IWWM-10 Session 5: Thursday, October 11, 2018, Pals

How does the microenvironment impact WM cell growth and drug resistance? Targeting tumor cell retention and homing in WM

Steven T. Pals, University of Amsterdam, The Netherlands

Department of Pathology, Amsterdam University Medical Centers (loc. AMC), and Lymphoma and Myeloma Center Amsterdam – LYMMCARE, Amsterdam, The Netherlands.

Tumor cells are greatly influenced by or even fully addicted to signals from the microenvironment. In B cell lymphomas, signals emanating from the B-cell antigen receptor (BCR) and from chemokine receptors play a central role in the regulation of tumor-cell interaction with the microenvironment. They govern the activity integrin adhesion molecules and thereby control the homing and retention of lymphoma cells within their growth-promoting microenvironments. In patients suffering from various B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle-cell lymphoma (MCL), and Waldenström's macroglobulinemia (WM) high response rates are obtained with the BCR-signaling pathway inhibitors ibrutinib (BTK inhibitor) and idelalisib (PI3Kδ inhibitor). We have previously demonstrated that ibrutinib targets BCR- and chemokine-controlled adhesion and homing and induces the egress of malignant cells from lymphoid tissues into peripheral blood, which ultimately leads to cell death by anoikis (homelessness).

WM can be regarded as archetype for misregulated homing/retention since it is characterized by i) aberrant accumulation of (malignant) post-germinal center B cells within the bone marrow; ii) activating (WHIM-like) mutations in the chemokine receptor CXCR4 present in ~40% of tumors, a unique feature among cancers. Based on this notion and our previous studies, we envisage that targeting integrin-mediated homing and retention of WM cells may provide a highly efficacious therapy, since it will dislodge the tumor cells from their niche, thus depriving them of growth and survival cues. To identify drugable targets controlling WM retention/homing, we have performed unbiased loss-of-adhesion screens by introducing a kinome-centered lentiviral CRISPR/CAS9 library in BCWM.1 WM cells. This appoach recently has resulted in identification of several candidate targets. Furthermore, exploring the contribution of the bone marrow stroma, we have identified the stromal CXCL12gamma isoform as a potential mediator of WM homing/retention.

.