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High-level expression of Mastermind-like 2 contributes to aberrant activation of the NOTCH signaling pathway in human lymphomas.

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Abstract

Inappropriate activation of the NOTCH signaling pathway, for example, by activating mutations, contributes to the pathogenesis of various human malignancies. Here, we demonstrate that aberrant expression of an essential NOTCH coactivator of the Mastermind-like (MAML) family provides an alternative mechanism to activate NOTCH signaling in human lymphoma cells. We detected high-level MAML2 expression in several B cell-derived lymphoma types, including classical Hodgkin lymphoma (cHL) cells, relative to normal B cells. Inhibition of MAML-protein activity by a dominant negative form of MAML or by small hairpin RNAs targeting MAML2 in cHL cells resulted in downregulation of the NOTCH target genes HES7 and HEY1, which we identified as overexpressed in cHL cells, and in reduced proliferation. Furthermore, a NOTCH gene-expression signature in cHL cells confirmed their cell-autonomous NOTCH activity. Finally, in line with the essential role of MAML proteins for assembly and activity of the NOTCH transcriptional complex (NTC), we show that MAML-derived small-peptide constructs block NOTCH activity and disrupt NTC formation in vitro. These data strongly suggest direct targeting of the NTC as treatment strategy for NOTCH-dependent malignancies.

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