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CANCER

Activating Notch ameliorates AML

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The Notch signalling pathway — which is involved in a multitude of cellular processes, such as cell fate determination and angiogenesis — is oncogenic or tumour suppressive depending on the cell type. The precise role of this pathway in acute myeloid leukaemia (AML) is unclear. Now, two papers published in the *Journal of Experimental Medicine* show that Notch signalling is silenced in AML, implying that this pathway has a tumour-suppressive role in this disease. Moreover, activation of this pathway inhibited the growth of AML cells *in vitro* and *in vivo*, suggesting that induced activation of Notch signalling could be a potential therapeutic strategy.

First, both Kannan *et al.* and Lobry *et al.* used human AML samples to examine the expression patterns of the four Notch receptors and their associated target genes. Both studies noted higher levels of *NOTCH2* mRNA expression in most of the AML samples compared to normal bone marrow-derived haematopoietic stem cells (HSCs). However, protein levels of cleaved (activated) Notch receptors were lower in AML samples than in normal HSCs. This lack of Notch activation correlated with lower expression levels of the target genes of Notch, such as hairy and enhancer of split 1 (*HES1*), Deltex 1 (*DTX1*) and Notch-regulated ankyrin repeat protein (*NRARP*).

Together, these results show that Notch receptors have distinct patterns of expression depending on the cell type (that is, normal versus AML), which could reflect their route of myeloid development. Moreover, Notch signalling is silenced in AML, in contrast to what occurs in T cell leukaemia, in which a constitutive activation of the Notch pathway is seen.

Next, the two groups conducted detailed *in vitro* and *in vivo* experiments to examine the precise role of the Notch signalling pathway in AML. They showed that the Notch–HES1 pathway induces the caspase-mediated apoptosis of AML cells and that this may be mediated by B cell lymphoma 2 (BCL-2) and tumour suppressor p53, as these were significantly downregulated (BCL-2) or upregulated (p53) in response to induction of Notch signalling. As well as inducing apoptosis, Notch activation induced the differentiation of leukaemia-inducing cells towards macrophage and dendritic cell types, which could also lead to disease regression. Importantly, activation of the Notch pathway did not affect normal haematopoietic cells, indicating that the risk of inducing other leukaemias with this approach is low.

In addition to these results, two novel concepts were uncovered by the two groups. Kannan *et al.* showed that host-based, Notch ligand-mediated signalling effects can also inhibit AML growth, as dnMAML (a pan-Notch inhibitor) did not affect AML proliferation *in vitro* but led to dramatic increases in leukaemia burden in two xenograft mouse models. Lobry *et al.* showed that Notch inactivation cooperates *in vivo* with the loss of the myeloid suppressor TET2 to induce AML-like disease, suggesting that TET2 could be an additive factor for suppressing Notch signalling.

Finally, they evaluated the effect of pharmacologically induced activation of Notch signalling. Kannan *et al.* used a short peptide based on the conserved DSL domain of the Notch ligand Jagged 1, whereas Lobry *et al.* used a recombinant human version of the Notch ligand Delta-like 4 extracellular domain fused to the Fc fragment of immunoglobulin G. In AML cell lines and in samples from patients with AML, both of these ligands were able to activate Notch signalling pathways to induce apoptosis of AML cells.

Together, these papers highlight the contrasting role of the Notch signalling pathway in AML versus T cell leukaemia, and suggest that the activation of this pathway with Notch agonists could be a viable approach for treating AML.

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ORIGINAL RESEARCH PAPERS Lobry, C. *et al.* Notch pathway activation targets AML-initiating cell homeostasis and differentiation. *J. Exp. Med.* **210**, 301–319 (2013) | Kannan, S. *et al.* Notch activation inhibits AML growth and survival: a potential therapeutic approach. *J. Exp. Med.* **210**, 321–337 (2013)