What are the functional consequences of CXCR4 WHIM mutations in WM?

Aldo M. Roccaro

Whole-genome sequencing studies have contributed to major advances in understanding the molecular mechanisms that contribute to the pathogenesis of WaldenstromMacroglobulinemia (WM). Indeed, the L265P/MYD88 somatic variant has been described as the prevalent somatic mutation in WM patients. In vitro studies have demonstrated that the variant may lead to increased tumor cells proliferation, and this may be explained, at least in part, by MYD88-dependent activation of NFkB, a well knownsignaling pathway that modulates tumor B-cell survival, growth and resistance to therapy.In parallel, other somatic mutations are present in WM patients, including the C1013G/CXCR4 variant which has been also described in patients with the WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome. It is known that WM disease present with a widespread involvement of the bone marrow (BM) at the time of diagnosis, thus suggesting the importance of clonal B-cell trafficking into the BM. CXCR4, indeed, represents one of the major regulator of WM cell-BM homing and the presence of the WHIM-like CXCR4 mutation has been shown to support WM progression, as demonstrated in vivo preclinical models, where C1013/CXCR4-engineered WM cells presented with enhanced tumor proliferation and dissemination to extramedullary organs, leading to disease progression and decreased survival. Of note, genes related to invasiveness, cell proliferation, anti-apoptosis, as well as genes known to be oncogenic were all enriched in C1013G/CXCR4-engineered WM cells compared to the WM control vector-infected cells, thus further explaining the more aggressive phenotype of mutated cells compared to the control cells. Importantly, drug resistance-related mRNAswere enriched in WM cell line harboring the mutation, thus suggesting a potential role of the WHIM-like mutation in mediating drug resistance. Specifically, resistance to ibrutinib, idelalisib, fludarabinewas documented in C1013G/CXCr4-mutated WM cells. In contrast the monoclonal antibody anti-CXCR4,Ulocuplumab, showed anti-tumor activity directed against both C1013G/CXCR4 mutated and wild type WM cells.

Taken together, these findings suggest the functional relevance of the WHIM-like C1013G/CXCR4 somatic variant in WM, as demonstrated by its ability to enhance WM cell proliferation, anti-apoptosis, dissemination as well as drug resistance to conventionally used anti-WM agents.