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FBXO11 is a frequently mutated oncosuppressor in Burkitt Lymphoma

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Introduction: FBXO11 is a ubiquitin ligase involved in the degradation of BCL6, a key oncogene in lymphoma pathogenesis. We previously described inactivating mutations of the FBXO11 gene in Diffuse Large B Cell Lymphoma (DLBCL) (Duan et al, Nature 2012). Thus, FBXO11 acts as an oncosuppressor in DLBCL by promoting the accumulation of BCL6. In the present work we searched for FBXO11 mutations in BCL6-positive lymphomas and we investigated its role in lymphoma development in vivo.

Methods: We sequenced the FBXO11 coding sequence in 100 cases of Follicular Lymphoma (FL), 36 cases of Burkitt Lymphoma (BL), 8 BL cell lines and 8 Anaplastic Large cell lymphoma cell lines, all BCL6-positive lymphomas, and 50 cases of Marginal Zone B Cell Lymphoma (MZL), with variable expression of BCL6. We functionally validated the FBXO11 mutations by testing their ability to induce BCL6 degradation. We then applied the CRISPR/Cas9 system to disrupt the endogenous FBXO11 gene in BL cells and evaluated its effect on BCL6 stability. We tested the sensitivity of FBXO11 knock-out (KO) BL cells to a BCL6 inhibitor (FX1) alone or in combination with chemotherapy (doxorubicin). To dissect the in vivo role of FBXO11 in lymphomagenesis we generated conditional FBXO11 KO mice (CD19/Cre-FBXO11fl/fl) and we crossed them with Eμ-myc transgenic mice to investigate whether FBXO11 inactivation cooperates with c-myc in lymphomagenesis.

Results: We identified FBXO11 mutations in BL cases and cell lines (10/44, 22.7%), one case of FL (1/100) and one case of MZL (1/50). Recurrent FBXO11 mutations in BL were further identified in publicly available sequencing databases of 66 BL cases (13/66, 19.7%) (Love et al Nat Genet 2012, Grobner et al Nature 2018). BL mutations found in our series were mostly missense and splice-site mutations located in the functional domains and all of them impaired FBXO11 ability to induce BCL6 degradation. CRISPR/Cas9 mediated KO of FBXO11 in BL cells resulted in an almost complete stabilization of BCL6, thus suggesting that FBXO11 is the main ubiquitin ligase that controls BCL6 stability in BL. FBXO11-KO BL cells showed increased resistance to standard chemotherapy as well as increased sensitivity to BCL6 inhibition compared to the FBXO11 WT BL cells. The simultaneous combination of FX1 with doxorubicin restored the sensitivity of FBXO11-KO BL cells to standard chemotherapy. Finally, we observed an acceleration of lymphoma development in the CD19/Cre-FBXO11fl/fl mice crossed with Eμ-myc transgenic mice. The lymphomas showed histologic features of high-grade disease with a more mature B-cell phenotype, stabilization of BCL6 and reduced apoptotic fraction compared to Eμ-myc only tumors.

Conclusion: Our results demonstrate that FBXO11 is frequently mutated in BL with a mutation frequency of about 20% of cases. Thus, FBXO11 is one of the top five most frequently mutated genes in BL. Biological experiments in vitro and in vivo show that FBXO11 deletion cooperates with c-myc in accelerating lymphomagenesis. Remarkably, FBXO11 deletion in the context of c-myc overexpression generates more mature lymphomas that closely resemble human BL, providing a novel tool for potential preclinical testing of therapies with BCL6 inhibitors. Indeed, the combination of BCL6-targeted therapy restored the sensitivity of FBXO11-KO BL cells to standard chemotherapy suggesting potential combinational strategies for the treatment of BL patients

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