Plasmacytoid Dendritic Cells Promote Multiple Myeloma Cell Growth and Drug Resistance

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The bone marrow (BM) microenvironment confers growth, survival, and drug resistance in multiple myeloma (MM) cells. We characterized the role of plasmacytoid dendritic cells (pDCs) in the MM BM milieu. Immunochemical analysis of tissue microarrays on MM patient BM biopsies with Abs specific against pDCs (BDCA-2) and MM cells (CD138) shows pDCs in proximity to MM cells. Quantification of pDCs reveals increased numbers and more frequent localization of pDCs in MM patient BM than normal BM. pDCs from normal healthy donors stimulate significant growth of MM cells. Irradiated pDCs retain their ability to trigger proliferation of MM cells; importantly, pDC-depleted BM cells did not trigger significant DNA synthesis in MM cells, confirming a specific MM cell growth-promoting activity of pDCs. To determine whether pDCs enhance MM cell growth in vivo we utilized the SCID-hu model, which recapitulates the human BM milieu in vivo. A more robust growth of tumor occurred in mice receiving human pDCs and INA-6 MM cells than in mice injected with INA-6 cells alone. Co-culture of pDCs with patient MM cells significantly increased the survival of patient tumor cells. Examination of the effect of anti-MM agents on the viability of pDCs showed that pDCs are relatively resistant to bortezomib, lenalidomide, and Dexamethasone therapies in comparison to tumor cells. Microarray analysis demonstrated that the pDCs-MM cell interaction triggered significant changes in transcriptional activity of genes related to growth, survival, anti-apoptosis, and migration in MM cells. Cytokine bead array analysis of supernatants from pDCs-MM cells co-cultures defined a marked increase in the secretion of MM cell growth, survival and chemotactic factors including IL-3, IL-10, IL-6, IL-8, IL-15, SDF-1alpha, CD40L, MCP-1, IP10 and VEGF. Although pDCs are resistant to novel therapies, targeting Toll-like Receptors with CpG ODNs both restores pDC immune function in stimulating effector cells and abrogates pDC-induced MM cell growth. Our study therefore validates targeting pDC-MM interactions as a therapeutic strategy to overcome drug resistance in MM.