Regulation of tumor cell retention and homing in Waldenström's macroglobulinemia

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Most B-cell malignancies dependent on signaling by the B-cell antigen receptor (BCR) and/or other growth and survival signals provided by the tumor microenvironment. In patients suffering from various B-cell malignancies, specifically chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenström's macroglobulinemia (WM) high objective response rates are obtained in with the BCR signaling pathway inhibitors ibrutinib (BTK inhibitor) and idelalisib (PI3Kδ inhibitor), which both result in a rapid and sustained reduction of lymphadenopathy accompanied by transient lymphocytosis. We have previously demonstrated that ibrutinib targets BCR- and chemokine-controlled adhesion and migration of CLL and MCL cells and induces the egress of malignant cells from lymphoid tissues into peripheral blood. These findings unexpectedly identified disrupted homing to and retention within lymphoid organs as a key mechanism of action of these drugs.

We next also investigated the potential of ibrutinib and idelalisib for WM. We show that idelalisib, but not ibrutinib, strongly inhibits proliferation of the WM cell lines BCWM.1 and MWCL-1. No direct cytotoxicity was observed at clinically achievable plasma concentrations.We demonstrate that ibrutinib and idelalisib both inhibit BCR-controlled signaling and integrin $\alpha_4\beta_1$-mediated adhesion to fibronectin and VCAM-1, but not CXCL12-controlled integrin-mediated adhesion. Taken together, our data indicate that inhibition of BTK and PI3Kδ by ibrutinib and idelalisib overcomes BCR-controlled integrin-mediated retention of WM cells in their growth- and survival-supporting bone marrow microenvironment, which results in WM regression.

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