Aberrant splicing of the tumor suppressor CYLD promotes the development of chronic lymphocytic leukemia via sustained NF-κB signaling.

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Abstract

The pathogenesis of chronic lymphocytic leukemia (CLL) has been linked to constitutive NF-κB activation but the underlying mechanisms are poorly understood. Here we show that alternative splicing of the negative regulator of NF-κB and tumor suppressor gene CYLD regulates the pool of CD5+ B cells through sustained canonical NF-κB signaling. Reinforced canonical NF-κB activity leads to the development of B1 cell-associated tumor formation in aging mice by promoting survival and proliferation of $CD5^+$ 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-κB activation in CLL. Thus, inhibition of alternative splicing of this negative regulator is essential for preventing NF-κB-driven clonal CD5+ B-cell expansion and ultimately CLL-like disease.