligase (STUbL) Uls1 as a key mediator of NHEJ inhibition at yeast telomeres, acting on SUMOylated Rap1.

The authors found that stationary yeast cells lacking Uls1 showed an increase in telomere–telomere fusions, a hallmark of aberrant telomeric NHEJ. Uls1 possesses translocase and ubiquitin ligase activities, and mutational analysis revealed that both were needed to prevent fusions. Furthermore, Uls1 localized to chromosome ends. SUMO mutations that prevent the accumulation of poly-SUMO chains rescued telomere fusions caused by loss of Uls1, suggesting that SUMOylated proteins perturb NHEJ inhibition. As published studies report a negative synthetic interaction between *uls1* deletion and a hypomorphic allele of *rap1*, as well as SUMOylation of Rap1, the authors went on to investigate the role of Rap1 in Uls1 telomere function. Indeed, they found that mutation of Rap1 SUMOylation sites bypasses the requirement for Uls1 in NHEJ inhibition at telomeres, and that poly-SUMOylated Rap1 accumulates in the absence of Uls1. Thus, Uls1 acts to limit the accumulation of poly-SUMOylated Rap1. Although the precise role of Rap1 poly-SUMOylation remains unclear, the data suggest an inhibitory effect on a subset of pathways downstream of Rap1 in NHEJ inhibition. CKR

Blood cells: Each to their own niche

CXCL12 is a chemokine required for maintenance of haematopoietic stem cells (HSCs) in mammals. HSCs reside in a specialized niche microenvironment in the bone marrow, but the identity of the niche cells providing the molecules required for HSC maintenance has been unclear. Ding and Morrison (*Nature* http://doi.org/krd; 2013) and Link and colleagues (*Nature* http://doi.org/krf; 2013) showed that HSCs depend on CXCL12 production in perivascular mesenchymal cells and in a subset of endothelial cells for their maintenance, whereas specific lymphoid progenitors rely on osteoblast-produced CXCL12.

Ding and Morrison used a mouse in which the fluorescent label ds-Red was knocked in at the endogenous CXCL12 locus. They found that it is expressed mainly in endothelial and perivascular stromal cells, and at lower levels in osteoblasts and haematopoietic cells; however, using a specific knockout, the authors ruled out that haematopoietic cells produce the CXCL12 maintains HSCs. An elegant series of cell-specific knockout experiments were performed by both groups. Deletion in endothelial cells led to loss of HSCs without an effect on myeloid or lymphoid progenitors, whereas deletion in osteoblasts depleted the lymphoid lineage. Deletion of CXCL12 from specific perivascular stromal cells induced a depletion of HSCs and some progenitors, and also mobilized the stem cells to the circulation. These data indicate the existence of distinct stem-cell- and progenitor-specific niches, and illustrate the complexity of niche–progenitor interactions in the bone marrow. NLB

By Nathalie Le Bot, Christina Karlsson Rosenthal, Maria Trajkovska and Alexia-Ileana Zaromytidou