Inhibition of MALT1 protease activity is selectively toxic for activated B cell-like diffuse large B cell lymphoma cells.

Diffuse large B cell lymphoma (DLBCL) is the most common type of lymphoma in humans. The aggressive activated B cell-like (ABC) subtype of DLBCL is characterized by constitutive NF-kappaB activity and requires signals from CARD11, BCL10, and the paracaspase MALT1 for survival. CARD11, BCL10, and MALT1 are scaffold proteins that normally associate upon antigen receptor ligation. Signal-induced CARD11-BCL10-MALT1 (CBM) complexes couple upstream events to IkappaB kinase (IKK)/NF-kappaB activation. MALT1 also possesses a recently recognized proteolytic activity that cleaves and inactivates the negative NF-kappaB regulator A20 and BCL10 upon antigen receptor ligation. Yet, the relevance of MALT1 proteolytic activity for malignant cell growth is unknown. Here, we demonstrate preassembled CBM complexes and constitutive proteolysis of the two known MALT1 substrates in ABC-DLBCL, but not in germinal center B cell-like (GCB) DLBCL. ABC-DLBCL cell treatment with a MALT1 protease inhibitor blocks A20 and BCL10 cleavage, reduces NF-kappaB activity, and decreases the expression of NF-kappaB targets genes. Finally, MALT1 paracaspase inhibition results in death and growth retardation selectively in ABC-DLBCL cells. Thus, our results indicate a growth-promoting role for MALT1 paracaspase activity in ABC-DLBCL.
and suggest that a pharmacological MALT1 protease inhibition could be a promising approach for lymphoma treatment.