Is MYD88 alone sufficient to induce a malignant phenotype?

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Lymphoplasmacytic lymphoma (LPL)/Waldenstorm macroglobulinemia (WM) is a B-cell disorder resulting from the accumulation of cloncal lymphoplasmacytic cells in the bone marrow (BM) along with excessive secretion of immunoglobulin M (IgM) paraprotein. Despite recent advances in treatment LPL/WM remains incurable. Generating a refined LPL/WM mouse that would facilitate studying this disease as well as enable stringent *in vivo* validation of potential therapeutic approaches has been a long-sought goal for the filed. Interestingly, the most common among mutations identified by recent high-throughput studies was a single gain of function point mutation in the Myeloid Differentiation Primary Response (MYD88) gene, with a predicted non--synonymous amino acid (L265P) change, found in over 91% of patients. Therefore, we hypothesized that generation of transgenic mice overexpressing MYD88 (L256P) could recapitulate the human setting of LPL/WM.

To overcome problems inherently related to embryonic lethality, we generated $MYD88^{WT}$ and $MYD88^{L256P}$ conditional transgenic mice expressing human proteins. To remove a transcriptional stop cassette and activate MYD88 expression *in vivo*, we mated the conditional mice with mice expressing Cre recombinase under the control of Activation-Induced Cytidine Deaminase (*AID*) gene promoter to generate $AID^{Cre/-}$; $MYD88^{WT/-}$ and $AID^{Cre/-}$; $MYD88^{L256P/-}$ double-mutant mice. Recombinase activity driven by the *AID* gene promoter caused removal of the stop cassette and expression of MYD88 in activated B cells, the appropriate B-cell compartment from which LPL/WM clones are thought to originate in humans. Young (up to 30 weeks of age) $AID^{Cre/-}$; $MYD88^{WT/-}$ and $AID^{Cre/-}$; $MYD88^{L256P/-}$ mice where indistinguishable from $AID^{Cre/-}$ mice as assessed by external physical examination. After 30 weeks of age, and at variable times thereafter, some of the $AID^{Cre/-}$; $MYD88^{L256P/-}$ aging cohort (n=20) mice developed skin rush and excoriation as well as loss of hair in the submandibular areas. Portion of $AID^{Cre/-}$; $MYD88^{L256P/-}$ animals that weren't sacrificed because of the sever dermatitis, had enlarged lymph nodes and appeared sick. To assess whether MYD88 transgenic mice develop B-cell lymphomas or major pathologic alterations consistent with the diagnosis of LPL/WM, animals were euthanized at different ages and lymphoid organs were examined by gross inspection, histology and immunohistochemistry as well as flow cytometry, protein serum electrophoresis, and molecular studies. The result of these studies will be presented at the meeting.