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Dissecting The Oncogenic Functions of MYD88 Mutations and Chromosome 6q Deletion in Waldenström's Macroglobulinemia

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Recent genomic studies have identified the MYD88^{L265P} mutation and chromosome 6q deletion (Chr6q del) as prevalent genetic alterations in Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL). These genetic changes are crucial in activating oncogenic NF-κB signaling and are also frequently observed in activated B-cell diffuse large B-cell lymphoma (ABC DLBCL). Previous research, including our own, has shown that neither human MYD88^{L265P} nor murine Myd88^{L252P} alone is sufficient to drive the neoplastic transformation of murine B-cells. Clonal lymphomas likely require additional genetic alterations Chr6q del, common in WM/LPL and DLBCL patients, might constitute a critical "second hit" necessary for sustaining MYD88^{L265P} induced signaling. This study aimed to elucidate the roles of MYD88^{L265P} and Chr6q del in B-cell fate and lymphoma pathogenesis using preclinical murine models to uncover therapeutic targets and develop novel treatments.

We engineered a conditional murine model lacking a region on murine Chr10 that is syntenic to Chr6 in humans (*Hivep2*^{lox}*;Prdm1*$^{lox/-}$, abbreviated Q) and intercrossed it with conditional mice expressing the murine counterpart of mutant human MYD88 (*Myd88*$^{p.L252P/wt}$, abbreviated MY), and with mice expressing Cre recombinase in CD19-positive B-cells (*Cd19*$^{Cre/wt}$, abbreviated C). This allowed us to study the role of these genetic alterations on B cell lymphomagenesis. For this reason, we generated the following compound murine models: *Myd88*$^{p.L252P/wt}$*;Cd19*$^{Cre/wt}$ (MYC), *Hivep2*$^{lox/-}$*;Prdm1*$^{lox/-}$*;Cd19*$^{Cre/wt}$ (QC), and *Myd88*$^{p.L252P/wt}$*;Hivep2*$^{lox/-}$*;Prdm1*$^{lox/-}$*;Cd19*$^{Cre/wt}$ (MYQC) mice. We observed spontaneous development of low-grade and high grade B cell lymphomas in aged animal cohorts of both QC and MYQC animals, and, less frequently, in MYC animals. Histopathological examination of lymph nodes and spleens revealed expansion of B220^{-} PAX5^{+} B cells, with frequent plasmacytic differentiation and high IRF4 expression. Bone marrow examination showed infiltration with IRF4-positive plasma and lymphoplasmacytic cells, which was evident only in QC and MYQC animals but not in the MYC model.

To delineate the changes occurring in B cells at the premalignant and malignant stages, we performed single-cell RNA sequencing on murine spleen, lymph node, and bone marrow samples from C, MYC, QC, and MYQC mice. We observed a clonal expansion of innate-like atypical B cells in QC and MYQC animals, which were replaced in late-stage disease by aberrant IgM-positive B cells with higher proliferation rates and extensive plasmacytic differentiation. The combination of Myd88 mutation and chr6q del (syntenic to chromosome 10q in mice) acted synergistically to enable the aberrant B cells and plasma cells to home to the bone marrow.

This study demonstrates that MYD88^{L265P} mutation requires additional genetic events, such as Chr6q deletion, to drive lymphomagenesis in WM/LPL and ABC-DLBCL. The generated mouse models provide valuable platforms for investigating the mechanistic roles of these genetic alterations and testing therapeutic strategies. We intend to further validate the murine models as practical tools for studying MYD88^{L265P} and Chr6q del-driven lymphomagenesis.

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July 18, 2024

Dear Chris,

I am writing to confirm that Filip Garbicz, a Postdoctoral Fellow in our research group at the Department of Pathology, Dana-Farber Cancer Institute, is a Delegate in Training for the upcoming 12th International Workshop on Waldenström's Macroglobulinemia.

We fully support Filip's participation in this event and believe that his attendance will further enhance their professional development.

If you require any further information, please do not hesitate to contact me.

Sincerely,

Ruben Carrasco