MICROENVIRONMENT

Boning up on blood

The contribution of the microenvironment to oncogenesis has been extensively reported. Raaijmakers *et al.* have made a valuable contribution to this field by describing how specific changes in the microenvironment can initiate cancer development by triggering secondary genetic changes in other cells.

Mesenchymal stromal cells are a constituent of almost all tissues and take part in organ formation and homeostasis. Working on the principle that mesenchymal cells of the osteoblast lineage modulate haematopoiesis, the authors investigated which stage of differentiation of osteoblastic cells was crucial for the regulation of haematopoiesis. To that end, they deleted *Dicer1*, a gene required for RNA and micro-RNA processing, so that many of the resulting gene products would be altered. Mice lacking *Dicer1* in osteoprogenitors, but not mature osteoblasts, showed severely altered haematopoiesis, including cytopenia, multilineage dysplasia, increased proliferation and apoptosis of primitive haematopoietic progenitors, decreased B cell levels and increased bone marrow vascularity, all of which are principle characteristics of myelodysplastic syndrome. In

addition, a small proportion of the animals developed facial myeloid sarcomas and acute myelogenous leukaemia.

To assess how much the microenvironment contributes to this haematopoietic phenotype, the authors then transplanted bone marrow cells of *Dicer1*-mutant mice into wild-type mice. Analysis of the bone marrow and peripheral blood 16 weeks after the transplant showed complete normalization of haematopoiesis. By contrast, when bone marrow cells from wild-type mice were transplanted into mice with the *Dicer1*-deleted microenvironment, the recipients developed haematopoietic abnormalities.

Microarray analysis of primary osteolineage cells lacking *Dicer1* showed decreased expression of *Sbds*, a gene mutated in Schwachman–Bodian–Diamond syndrome, a condition that is characterized by haematopoietic abnormalities as well as a propensity to develop myelodysplastic syndrome and acute myelogenous leukaemia. Accordingly, when the authors deleted *Sbds* in osteoprogenitor cells they obtained a similar phenotype to that observed when

deleting *Dicer1*, with resulting severe bone marrow dysfunction and myelodysplasia.

These findings demonstrate that alterations in a specific mesenchymal microenvironment can be sufficient to initiate a disordered haemostasia that can result in cancer initiation. Raaijmakers *et al.* postulate a niche-based model of oncogenesis in which the microenvironment becomes the starting point for a series of genetic changes that lead to malignancy in a different type of cell.

Teresa Villanueva

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