

 TUMOUR MICROENVIRONMENT

A β -catenin mutation in osteoblasts induces leukaemia

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A new study has shown that mice with an activating β -catenin mutation that is specifically expressed in osteoblasts develop acute myeloid leukaemia (AML).

Osteoblasts influence normal haematopoietic processes, such as lineage determination, as they form part of the haematopoietic stem cell (HSC) niche, and previous studies in mice have associated mutations in osteoblasts with the development of pre-leukaemic conditions. To investigate whether osteoblasts that carry a single oncogenic mutation could induce leukaemia, Kode and colleagues generated mice with a mutation, *Ctnnb1*^{CAosb}, that results in the expression of constitutively active β -catenin, which is confined

to osteoblasts. Mice with this mutation exhibited cellular anomalies that were characteristic of AML in humans.

To determine whether the osteoblasts caused AML and whether they induced permanent changes in HSCs that would perpetuate the disease, the authors carried out transplantation experiments. Bone marrow cells from leukaemic mice that expressed *Ctnnb1*^{CAosb} were transplanted into lethally irradiated wild-type mice; this induced AML. The converse experiment, in which bone marrow from wild-type mice was transplanted into lethally irradiated mice that expressed *Ctnnb1*^{CAosb}, also resulted in AML in the recipient mice. Furthermore, transplantation of long-term repopulating HSCs (LT-HSCs), but not other haematopoietic populations from mice that expressed *Ctnnb1*^{CAosb}, also resulted in AML. Thus, osteoblasts that express *Ctnnb1*^{CAosb} cause AML in this model, and it seems likely that the *Ctnnb1*^{CAosb} mutation causes a permanent alteration in LT-HSCs, which results in leukaemia-initiating cells.

To further investigate the molecular pathways involved, the authors used a gene expression microarray, which showed that jagged 1 (*Jag1*; the ligand for Notch) was upregulated in osteoblasts of mice that expressed *Ctnnb1*^{CAosb}. Notch has previously been implicated

in haematopoiesis and is regulated by β -catenin. To determine the effect of *Jag1* on the development of AML, one allele was knocked out in mice that carried the *Ctnnb1*^{CAosb} mutation. This decreased Notch signalling in HSC progenitors, and these mice did not develop AML. The authors also used a γ -secretase inhibitor to suppress JAG1–Notch signalling in mice with the *Ctnnb1*^{CAosb} mutation, and this reversed the development of AML in these mice.

To determine whether these findings are clinically relevant, the authors examined bone marrow biopsy samples from patients with myeloid dysplastic syndromes (MDS) and AML. They found that 38% of these patients showed nuclear (activated) β -catenin in osteoblasts and upregulation of Notch signalling in haematopoietic cells; nuclear staining of β -catenin was absent in healthy controls. Interestingly, during the screening of assumed healthy controls, two participants were found to have increased nuclear β -catenin staining in their osteoblasts and later developed MDS. These findings suggest that nuclear localization of β -catenin might be a useful biomarker for diagnosis of MDS.

Collectively, these data indicate that alteration of the HSC niche by mutation in osteoblasts is sufficient to drive the development of leukaemia in mice. Furthermore, these data indicate that the JAG1–Notch pathway may be a feasible pharmacological target for the treatment of a subset of human AMLs.

Isabel Lokody

ORIGINAL RESEARCH PAPER Kode, A. et al. Leukaemogenesis induced by an activating β -catenin mutation in osteoblasts. *Nature* <http://dx.doi.org/10.1038/nature12883> (2014)

