OFFICIAL ABSTRACT and CERTIFICATION

Targeted inhibition of a novel MALT1 and MAPK signaling network synergistically suppresses aggressive B cell lymphoma growth

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Mucosa associated lymphoid translocation protein 1 (MALT1) mediates pathogenesis of the Activated B cell subtype of Diffuse large B cell lymphoma (ABC DLBCL) via cleaving negative regulators of the Nuclear Factor kappa Beta pathway (Nf-κB) pathway. Targeted degradation of MALT1 proteolytic domain induces cytotoxicity among ABC DLBCLs but unknown resistance mechanisms have prevented clinical translation of MALT1 protease inhibitors. This study sought to identify novel targets on MALT1 by suppressing its caspase domain and analyzing MALT1 protein expression at varying time points. Treatment of ABC DLBCL cell lines HBL-1, OCI-ly3, and TMD8 with MALT1 protease inhibitors SCM-02-138, MI-2, and Mepazine did not affect the MALT1 expression at 1hr time point, but MALT1 expression upregulated after the 48 and 96 hr. timepoints. Western Blot analysis further suggested that MALT1 protease suppression induces upregulation of the MAPK signaling pathway by activating the ERK kinase, uncovering a novel Nf-κB and MAPK signaling crosstalk network. ABC DLBCLs were then administered with Trametinib in order to suppress ERK, which also led to attenuation of the MALT protein expression. To address phenotypical implications of this network, fixed ratio growth inhibition experiments were conducted, which elucidated that combinatorial inhibition of MALT1 and ERK suppresses ABC DLBCL progression. Chou-Talalay analysis further suggested that combinatorial inhibition induces synergistictic cytotoxicity (CI < 1) among lymphoma clones. Taken together, by diagnosing a novel signaling network and developing a therapeutic approach, this study has provided a rationale for exploring combination therapies for numerous MALT1-addicted tumors.

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