Membrane-associated Hsp72 from tumor-derived exosomes mediates STAT3-dependent immunosuppressive function of mouse and human myeloid-derived suppressor cells.

Abstract:
Myeloid-derived suppressor cells (MDSCs) have been identified in humans and mice as a population of immature myeloid cells with the ability to suppress T cell activation. They accumulate in tumor-bearing mice and humans and have been shown to contribute to cancer development. Here, we have isolated tumor-derived exosomes (TDEs) from mouse cell lines and shown that an interaction between TDE-associated Hsp72 and MDSCs determines the suppressive activity of the MDSCs via activation of Stat3. In addition, tumor-derived soluble factors triggered MDSC expansion via activation of Erk. TDE-associated Hsp72 triggered Stat3 activation in MDSCs in a TLR2/MyD88-dependent manner through autocrine production of IL-6. Importantly, decreasing exosome production using dimethyl amiloride enhanced the in vivo antitumor efficacy of the chemotherapeutic drug cyclophosphamid in 3 different mouse tumor models. We also demonstrated that this mechanism is relevant in cancer patients, as TDEs from a human tumor cell line activated human MDSCs and triggered their suppressive function in an
Hsp72/TLR2-dependent manner. Further, MDSCs from cancer patients treated with amiloride, a drug used to treat high blood pressure that also inhibits exosome formation, exhibited reduced suppressor functions. Collectively, our findings show in both mice and humans that Hsp72 expressed at the surface of TDEs restrains tumor immune surveillance by promoting MDSC suppressive functions.