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Abstract: PURPOSE: Tumor-induced immunosuppression remains a significant obstacle that limits the efficacy of biological therapy for renal cell carcinoma. Here we evaluate the role of CD33 myeloid-derived suppressor cells (MDSC) in the regulation of T-cell responses in renal cell carcinoma patients. We also examine effect of all-trans-retinoic acid (ATRA) on MDSC-mediated immune suppression. EXPERIMENTAL DESIGN: CD33-positive myeloid cells were isolated from the peripheral blood of renal cell carcinoma patients with magnetic beads and tested in vitro for their ability to inhibit T-cell responses. T-cell function was evaluated using ELISPOT and CTL assays. RESULTS: MDSC isolated from renal cell carcinoma patients, but not from healthy donors, were capable of suppressing antigen-specific T-cell responses in vitro through the secretion of reactive oxygen species and nitric oxide upon interaction with CTL. MDSC-mediated immune suppression and IFN-gamma down-regulation was reversible in vitro by exposing cells to the reactive oxygen species inhibitors. Moreover, ATRA was capable of abrogating MDSC-mediated immunosuppression and improving T-cell function by direct differentiation into antigen-presenting cell precursors. CONCLUSIONS: These results may have significant implications regarding the future design of active immunotherapy protocols that may include
differentiation agents as part of a multimodal approach to renal cell carcinoma immunotherapy.

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