ALDH1A INHIBITION AS ADJUVANT TO OVARIAN CANCER IMMUNOTHERAPY

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Background Despite some recent advances, new therapeutic approaches for ovarian cancer (OvCa), the 5th leading cause of cancer deaths in women, are clearly needed. Aldehyde dehydrogenase-1A (ALDH1A) enzymes represent a novel therapeutic target for OvCa. ALDH1A is upregulated in OvCa initiating cells and mediate the biosynthesis of retinoic acid (RA) to regulate numerous cellular processes, including proliferation, metastasis, and chemotherapy resistance. We recently identified novel pan-ALDH1A family inhibitors (ALDHi) that induce necroptosis in OvCa stem-like cells and synergize with chemotherapy, leading to tumor eradication in vivo. Here, we hypothesize that, in addition to controlling tumor progression, ALDHi trigger immunogenic cell death (ICD) via necroptosis and can potentiate anti-tumor immunity.

Methods We performed RNA-Seq on four human OvCa cell lines (A2780, CAOV-3, OVCAR-5, OVSAHO) treated for 8 hours with two different ALDHi. To measure the impact on T cell immunity we performed flow cytometry to measure cell proliferation assays and CD4 naïve differentiation into Th1/Th17/Treg subsets. Molecular targets in the RA pathway were confirmed by western blot.

Results ALDHi triggered significant changes in (i) ER stress unfolded protein response and regulators of the ER stress response, such as ATF4 and EIF2αK3 (PERK), (ii) inflammatory pathways, (iii) cell death, survival, and (iv) gene transcription-RAR signaling. Treatment of cancer cell lines with ALDHi induced expression of Phospho-eIF2α, a marker for the ICD, along with increased expression of ATF3 and ATF4, and calreticulin, suggesting cancer cells undergoing ICD.

Using polyclonal stimulation of murine splenocytes and human PBMC, we observed that ALDHi promote T cell proliferation, especially of CD8 T cells. Furthermore, exposure of naïve CD4 cells to Th1 and Treg differentiation conditions leads to increased production of INFγ and reduced number of Foxp3+ iTregs, respectively. Further, in a co-culture of iTreg and stimulated splenocyte, ALDHi treatment diminishes the iTreg’s capacity to induce immune suppression. Ex vivo treatment of ovarian cancer ascites cells with various ALDHi leads to significant decrease of CD14+ cells, an effect associated with downregulation of NR4A1 (NUR77), a nuclear receptor that interacts RAR/RXR, downstream of RA signaling.

Conclusions ALDHi induce immunogenic cell death in cancer cells. Immune cells respond to ALDHi in a cell specific manner. ALDHi support CD8 T cell proliferation and CD4 Th1 induction, while inhibiting iTregs. Exposure to ALDHi leads to downregulation of NR4A1 and reduction in suppressive macrophage numbers. Our results support the use of ALDHi as immune modulators in ovarian cancer and adjuvants to immunotherapy.

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785 ESTROGEN-DEPRIVATION PROMOTES TH1 POLARIZATION OF TUMOR-ASSOCIATED T CELLS IN A MOUSE MODEL OF HIGH GRADE SEROUS OVARIAN CANCER

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Background Immunotherapy has achieved long-term survival in patients with melanoma and other tumors, introducing a new paradigm in cancer treatment. Differential outcomes among men and women receiving immune checkpoint inhibitors implicate sex steroids as modulators of treatment response. Estrogen signaling has a profound impact on T cell function in melanoma, but its role in ovarian cancer is not well defined. We show here that estrogen-deprivation promotes Th1 polarization of tumor-associated T cells in a mouse model of high grade serous ovarian cancer (HGSOV).