[ABSTRACT WM3.4]

Novel splice variant transcript of Siva in Waldenstrom's Macroglobulinemia

Hatjiharissi E. (1, 2, *), Adamia S. (1, 2, *), Cao Y. (1), Ciccarelli BT. (1), Xu L. (1), and Treon SP. (1, 2).

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

Introduction: The transmembrane protein CD27 is a member of the tumor necrosis factor receptor (TNFR) family that binds to its ligand CD70. Recently, we demonstrated that CD27-CD70 interaction supports growth and survival of Waldenstrom's macroglobulinemia (WM) cells. We also detected high levels of soluble CD27 (sCD27) in the sera of patients with WM; however, the mechanisms of soluble CD27 secretion in the sera of WM patients remain unclear. SIVA, a proapoptotic protein, binds to the cytoplasmic tail of CD27. Overexpression of full-length, wild type SIVA has been associated with the induction of apoptosis in several malignancies that suggests an important role for SIVA in the CD27-dependent apoptotic pathway. Two splice variants of SIVA, SIVA1 and SIVA 2, have been identified in humans thus far. Methods and Results: To elucidate underlying mechanisms of sCD27 release in the sera of WM patients, we first examined the expression patterns of SIVA transcripts in WM tumor cells (n=8) by RT-PCR. We found that all patients expressed both previously- reported splice variants, SIVA 1 and SIVA 2. Herein, we describe for the first time, a novel splice variant of SIVA detected in 4/8 WM patients. To further characterize the novel splice variant transcripts of SIVA, designated SIVA-Va, we cloned RT-PCR products obtained from the two WM patients into the TOPO TA vector. Positive sub-clones were identified by PCR with SIVA1 gene specific primers. Plasmids isolated from positive clones were sequenced. Sequences were identified through alignment with the published sequence of human SIVA mRNA. Further bioinformatic analysis demonstrated that the novel variant of SIVA is a result of partial retention of an intron. In general, this type of splicing is associated with a malignant phenotype. In conclusion, the aberrant novel variant of SIVA, SIVA-Va, may compromise binding of full-length, wild type SIVA to CD27; thereby facilitating the cleavage of CD27 from the plasma membrane of WM tumor cells leading to the disruption of the CD27-CD70 signaling in WM.