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Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications.

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Increased angiogenesis has recently been recognized in active multiple myeloma (MM). Since vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are two key mediators of angiogenesis, we characterized the production of VEGF, b-FGF and interleukin-6 (IL-6) (a MM growth and survival factor) in MM cell lines and Epstein-Barr virus (EBV) transformed B cell lines from MM patients, patient MM cells, as well as bone marrow stromal cells (BMSCs) from normal healthy donors and MM patients. We detected secretion of VEGF, but no bFGF and IL-6, in MM cell lines (MM.1S, RPMI 8226 and U266); EBV transformed B cell lines from MM patients (IM-9, HS-Sultan and ARH77); MM cell lines resistant to doxorubicin (RPMI-DOX40), mitoxantrone (RPMI-MR20), melphalan (RPMI-LR5) and dexamethasone (MM.1R); and patient MM cells (MM1 and MM2). BMSCs from MM patients and normal donors secreted VEGF, b-FGF and IL-6. Importantly, when MM cells were adhered to BMSCs, there was a significant increase in VEGF (1.5- to 3.1-fold) and IL-6 (1.9- to 56-fold) secretion. In contrast, the bFGF decreased in co-cultures of BMSCs and MM cells. Paraformaldehyde fixation of BMSCs or MM cells prior to adhesion revealed that VEGF was produced both from BMSCs and MM cells, though it may come primarily from BMSCs in some cultures. IL-6 was produced exclusively in BMSCs, rather than MM cells. Moreover, when MM cells were placed in Transwell insert chambers to allow their juxtaposition to BMSCs without cell to cell contact, induction of VEGF and IL-6 secretion persisted, suggesting the importance of humoral factors. Addition of exogenous IL-6 (10 ng/ml) increased VEGF secretion by BMSCs. Conversely, VEGF (100 ng/ml) significantly increased IL-6 secretion by BMSCs. Moreover, anti-human VEGF (1 microg/ml) and anti-human IL-6 (10 microg/ml) neutralizing antibodies reduced IL-6 and VEGF secretion, respectively, in cultures of BMSCs alone and co-cultures of BMSCs and MM cells. Finally, thalidomide (100 microM) and its immunomodulatory analog IMiD1-CC4047 (1 microM) decreased the upregulation of IL-6 and VEGF secretion in cultures of BMSCs, MM cells and co-cultures of BMSCs with MM cells. These data demonstrate the importance of stromal-MM cell interactions in regulating VEGF and IL-6 secretion, and suggest additional mechanisms whereby thalidomide and IMiD1-CC4047 act against MM cells in the BM milieu.