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VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) IS A GROWTH AND SURVIVAL FACTOR IN WALDENSTROM'S MACROGLOBULINEMIA.

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Waldenstrom's macroglobulinemia (WM) is a B-cell disorder characterized by excess of bone marrow (BM) IgM secreting lymphoplasmacytic cells (LPC). In previous studies, we and others have demonstrated that VEGF within the BM micro-environment plays a role in the growth, survival and migration of myeloma plasma cells. Conversely, we demonstrated that BM mast cells (MC), which produce and secrete VEGF (Boesiger, J Exp Med, 1998) support growth and survival of WM LPC (Tournilhac et al, JCO 2004; 22:517S). In the present studies we therefore explored the role of VEGF in WM pathogenesis. Using RT-PCR analysis, we detected VEGF receptors R1 (Flt-1) and R2 (flk1/KDR) transcripts in sorted LPC from 4/4 (100%) and 15/16 (94%) WM patients respectively. Moreover, we showed functionality for VEGF as a growth and survival factor in WM. Specifically, recombinant human VEGF (rh-VEGF) at 25 ng/ml induced dose dependent proliferation of sorted LPC from WM patients and prevented serum starvation- induced apoptosis. Inhibition of VEGF signaling pathways both induced apoptosis and blocked mast cell- induced proliferation of sorted WM LPCs in 4 of 6 and 4 of 4 patients, respectively. Besides the known MC-derived WM LPC growth and survival factors CD40 ligand (CD40L) (JCO 2004; 22:517S) and B-lymphocyte stimulator protein (BLYS) (Ditzel Santos et al, ASH 2004 submitted), the present study demonstrates also a role of VEGF in WM pathogenesis. We therefore suggest VEGF as an additional therapeutic target in WM treatment regimens.