Targeting adhesion and migration in Waldenström's macroglobulinemia

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The pathogenesis of most types of B-cell malignancies is 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, in particular chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenström's macroglobulinemia (WM) high objective response rates were obtained in clinical trials with the BCR signalosome inhibitors Ibrutinib (BTK inhibitor) and Idelalisib (PI3Kδ inhibitor), which both result in a rapid and sustained reduction in 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 now investigated the potential of Ibrutinib and Idelalisib in WM. We show that Idelalisib, but not Ibrutinib, strongly reduces proliferation of the WM cell lines BCWM.1 and MWCL-1. Direct cytotoxicity was not observed at clinically achievable plasma concentrations (100nM Ibrutinib and 1μM Idelalisib). Furthermore, we demonstrate that Ibrutinib and Idelalisib inhibit BCR-controlled signaling and integrin $\alpha_4\beta_1$-mediated adhesion to fibronectin and VCAM-1 and that Ibrutinib, but not Idelalisib, also inhibits 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 clinically evident WM regression.