RESEARCH HIGHLIGHTS

Partial loss of Dicer promotes cancer

MicroRNAs (miRNAs) can act either as oncogenes or tumour suppressors when regulating mRNAs in cancer. The miRNA-processing factor, Dicer, is required for miRNA maturation and is essential for mouse development. Jacks and colleagues now show that loss of one *Dicer1* allele enhances tumour formation in mice, suggesting that Dicer1 is a haploinsufficient tumour suppressor (*Genes Dev.* **23,** 2700–2704; 2009). The authors showed previously that conditional deletion of *Dicer1* promotes tumour formation in a mouse lung cancer model. Now they show that mice heterozygous for the *Dicer1* mutation have a survival disadvantage compared with mice lacking both *Dicer1* alleles, both in the lung cancer model and in a model for soft tissue carcinoma. Cells from either tumour were found to always retain a copy of *Dicer1*. Nevertheless, there was a global decrease of miRNA levels in the lung cancer cells, demonstrating that the retained *Dicer1* allele was insufficient to fully support the processing machinery. Induction of complete loss of *Dicer1* reduced tumour formation compared with heterozygotes, suggesting selection against losing both alleles.

To probe the relevance of these findings for human cancer, the authors analysed available data on various cancers for *DICER1* copy number. *DICER1* was frequently deleted, but homozygous deletion of the *DICER1* locus was never observed, suggesting that DICER1 functions as a haploinsufficient tumour suppressor in humans as well. It will be interesting to see whether other components of the miRNA maturation machinery function this way. CKR

Ageing stem cells rejuvenated

Haematopoiesis and lymphopoiesis decline in ageing organisms due to decreased functionality of haematopoietic stem cells (HSCs). These changes probably contribute to age-related conditions, such as weakened adaptive immunity and anaemia. The molecular pathways underlying this reduced HSC functionality are unclear. Zheng and colleagues now report (*Sci. Signal.* **2**, ra75; 2009) that mTOR signalling is elevated in HSCs from aged mice, and that inhibition of mTOR restores HSC function and improves immunity in old mice.

Zheng and colleagues found that the amount of phosphorylated mTOR and its downstream substrate S6K was higher in HSCs from aged mice. Deletion of the mTOR inhibitor *Tsc1* results in increased mTOR activity and, interestingly,Tsc1-depleted HSCs showed reduced capacity of self-renewal and haematopoiesis in transplanted recipients, mimicking the behaviour of aged HSCs. Treatment of old mice with rapamycin (mTOR-specific inhibitor) increased their life span, enhanced HSC regenerative capacity and reduced expression of p16 and p19, cell-cycle inhibitors known to contribute to cellular senescence and ageing. Moreover, rapamycin enhanced the generation of B cells in aged mice, and boosted their immune response to the influenza virus.

These findings point to mTOR as a potential target for restoring haematopoiesis in older individuals. It will be important to establish the mechanisms responsible for altered mTOR signalling in ageing HSCs, and to expand this analysis to other types of adult stem cells. SG

Matrix stiffness drives tumour invasion

Remodelling of the extracellular matrix (ECM) is important for tumour progression. Stiffening of the matrix is also a hallmark of tumorigenesis, but how this is triggered and its importance has been less clear. Weaver and colleagues now report (*Cell* **139,** 891–906; 2009) that during breast cancer development, collagen crosslinking stiffens the matrix and promotes tumour invasion through integrin-mediated mechanotransduction.

The authors first confirmed that collagen crosslinking increases and the ECM stiffens during breast cancer progression to an invasive state. They then showed that increasing collagen crosslinking *in vivo*, by the addition of fibroblasts expressing the crosslinking enzyme LOX, increased tissue stiffening, induced more focal adhesions and increased growth and invasion of subsequently transplanted pre-malignant tumour cells; inhibiting collagen crosslinking had the opposite effects. By examining the effects of non-specifically inducing collagen crosslinking in tumour cells with altered ErbB2 activity in 3D culture, the authors found that changes in the matrix must cooperate with oncogene signalling to drive tumour invasion. This invasion required β1 integrin signalling, and the induction of integrin clustering was sufficient to promote focal adhesions and drive invasion of pre-malignant tumour cells *in vitro* and *in vivo*. Integrins are known to activate PI(3)K, and the authors found that the effects of collagen crosslinking and integrin signalling on tumour progression occur via PI(3)K signalling.

These results may help to explain the previous correlations seen between tissue stiffening, fibrosis and cancer risk, and suggest that the mechanical effects of the ECM on tumour progression are important considerations when devising potential anti-cancer strategies. AS

RANKing body temperature

The receptor-activator of NF-κB ligand (RANKL) and its receptor, RANK, exert their remodelling function in both bone and mammary glands, but they are also expressed in the brain. Penninger and colleagues now show that RANKL/RANK act in the central nervous system to regulate the fever response and female body temperature (*Nature* **462,** 505–509; 2009). They injected RANKL in rat and mice brains and noticed that the animals had reduced diurnal activity and exhibited high fever. Both phenotypes could be suppressed by an additional injection of the natural RANKL antagonist osteoprotegerin into the central nervous system. Further analysis showed that both RANKL/RANK are expressed in neurons and astrocytes in brain regions that are involved in body temperature control, and that conditional knockout of RANK in neurons and astrocytes prevented the normal inflammatory fever response after LPS, IL1-β and TNF-α challenges. RANKL/RANK stimulation appears to induce Cox2 and prostaglandin E2 synthesis, which triggers the fever response in the central nervous system. Female mice carrying a brain-specific deletion of RANK show an increased basal body temperature during the day, which depends on ovarian hormones, indicating that the effects of RANK on temperature might be affected by sex hormones. Interestingly, two osteopetrosis patients carrying a RANK mutation did not display pneumonia-associated fever, suggesting that RANKL/RANK might also control body temperature in humans. NLB

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