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Identification and characterization of somatic mutations in *ZC3H12A* in ABC DLBCL

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Survival of aggressive ABC-DLBCL cells depends on aberrant NF-κB activation, often caused by driver mutations in BCR and TLR signaling pathways that provoke the assembly of the oncogenic My-T-BCR supercomplex. In the My-T-BCR complex, MALT1 acts as a scaffold and a protease to drive lymphomagenesis and MALT1 inhibitors are currently tested in clinical trials for the treatment of non-Hodgkin lymphomas (NHL). However, the pathological functions of MALT1 protease in aggressive lymphomas are not well understood. Recently, we demonstrated that MALT1 cleaves and inactivates the RNA binding protein (RBPs) Roquin-1/2 (RC3H1/2) and Regnase-1 (ZC3H12A) in DLBCL addicted to chronic BCR signaling. By inactivating these RBPs, MALT1 protease enhances oncogene-induced NF-kB target gene signatures in DLBCL. Here, we describe the identification of somatic mutations in *ZC3H12A* in primary DLBCL patients. We show that missense and truncating mutations lead to a Regnase-1 (ZC3H12A) loss of function, eventually inducing expression of targets that are typically repressed by the RBP. Regnase-1 mutations strongly affect the expression of the atypical nuclear IkB protein NFKBIZ/IkBz, which is known for its tumor promoting potential by acting as strong activator of NF-kB transcriptional responses in DLBCL. Thus, oncogenic mutations in Regnase-1 act at the post-transcriptional level of gene expression, and bypass upstream signaling processes to promote tumor growth and survival in aggressive ABC DLBCL.