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

Hahn M¹, Bürckert JP², Luttenberger CA¹, Klebow S¹, Hess M³, Al-Maarri M⁴, Vogt M⁴, Reißig S¹, Hallek M⁵, Wienecke-Baldacchino A⁶, Buch T⁷, Muller CP², Pallasch CP⁵, Wunderlich FT⁴, Waisman A¹, Hövelmeyer N¹.

Author information
1 Institute for Molecular Medicine, University Medical Centre of the Johannes Gutenberg-University of Mainz, Mainz, Germany.
2 Department of Infection and Immunity, Luxembourg Institute of Health, Strassen, Luxembourg.
3 Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Centre of the Johannes Gutenberg-University of Mainz, Mainz, Germany.
4 Max Planck Institute for Metabolism Research, CECAD, CMMC, Institute for Genetics, Cologne, Germany.
5 Department I of Internal Medicine, CMMC, CECAD, University of Cologne, Cologne, Germany.
6 Life Science Research Unit (LSRU), University of Luxembourg, Esch-sur-Alzette, Luxembourg.
7 Institute of Laboratory Animal Science, University of Zürich, Zürich, Switzerland.

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.