CXCR4 targeted therapy in WM

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Whole-genome sequencing studies have recently enhanced our understanding of the molecular mechanisms that may contribute to the pathogenesis of Waldenstrom Macroglobulinemia (WM); and the L265P/MYD88 somatic variant has been described as a prevalent somatic mutation in WM patients. Importantly, in vitro studies have demonstrated that the L265P/MYD88 variant may lead to increased tumor cells proliferation, and this may be explained, at least in part, by MYD88-dependent activation of NFkB, a known signaling pathway that modulates tumor B-cell survival, growth and resistance to therapy. The evidence for a widespread involvement of the bone marrow (BM) at the time of diagnosis implies cell trafficking of clonal B-cells into the BM. In this context, one of the main regulators of tumor B-cell homing to the BM is represented by CXCR4 through the interaction with its related ligand SDF-1. CXCR4 has been shown to be mutated in patients with an inherited heterozygous autosomal dominant disease characterized by aberrantly functioning immunity, known as WHIM syndrome, due to the presence, among others, of an activating mutation of the CXCR4 gene, represented by the C1013G variant; and the same variant has been also identified in WM patients. Its functional role in supporting progression of WM has been recently described, together with the demonstration of the anti-WM activity of a novel monoclonal antibody anti-CXCR4 (BMS-936564), as shown both in vivo and in vitro. Of note, BMS-936564 was able to target both wild type and C1013G/CXCR4-mutated WM cells. These findings provide the preclinical rational for using novel CXCR4-targeted therapies in WM.