Multiple myeloma (MM) remains incurable despite the advent of novel drugs, highlighting the need for a greater understanding of the mechanisms(s) mediating disease progression and drug resistance. The bone marrow (BM) microenvironment confers growth, survival, and drug resistance. Our recent study showed that plasmacytoid dendritic cells (pDCs) are significantly increased in numbers in MM patient BM and promote MM cell growth (Chauhan et al., Cancer Cell 2009, 16:329-329). Importantly, IL-3 levels are increased upon pDC-MM interaction, which in turn, trigger MM cell growth and pDCs survival. IL-3R is highly expressed on pDCs. We used SL-401, a novel biologic conjugate that targets IL-3R, to examine whether inhibition of the IL-3-IL-3R signaling axis affects the pDC-MM interaction and its tumor promoting biologic sequelae. MM cell lines, patient MM cells, and pDCs from healthy donors or MM patients were studied for the anti-MM activity of SL-401. MM cells and pDCs were cultured alone or together in the presence or absence of SL-401, followed by analysis of cell growth or viability. SL-401 significantly decreased the viability of pDCs at low nanomolar concentrations. SL-401 also decreased the viability of MM cells at concentrations that can be obtained at clinically achievable doses. Co-culture of MM cells with pDCs triggered MM cell growth, and importantly, SL-401 blocked tumor promoting activity of pDCs. Specifically, MM patient-derived pDCs triggered growth of MM cell lines and primary MM cells; conversely, SL-401 inhibited pDC-derived MM cell growth. Tumor cells from 4 of the 6 patients were obtained from patients whose disease was progressing while on bortezomib, dexamethasone and Revlimid therapies. Similarly, SL-401 blocked pDC-induced growth of Dexamethasone-, Doxorubicin- or Melphalan-resistant MM cell lines. Finally, combinations of SL-401 with bortezomib, melphalan, lenalidomide, SAHA or dexamethasone showed synergistic anti-MM activity. Our preclinical study provides the basis for a clinical trial targeting pDCs and inhibiting the pDC-MM interaction, as well as targeting MM, in novel therapeutic strategies with SL-401 to enhance drug sensitivity, overcome drug-resistance, and improve patient outcome.

**Results**

**SL-401 inhibits the viability of pDCs and MM cell lines**

**Figure 1.** (A) Freshly isolated pDCs were cultured in the presence or absence of indicated concentrations of SL-401 for 72 h, followed by assessment for viability using MTT assay (mean ± SD of triplicate cultures from 5 different samples; p < 0.005 in all cases). The IL-3-dependent erythroleukemic cell line TF-1 served as a positive control for SL-401 activity. **(B)** MM.1S (Dexamethasone-sensitive), MM.1R (Dex-resistant), RPMI 8226, Dox-40 (Doxorubicin-resistant RPMI-8226), and LR-5 (Melphalan-resistant RPMI-8226) cell lines were cultured in the presence or absence of SL-401 for 72 h followed by assessment for viability.

**Conclusions**

Our earlier report identified an integral role of pDCs in MM pathogenesis (Chauhan et al., Cancer Cell 2009, 16:329-329). Here, we provide the basis for targeting pDC-MM interactions with SL-401 as a novel therapeutic strategy to enhance MM cytotoxicity, overcome drug-resistance, and improve patient outcome.

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