[ABSTRACT WM3.5]

Aberrant post-transcriptional regulation of TNF family members and their adaptor molecules essential to B-cell growth and survival in waldenstrom's macroglobulinemia

Adamia S. (1, 2), Xu L. (1), Hatjiharissi E.(1, 2), Ciccarelli BT.(1), Cao Y. (1), Sacco A.(1), Hunter ZR.(1), Patterson CJ.(1), and Treon SP.(1, 2).

(1) Bing Center for Waldenstrom's Macroglobulinemia, Dana Farber Cancer Institute; (2) Harvard Medical School; Boston MA USA.

Introduction: Despite considerable advances to date, the genetic basis for Waldenstrom's macroglobulinemia (WM) remains unclear. We have focused our studies on members of the tumor necrosis factor (TNF) family, given their integral role in neoplastic, as well as normal B-cell growth and survival. TNF receptors use specific but overlapping sets of cytoplasmic adaptor proteins (TRAFs) for signaling. TRAFs are known to play an important role in cell growth and cell survival through the activation of the key transcription factor NF-kB. Activation of this molecule has been noted in many B-cell malignancies. However, the role of these molecules on WM B-cell survival and growth remains to be defined. As part of these studies, we elucidate the critical importance of splicing aberrations of TRAF and some of the TNF family member genes as modulators of WM cell growth and survival. Methods and Results: Using RT-PCR and multiplex RT-PCR, we identified expression patterns for TRAF2, TRAF5, CD40 and BLYS in CD19+, CD34+, CD3+, and CD14+ cells obtained from the BM aspirates of 12 WM patients. Differences in TRAF2, TRAF5, CD40 and BLYS splice variant expressions were observed in CD19+ versus other cell populations obtained from the same WM patients. In CD19+, CD34+, CD3+, and CD14+ cells from BM of WM patients we observed distribution patterns of splice variants of CD40 and BLYS similar to those observed for TRAF variants. Most importantly we identified novel splice variant for TRAF2 (TRAF2Va) in CD19+ cells from 8/12 WM patients. Sequence alignment analysis identified TRAF2Va novel variant resulting from a deletion of an exon leading to inframeshift. By bioinformatic analysis, TRAF2Va was predicted to encode a region essential for protein-protein interactions as well as DNA binding, suggesting disrupted TNF signaling pathways and NF-kB activation. Conclusions: Taken together, these results suggest that in WM patients, TNF-family members and their adaptor molecules responsible for normal B-cell growth and survival are subjected to aberrant post-transcriptional regulation. As a result, these aberrations most likely alter both canonical and noncanonical NF-kB signaling. The clinical consequences and significance of this finding, as well as frequency of novel variant transcripts in large population of WM is currently the focus of further investigation.