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Myeloid-derived Suppressor Cells EN-RAGE Antitumor Immunity

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Abstract

Immune checkpoint inhibitors (ICI) have radically altered cancer therapy and enable delayed tumor progression and in some cases cures for some cancer patients. However, ICI efficacy is mixed depending on the type of cancer and individual cancer patients. Myeloid-derived suppressor cells (MDSCs) are potent inhibitory cells that are present in most cancer patients where they suppress T cell and NK cell-mediated antitumor immunity. They are likely to contribute to the lack of effect of ICI, and therefore, eliminating MDSCs may enhance the efficacy of ICI. MDSCs are activated by multiple proinflammatory mediators that are typically present in many cancers, and MDSCs are homeostatically regulated so that depletion of MDSCs in circulation or within solid tumors increases their rate of production from the bone marrow.
Multiple clinical trials have been conducted using drugs targeting individual mediators that either eliminate MDSCs in the periphery or neutralize the suppressive activity of MDSCs. Unfortunately, the trials have been largely ineffective in limiting MDSCs and enhancing ICI-induced antitumor immunity. Given the homeostatic regulation of MDSCs and the variety of proinflammatory molecules in individual patients capable of inducing MDSC differentiation, optimal reduction of MDSCs will likely require blocking the relevant proinflammatory mediators and preventing the development of MDSCs in bone marrow.
Signal transduction through The *Receptor for Advanced Glycation Endproducts (RAGE)* activates many of the pro-inflammatory mediators that are established activators of MDSC. Our studies in mice have established RAGE as a receptor on MDSC bone marrow progenitor cells and have demonstrated that blocking RAGE on murine bone marrow stem cells prevents the development of MDSC. Studies by others have demonstrated that RAGE inhibitors also directly suppress the growth of RAGE-expressing tumor cells. Therefore, we hypothesize that RAGE may be a key receptor on myeloid progenitor cells for driving the differentiation, accumulation, and function of MDSC, and that inhibitors of RAGE may be efficacious therapeutics for use in conjunction with ICI.