Validated Critical Roles of Bruton’s Tyrosine Kinase (BTK) in Chronic Lymphocytic Leukemia (CLL)

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Chronic lymphocytic leukemia (CLL) is a type of blood cancer with accumulated abnormal B cells growing out of control in bone marrow, blood and secondary lymphoid organs. It is the most common adult leukemia in the western world and remains incurable 1. Identification of therapeutic targets and development of effective target therapies are crucial and highly demanding. The well tolerated Bruton’s tyrosine Kinase (BTK) inhibitor, ibrutinib (formally called PCI-32765) 2, represents one of the most exciting breakthroughs in the field of B cell malignancy therapy. In clinical investigation ibrutinib has been shown to have significant clinical activity against B cell malignancies including CLL and it was recently approved for the treatment of mantle cell lymphoma and CLL 3,4. BTK is a critical component of the B cell receptor (BCR) signaling pathway 5. Beside BTK, other kinases such as IL2-inducible T-cell kinase (ITK) have been identified as targets of ibrutinib 6. The lack of selectivity of ibrutinib makes it necessary to validate the critical role of BTK in CLL. In a recent study 7, Woyach and colleagues confirmed the critical function of BTK in the initiation and expansion of CLL and validated BTK as an important target of ibrutinib.

By using siRNA technology, Woyach et al. silenced BTK in primary CLL cells derived from 31 patients and found that loss of BTK resulted in CLL apoptosis, even in the presence of protective factors such as BCR stimulation or stromal cell co-culture. To determine the viable role of BTK in vivo, the XID mouse which has a mutated, non-functional BTK 8 was crossed with the well documented Eμ-TCL1 mouse model of CLL 9. Compared to WT/TCL1 littermates, XID/TCL1 mice had significantly decreased percentage and number of CD5+/CD19+ leukemic cells, delayed leukemia development, and improved overall survival, which demonstrated the importance of BTK in CLL disease progression.
To confirm that genetic ablation of functional BTK recapitulated long-term BTK inhibition by ibrutinib, Woyach and the colleagues treated the Eµ-TCL1 mice with ibrutinib or vehicle starting at 1 month of age and found that ibrutinib treated mice showed a significantly delayed leukemia onset and extended overall survival compared to control mice. These data were strikingly similar to genetic inactivation of BTK shown in XID/TCL1 mice. The authors also demonstrated that Eµ-TCL1 leukemic cell transplanted SCID mice treated with ibrutinib had inhibited BCR signaling and survived longer than vehicle treated mice, lending confidence to the notion that ibrutinib was having a direct inhibitory effect on the CLL cells themselves. Interestingly, clinical observations with ibrutinib show prolonged lymphocytosis after treatment initiation 10, an effect which was not accurately recapitulated in any mouse model.

Collectively, the data shown by Woyach et al. provides compelling evidence that BTK is critical to the development and expansion of CLL and that ibrutinib is effective in inhibiting this critical molecule. However, further investigations are needed to determine the contributions of other targets of ibrutinib such as ITK in CLL.

Reference:


