Overexpression and novel splice variants of Hyaluronan synthases
In Waldenstrom's Macroglobulinemia

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Waldenstrom's Macroglobulinemia (WM), which has clinical and pathological similarities with multiple myeloma (MM), is an indolent B cell malignancy. This lymphoplasmo-proliferative disorder is characterized by bone marrow (BM) infiltration by lymphocytes and plasmacytoid cells and IgM paraproteinemia. Little is known about the biology or spread of WM. Hyaluronan synthase (HAS), a plasma membrane protein, synthesizes an extracellular matrix (ECM) molecule, Hyaluronan (HA), which plays a significant role in malignant cell migration and the spread of many cancers including MM. Recently, an intracellular form of HA has been identified which is involved in cell signaling and mitosis. Evolutionarily conserved, three isozymes of HAS—HAS1, HAS2, and HAS3—have been detected in humans thus far. Each of these isozymes conducts different cell- and tissue-specific functions. Aberrant expression of the HASs is coupled with different abnormalities. Using the DNA fragment analysis approach we have analyzed the expression pattern of HAS genes in BM aspirates and the peripheral blood of patients with WM. HAS3 is expressed in all tested patients and normal donors. However, the expression of HAS1 and HAS2 varies among WM patients. This observation suggests the existence of a heterogeneous population of malignant cells in tested WM patients as well as a degree of patient specificity. In addition, we have detected novel splice variants of HAS1 in WM patients, one of which has also been detected in myeloma patients. HAS-1 variants are not detected in healthy donors. We speculate that HAS1 variants synthesize the intracellular HA ligand for RHAMM (a receptor for HA). RHAMM contributes to genetic instability in myeloma, and we speculate that it may also contribute to genetic instability in WM. Based on our preliminary results, we suggest that overexpression of full length HAS1 and HAS2 may form an extracellular HA matrix around WM cells, thus preventing their elimination by the immune system. Furthermore, the existence of an HA matrix around the malignant cells is likely to promote their migration, and consequently may facilitate the spread of disease. Thus, HASs may contribute to genetic instability and malignant spread in WM. (Supported by the Research Fund for Waldenstrom's).