Introduction: Myeloid-derived suppressor cells (MDSC) are a heterogeneous population of immature myeloid cells that have an increased ability to suppress T-cell immune response. This allows for tumors, infection, and inflammation to persist without any immune effector regulation. In this study, we aimed to determine the role of endoplasmic reticulum (ER) stress on the immune suppressive function of MDSC. To achieve this, we used a model in which MDSCs were generated in vitro from the bone marrow (BM) of mice. Briefly, BM cells were cultured for 3 days in media containing G-CSF and GM-CSF to generated MDSC. Then, these cells were treated with the ER stress inducing factor Thapsigargin for additional 24 hours. After which, we tested for the following: 1. The induction of ER-stress linked protein C/EBP homologous protein 10 (CHOP). 2. MDSC apoptosis. 3. The ability of the MDSC to suppress T cell proliferation.

Goal: To determine whether the induction of Endoplasmic Reticulum stress in vitro-generated MDSCs increases their suppressive potential.

Results:

Figure 1: Figure 1A, Thapsigargin does not impair the generation of MDSCs in vitro as suggested by the presence of CD11b and Gr1. Figure 1B, below, display western blots used to detect the activation of the ER-stress marker CHOP and Actin in these MDSCs.

Figure 2: a very slight increase in the induction of MDSC apoptosis, as demonstrated by Annexin V binding, was found after treatment with Thapsigargin.

Figure 3: Thapsigargin-treated MDSCs had a higher ability to suppress proliferation of activated T cells. Different MDSC numbers (DMSO or Thapsigargin –treated) were co-cultured with CFSE-labeled T cells. Then, T cell proliferation was evaluated 72 hours later.

Next Steps: Detection of molecules mediating suppression induced by MDSC (arginase, GP91 and INOS) will provide a mechanistic explanation of the enhanced inhibitory activity induced by Thapsigargin. Validation of the effect of thapsigargin on arginase, GP91 and INOS in MDSC suppression in vivo.

Conclusion: Thapsigargin causes the BM- MDSCs to express stronger suppressive abilities toward T-cells. Here we have recreated data that can be used to look further into the suppressive MDSCs and what other ER stress factors will increase their suppression.

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