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“Application of Hsp90 inhibitors to treat CLL by targeting the BCR-NFκB pathway”

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M008 Starling-Loving
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VITA

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most prevalent form of adult leukemia. Patients with CLL suffer from an accumulation of mature neoplastic B-cells which results in a compromised immune system that often leads to infection and death. While many effective therapies such as chemotherapy, kinase inhibitors, and immune therapies have been approved for CLL, these strategies are still not curative. Recent findings show that activation of the B-cell receptor (BCR) and its downstream NFκB signaling pathway are critical for CLL tumor cell survival. Although CLL patients have responded to kinase inhibitors targeting signaling proteins in this pathway, a proportion of patients often relapse and require additional therapeutic intervention. In fact, tumor cells often circumvent inhibitors targeting the BCR-NFκB pathway by developing activating mutations or upregulating compensatory pathways. Therefore, identifying novel agents and strategies to target the BCR- NFκB pathway are of particular interest.

It has been challenging to develop inhibitors that target the NFκB pathway. Part of the difficulty lies in identifying optimal protein targets to develop inhibitors for. While therapies targeting upstream regulators of NFκB have been in development, strategies to directly target the NFκB subunits (p50, p52, p65, RelB, etc.) directly responsible for gene transcription have been lacking. Many knockout mouse models of NFκB subunits are embryonic lethal which suggests that targeting these subunits may result in toxic side effects. However, mouse models with genetic knockout of p50 are viable and suggests that p50 may be a candidate target for drug development if it plays a role in carcinogenesis. In CLL, we show that p50 expression is important for disease pathogenesis. Genetic knockout of p50 delays disease development and reduces leukemic burden in a mouse model of CLL which indicates that development of inhibitors targeting p50 is viable.

Inhibitors of heat shock protein 90 (Hsp90) has emerged to be one potential strategy to treat cancer including CLL. Hsp90 is a chaperone protein responsible for folding and stabilizing a select group of client proteins that include many of those thought to be critical for CLL tumor cell survival. Hsp90 inhibitors have had limited clinical efficacy thus far in part due to unfavorable side effects and also induction of Hsf1 activity which increase compensatory heat shock proteins. A
better understanding of both toxicity and also resistance should help refine treatment strategies involving Hsp90 inhibitors. Our work shows that the Hsp90 inhibitor 17-DMAG mediates transcriptional induction or re-expression of genes typically silenced in CLL. In particular, we identify that 17-DMAG is able to re-express suppressor of cytokine signaling 3 (SOCS3), a negative regulator of JAK-STAT signaling, through the p38 pathway. The re-expression of SOCS3 is able to block IL6 induced JAK-STAT signaling, suppress CLL tumor cell migration, and is in part responsible for the cell death caused by 17-DMAG.

Inhibitors of Hsp90 are also potentially very effective at targeting aberrant oncogenic proteins. Fusion and mutant proteins are inherently unstable and rely more on their chaperone proteins for stability. Therefore, the mutated proteins that develop and cause resistance to BCR inhibitors may be sensitive to Hsp90 inhibition. We demonstrate that a second-generation Hsp90 inhibitor, SNX-5422/2112, is cytotoxic to primary CLL cells that are both stimulated and unstimulated with soluble factors. Additionally, we show that this cytotoxicity is maintained in primary CLL cells from patients that are resistant to the BTK inhibitor ibrutinib. We identify that BTK protein with a critical mutation in the region binding ibrutinib is more sensitive to SNX-5422 mediated degradation than wildtype BTK, suggesting that CLL clones with mutant BTK may be especially sensitive to SNX-5422. Finally, we confirm the efficacy of SNX-5422 in an ibrutinib resistant mouse model of CLL and the added benefit of combining SNX-5422 with ibrutinib.

Together, these studies enhance our knowledge of CLL biology, especially the role NFκB and p50 play in CLL disease pathogenesis, providing rationale for further development of small molecule inhibitors to target this pathway. These studies also contribute towards the development of Hsp90 inhibitors in CLL by examining additional mechanisms of action, particularly re-expression of silenced genes and preferential targeting of mutated proteins.
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