Session II: Genetic Basis and Pathogenesis

of WM and IgM Related Disorders

Abstract 112

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NF-kB abnormalities in Waldenström's Macroglobulinemia. Esteban Braggio, PhD., Rafael Fonseca, MD, Mayo Clinic, Scottsdale, AZ, USA.

Nuclear factor kappa B (NF-kB) comprises a family of transcription factors that regulate the transcription of hundreds of genes involved in inflammation, innate immunity, cell growth and apoptosis. Two signaling pathways are involved in the regulation of NF-kB complexes, the canonical and the non-canonical, which are responsible for the activation of p50 and p52 from their inactive precursors p105 and p100, respectively. Although the constitutive activation of NF-kB signaling pathways has been implicated in the pathogenesis of many tumor types, the molecular basis remains poorly understood. Using high-resolution aCGH and DNA sequencing we reported the inactivation of two negative regulator genes of the NF-kB pathways, TNF receptor-associated factor 3 (*TRAF3*) and tumor necrosis factor, alpha-induced protein 3 (A20/*TNFAIP3*), in Waldenström's macroglobulinemia (WM) patients. *TRAF3* inactivation was associated with an increased in NF-kB transcriptional signature and with the activation of the non-canonical pathway. Mutational activation of these pathways, which are normally activated by ligand-receptor interactions within the bone marrow microenvironment, highlights their biologic importance in WM pathogenesis. Furthermore, these findings might have therapeutic implications. Bortezomib is a first in class proteasome inhibitor, being the inhibition of the NF-kB pathways one of its principle mechanisms of action. Recent studies have demonstrated its anti-tumor activity in refractory and relapsed MM and more recently in untreated and relapsed WM. Thus, the identification of mutations affecting NF-kB pathways possibly identifies a subset of patients who might be benefit from a proteasome-inhibitors based treatment.