

# Aberrant splicing of the tumor suppressor CYLD promotes the development of chronic lymphocytic leukemia via sustained NF- $\kappa$ B signaling.

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## **Abstract**

The pathogenesis of chronic lymphocytic leukemia (CLL) has been linked to constitutive NF- $\kappa$ B activation but the underlying mechanisms are poorly understood. Here we show that alternative splicing of the negative regulator of NF- $\kappa$ B and tumor suppressor gene CYLD regulates the pool of CD5<sup>+</sup> B cells through sustained canonical NF- $\kappa$ B signaling. Reinforced canonical NF- $\kappa$ B activity leads to the development of B1 cell-associated tumor formation in aging mice by promoting survival and proliferation of CD5<sup>+</sup> B cells, highly reminiscent of human B-CLL. We show that a substantial number of CLL patient samples express sCYLD, strongly implicating a role for it in human B-CLL. We propose that our new CLL-like mouse model represents an appropriate tool for studying ubiquitination-driven canonical NF- $\kappa$ B activation in CLL. Thus, inhibition of alternative splicing of this negative regulator is essential for preventing NF- $\kappa$ B-driven clonal CD5<sup>+</sup> B-cell expansion and ultimately CLL-like disease.