972 PLATINUM-BASED CHEMOTHERAPY REVERSES HUMAN MDSC PHENOTYPE AND SUPPRESSIVE ACTIVITY ON CD8+ T CELLS

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Background Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells that suppress T-cell effector function and proliferation. Elevated blood MDSCs are associated with poor outcomes across multiple tumor types in clinical studies and are suggested to be an immunotherapy resistance mechanism. Several chemotherapeutic agents used in conventional cancer chemotherapy regimens reduce MDSC numbers in preclinical models, however, their impact on human MDSC phenotype and function is less. In this study, we show that Cisplatin modulates the expression of specific markers of human MDSCs while Carboplatin and Cisplatin revert their suppressive activity on CD8+ T cells.

Methods Human CD14+ monocytes were isolated from frozen PBMCs of healthy donors using positive selection. Autologous CD8+T cells were purified via negative selection. To generate MDSCs, CD14+ monocytes were cultured in RPMI medium supplemented with 10% FBS, with cytokine mixtures, which consist of GM-CSF, IL-6 and TGF-β, for 7 days. At day 4, chemotherapeutic agents were added to the culture. At day 7, the cells were harvested and co-cultured with activated and dye-labelled (anti-CD3/CFSE) CD8+ T cells for 72h. Cells were analyzed by flow cytometry to assess proliferation and supernatants were collected for cytokine expression analyses.

Results In vitro generated MDSCs show increased expression of CD33, CD11b and PD-L1 and reduced expression of HLA-DR and CD68 on the surface relative to control CD14+ cells. Cisplatin treatment inhibits the cell growth of these MDSCs and induces apoptosis during the differentiation stage in a dose dependent manner. Cisplatin-treated MDSCs also display a modulation of their phenotype (increased expression of HLA-DR and downregulation of PD-L1). Additionally, Cisplatin and Carboplatin abrogate the MDSC suppressive activity as shown by increased CD8+ T cell proliferation and IFN-g secretion in co-culture assays. Cisplatin also increased the secretion of other T cell related cytokines while reducing the secretion of myeloid-related cytokines. Other commonly used chemotherapeutic agents tested in this study, such as Paclitaxel and Pemetrexed did not show any effects on reversing either MDSC phenotype or suppressive activity.

Conclusions Our data suggest that Cisplatin may reduce MDSC levels in cancer patients through depletion as well as reversing their phenotype and suppressive function. Carboplatin did not affect the MDSC phenotype but had a significant impact in reducing their suppressive capacity. Taken together, our observations suggest that platinum-based chemotherapy have a modulatory effect on MDSCs which may improve immunotherapy efficacy in patients with high levels of these cells through depletion and reversion of their inhibitory activity.

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