LEUKAEMIA

Notch has commitment issues

Notch signalling is normally considered oncogenic in the haematopoietic system. However, Klinakis, Lobry and colleagues now show that inactivation of the Notch pathway is associated with a subset of patients with chronic myelomonocytic leukaemia (CMML), which suggests that Notch signalling can be both oncogenic and tumour suppressive in haematological malignancies, as is the case for solid tumours.

> “a new tumour suppressor function for the Notch pathway in suppressing myeloid-biased lineage commitment in haematopoiesis.”

Activating mutations of *NOTCH1* are particularly associated with T cell acute lymphoblastic leukaemia (T-ALL), as Notch signalling regulates the differentiation of haematopoietic stem cells towards the T cell lineage. To examine haematopoiesis in the absence of Notch signalling, Aifantis and colleagues knocked out nicastrin (*Ncstn*), which is a member of the γ-secretase complex that activates Notch receptors. *Ncstn*$^{-/-}$ mice did not survive beyond 20 weeks, and histological analyses revealed that they had abnormally high levels of monocytes (moncytosis) and leukocytes (leukocytosis) in their peripheral blood, as well as enlargement of the spleen. These phenotypes are indicative of a myeloproliferative disorder, particularly CMML. Monocytes originate from granulocyte-monocyte progenitors (GMPs), and the authors found that loss of *Ncstn* enlarged the myeloid-biased lineage^{-} SCA1^{+} KIT^{+} (LSK) population in the bone marrow and increased the GMP population in the bone marrow and spleen. In addition, the population of lymphoid-biased multipotential progenitors (MPPs) was significantly reduced in the bone marrow. Moreover, *Notch1*$^{-/-}$*Notch2*$^{-/-}$-double knockout mice phenocopied *Ncstn*$^{-/-}$ mice, indicating that inhibition of NOTCH1- and NOTCH2-mediated signalling is responsible for the *Ncstn*$^{-/-}$ phenotype.

Transcript profiles of LSK and GMP cells from *Ncstn*$^{-/-}$ mice showed significant derepression of myeloid-specific genes and expression of a GMP-specific gene expression profile that persisted in later stages of differentiation (including in MPPs). So, the authors investigated whether Notch, which is usually considered to be an activator of transcription, induces a transcriptional repressor that suppresses genes that are associated with differentiation along the myeloid lineage. Hairy and enhancer of split 1 (HES1) is a target of Notch and a transcriptional repressor, and the authors showed that expression of HES1 suppressed the expression of granulocyte-monocyte commitment genes, including CCAAT/enhancer binding protein-α (*Cebpa*) and *Sfpi1* (also known as *Pu.1*). Furthermore, culturing wild-type GMPs in the presence of the Notch ligand delta-like 4 (DLL4) increased apoptosis, indicating that Notch signalling affects GMP lineage commitment and homeostasis. Indeed, hyperactivation of NOTCH1 (using the NOTCH1-IC mutant) suppressed GMP expansion and disease development in *Ncstn*$^{-/-}$ mice and drove progenitor commitment towards the lymphoid and megakaryocyte-erythrocyte lineages. Together, these data show that NOTCH1- and NOTCH2-mediated activation of HES1 suppresses myeloid commitment and that loss of this pathway in haematopoiesis induces myeloproliferation.

So, is this relevant to human haematopoiesis and CMML? The authors found that the expression of Notch ligands suppressed the differentiation towards granulocyte and monocyte lineages of human MPPs from bone marrow and cord blood. Moreover, exon sequencing of 42 CMML samples identified six somatic heterozygous mutations in genes encoding members of the Notch pathway, including *NCSTN*, anterior pharynx defective 1A (*APH1A*), mastermind-like 1 (*MAML1*) and *NOTCH2*. Further analyses *in vitro* showed that the MAML1-Q345X mutant had dominant-negative affects and that NCSTN-A433T was a loss-of-function mutation.

These data identify a new tumour suppressor function for the Notch pathway in suppressing myeloid-biased lineage commitment in haematopoiesis.

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