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Research Laboratory

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1063 Medical Laboratories

Welcome to our laboratory website! Currently, we are actively investigating the following two cancer projects:

1) Role of non-canonical NF-κB signaling in regulating hematopoietic/leukemic stem cells
A key common characteristic of hematopoietic stem cells (HSCs) and leukemic stem cells (LSCs) is the ability of self-renewal. Because of this shared property, the signaling pathways that regulate normal HSC functions will also cause leukemia when dysregulated. Dissecting the difference in signal transduction pathways utilized by HSCs and LSCs, and specifically targeting LSCs will provide more effective strategies to improve marrow regeneration and to eradicate leukemia. These are fundamental questions that need to be answered in hematopoietic/leukemic stem cell biology. The canonical NF-κB pathway is constitutively activated in chronic myelogenous leukemia (CML) and acute myeloid leukemia (AML) and is required for maintaining self-renewal of LSCs. However, any role for the alternative pathway in regulating LSCs has not generally been considered or functionally tested. Due to feed forward mechanisms, in which the canonical pathway can prime the activity of the alternative pathway by inducing the expression of p52 and RelB genes, it is possible that some effects have been assigned to the canonical pathway but in fact result from the alternative pathway. Currently, we are investigating how alternative NF-κB signaling differentially regulates HSCs and LSCs.

2) Role of non-canonical NF-κB signaling in lymphomagenesis
Splenic marginal zone lymphoma (SMZL) is an indolent small B cell lymphoma with occasional large cell transformation. It is a diagnosis of exclusion due to the lack of tumor specific biomarkers. A large body of evidence shows that up to 40% of SMZLs have activated mutations in NF-κB pathway genes (TRAF3, BIRC3, TNFAIP3, and MAP3K14). In addition, next generation sequencing studies have shown that Notch2, a master regulator of marginal zone B-cell differentiation, is mutated in 20% of SMZL, suggesting that both pathways are important for SMZL development. However, neither activated NF-κB nor Notch2 alone in committed B cells is sufficient to induce SMZL, although marginal zone hyperplasia is observed in singly mutated mice. Intriguingly, the expression of alternative NF-κB pathway molecules has been largely suppressed in Notch2-activated B cells for unknown reasons. We hypothesize that concurrent activation of both alternative NF-κB and Notch2 signaling is sufficient to induce SMZL in vivo. We currently are using conditional constitutively activated NF-κB inducing kinase (NIK) and Notch2 mice to address this hypothesis. Our goal is to establish a mouse model of SMZL and identify, characterize and manipulate SMZL initiating cells, and further explore their interactions with the microenvironment.