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Early events of B-cell receptor signaling are not essential for the proliferation and viability of AIDS-related lymphoma

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We have evaluated whether targeting the Src family kinase cascade, an early component of B-cell receptor (BCR) signaling, is an effective strategy to treat AIDS-related lymphoma (ARL). Src kinases are activated after ligation of the BCR and they phosphorylate downstream signaling proteins in tyrosine residues relaying B-cell signaling cascades that lead to B cell activation and proliferation. These kinases play an important role in lymphoma pathogenesis. We have shown that Src kinases are constitutively active in diffuse large cell lymphoma (DLBCL) cells occurring in immunocompetent individuals and inhibition of these kinases using dasatinib inhibits proliferation of the lymphoma cells.

Therefore, we postulated that targeting Src tyrosine kinases pharmacologically would also inhibit the survival and growth of the ARL cells. We tested the effect of dasatinib in 11 ARL cell lines, including six primary effusion lymphomas, three EBV(+) DLBCL (immunoblastic) lymphomas, one EBV(-) DLBCL, and one EBV(+) Burkitt lymphoma. Cell proliferation and viability in the presence of increasing doses of dasatinib were determined by the MTT assay. In contrast to DLBCL in HIV-negative individuals, most of which show sensitivity to dasatinib in the nanomolar range, none of the ARL cell lines tested showed sensitivity at doses as high as 1 uM. One EBV(+) Hodgkin lymphoma cell line was also evaluated, and found to be resistant to dasatinib treatment.

Non-AIDS DLBCLs have activation of SRC family kinases (SFK). The activity of SFK including Src, Lyn, Hck and Blk are invariably inhibited in both sensitive and resistant DLBCL cell lines, whereas the activity of two downstream signaling molecules, Syk and PLCγ2, are inhibited by dasatinib only in sensitive cell lines. To determine the molecular events that occur in ARL after dasatinib treatment in comparison to non-AIDS HIV DLBCL, we performed immunoblot analyses and phosphospecific flow cytometry. Both primary effusion lymphoma (KSHV+) cell lines evaluated (BC2 and VG-1) revealed very low basal levels of total phosphotyrosine, which did not change upon treatment with dasatinib. In contrast, the EBV-associated (LCL-JP06 and BCKN-1) and the virus-negative ARL cell line (BCHN-1) had significantly higher basal tyrosine kinase activity. The HL cell line, L591 has low but detectable level of phosphotyrosines. In these non-PEL cell lines, dasatinib was able to inhibit tyrosine phosphorylation at doses between 10 to 50 nM. In cell lines that had total tyrosine phosphorylation, basal phosphorylation of Src and Lyn was detected, and their activities were efficiently inhibited by treatment with dasatinib.

When we examined ARL cell lines for phosphorylation of Syk and PLCγ2, in those that have little or no basal phosphotyrosines including the PEL cell lines (BC2 and VG-1) and the HL cell line L591, cells did not respond to dasatinib treatment. In contrast, the DLBCL cell line BCHN-1 that had basal tyrosine phosphorylation, pSyk and p-

PLCγ2 responded to BCR stimulation and dasatinib treatment in a similar fashion to the control DLBCL cell lines. However, in spite of this molecular response, this cell line did not respond to the inhibitor at cellular level as no inhibition in proliferation or viability was detected.

Our results indicate that in ARLs, inhibition of BCR signaling is not detrimental to cellular survival or proliferation. These results suggest that viral proteins may provide survival and proliferation signals through interaction with cellular proteins that are further downstream from these early events of BCR signaling. Lack of inhibition by dasatinib was unexpected and in marked contrast to observations made in DLBCL occurring in immunocompetent individuals. These findings have therapeutic as well as pathobiological implications. From the therapeutic standpoint, while dasatinib is likely to be beneficial in lymphoma patients without HIV infection, this approach is unlikely to be successful in patients with AIDS.