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Efficacy of vaccination with tumor-exosome loaded dendritic cells combined with cytotoxic drug treatment in pancreatic cancer

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Immunotherapy could be a promising option in pancreatic cancer (PaCa) therapy. However, immunotherapeutic trials frequently do not fulfill expectation due to immunosuppressive properties of PaCa, partly via myeloid-derived suppressor cell (MDSC) activation and recruitment. A previous trial in less immunosuppressive tumors than PaCa showed that tumor exosome (TEX)-loaded dendritic cell (DC) were a superior vaccine compared with peptide-loaded DC. Therefore, I explored in a murine PaCa model, whether vaccination with TEX-loaded DC showed any therapeutic efficacy and whether this could be strengthened by concomitantly attacking MDSC.

To investigate whether TEX could serve as a source of tumor antigens for DC-loading, and whether vaccination with TEX-loaded DC showed any therapeutic efficacy in Paca, I used the mouse Paca cell line-UNKC6141 (UNKC). TEX, indeed, expressed several tumor markers making them a suited antigenic entity for DC-loading. In the UNKC-bearing mice, vaccination with DC-TEX significantly prolonged the survival time. DC-TEX preferentially interacted with activated (CD69+) T cells and home into lymphoid node(LN), bone marrow (BM) and in vaccinated mice more efficiently in tumor and lung, the efficacy of DC-TEX vaccination demanding for a combined therapy with cytotoxic drugs.

In advance of selecting for suitable cytotoxic drugs, I evaluated the particular immunosuppressive features of PaCa during intrapancreatic UNKC growth. Compared to the naïve pancreas, intrapancreatic UNKC growth induces a strong stroma reaction with enrichment of suppressor cells, suppressive factors and 93 chemokines attracting MDSC, the immunosuppressive elements being stronger than in mice carrying s.c. tumors.

Based on this analysis I selected for the cytotoxic drugs Gemcitabine (GEM) and/or all-trans retinoic acid (ATRA) and/or Sunitinib (Sun) that, beside other effects, attack MDSC. UNKC6141-bearing mice received weekly intravenous TEX-loaded DC injections and additionally ATRA, Sun or GEM, which affect MDSC at distinct maturation and activation stages. ATRA, Sun and most efficiently GEM, sufficed for a pronounced reduction of MDSC including tumor-infiltrating MDSC, which was

accompanied by a decrease in migrating and metastasizing tumor cells. When combined with DC-TEX vaccination, a higher number of activated T cells was recovered in the tumor and the survival time was prolonged compared with only DC-TEX vaccinated mice. Intrapancreatic tumor growth was prevented beyond the death of control mice.

Taken together, TEX are a suited antigenic entity for DC-loading. Vaccination with DC-TEX significantly prolongs the survival time, and affects UNKC dissemination. The strong immunosuppressive stroma reaction of PaCa, at least partly, due to MDSC, becomes mitigated by ATRA, GEM and Sun. DC-TEX vaccination supported by the drug combination exerted an even stronger therapeutic effect. Though an optimized drug tuning remains to be elaborated, preventing MDSC maturation and activation concomitantly with TEX-loaded DC vaccination appears a most promising option of an individualized adjuvant PaCa therapy.