Lymphomagenic CARD11/BCL10/MALT1 signaling drives malignant B-cell proliferation via cooperative NF-κB and JNK activation.

Abstract:
The aggressive activated B cell-like subtype of diffuse large B-cell lymphoma is characterized by aberrant B-cell receptor (BCR) signaling and constitutive nuclear factor kappa-B (NF-κB) activation, which is required for tumor cell survival. BCR-induced NF-κB activation requires caspase recruitment domain-containing protein 11 (CARD11), and CARD11 gain-of-function mutations are recurrently detected in human diffuse large B-cell lymphoma (DLBCL). To investigate the consequences of dysregulated CARD11 signaling in vivo, we generated mice that conditionally express the human DLBCL-derived CARD11(L225LI) mutant. Surprisingly, CARD11(L225LI) was sufficient to trigger aggressive B-cell lymphoproliferation, leading to early postnatal lethality. CARD11(L225LI) constitutively associated with B-cell CLL/lymphoma 10 (BCL10) and mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1) to simultaneously activate the NF-κB and c-Jun N-terminal kinase (JNK) signaling cascades. Genetic deficiencies of either BCL10 or MALT1 completely rescued the phenotype, and pharmacological inhibition of JNK was, similar to NF-κB blockage, toxic to autonomously proliferating
CARD11(L225L1)-expressing B cells. Moreover, constitutive JNK activity was observed in primary human activated B cell-like (ABC)-DLBCL specimens, and human ABC-DLBCL cells were also sensitive to JNK inhibitors. Thus, our results demonstrate that enforced activation of CARD11/BCL10/MALT1 signaling is sufficient to drive transformed B-cell expansion in vivo and identify the JNK pathway as a therapeutic target for ABC-DLBCL.