859 REGRESSION OF AN IMMUNOLOGICALLY 'COLD' ORAL CANCER MODEL INDUCED BY MODULATION OF THE TUMOR MICROENVIRONMENT WITH DOXIL, ANTI-CTLA-4, AND RADIATION

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Background The immune-suppressive tumor microenvironment (TME) of oral cancer often hinders the effectiveness of standard treatments, including surgery, chemoradiotherapy, and immunotherapy. This is true for the highly aggressive MOC2 syngeneic oral cancer cell line, which promotes a 'cold' immunological landscape that limits the efficacy of checkpoint inhibition and other immunotherapies. In addition to its direct cytotoxic activity, liposomal doxorubicin (DOXIL) has immune modulatory properties, including modulation of tumor-infiltrating myeloid cell accumulation and polarization. We hypothesized that DOXIL-induced remodeling of the myeloid microenvironment, in combination with radiotherapy, could reverse MOC2 resistance to anti-CTLA-4 and anti-PD-1 checkpoint inhibition.

Methods We utilized the well-described MOC2 syngeneic murine model of oral cancer to grow flank tumors. Mice (n=/>20 for each condition, divided over 2–3 experiments) were randomized to each of the following treatments: DOXIL (I.V.), anti-PD-1 (I.P.), anti-CTLA-4 (I.P.), radiation therapy (3 x 8 Gy), and combinations thereof. Treatments began two weeks after MOC2 inoculation. Tumor growth was monitored twice a week and changes in the TME post-treatment were assessed via flow cytometry. We further investigated DOXIL's influence on myeloid differentiation and macrophage polarization by culturing murine bone marrow cells with MOC2-conditioned medium in the presence and absence of DOXIL.

Results DOXIL monotherapy potently inhibited tumor growth, but growth resumed shortly after treatment was completed. The combination of DOXIL and anti-CTLA-4, with or without radiation, induced significant anti-tumor activity including complete regressions in most mice. In contrast, anti-CTLA-4 alone or anti-PD-1 and/or radiation (alone or combined with DOXIL) had little effect on tumor growth. Notably, flow cytometry analysis revealed that animals treated with DOXIL displayed nearly a three-fold depletion of MHCII+ macrophages (~23% vs 8% of CD45+ cells. Supporting these observations, in our *ex vivo* bone marrow cultures, DOXIL also induced a 3–5-fold reduction of the same MHCII+ macrophages, as well a significant decrease in M2 macrophages.

Conclusions Our study indicates that in an aggressive, immunologically cold oral cancer model, a combined approach using DOXIL, anti-CTLA-4, and radiation can instigate robust tumor regression. Potential induction of immunogenic cell death and selective macrophage depletion by DOXIL could contribute to the reshaping of the TME, which, in concert with CTLA-4 blockade and radiation, leading to effective anti-tumor responses. This underlines the significance of combination therapies to overcome resistance to immunotherapy in hard to treat cancer models. Ongoing studies are further defining the specific mechanisms by which DOXIL modulates the TME.

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