889 IFN-γ MODULATED DCSION MAKING ON T-CELL ANTI-TUMOR IMMUNITY

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Background Resistance to immune checkpoint blockade (ICB) treatments represents a major challenge in cancer therapy. Emerging evidence suggests that interferon-gamma (IFN-γ) plays a crucial role in modulating the response to checkpoint blockade. In combination with ICB treatment, anti-CTLA-4 and anti-PD-1 activate CD8+ T cells to produce high level of IFN-γ which in consequence kill CD8+ T cells and lead to tumor progression.[1] Furthermore, continuous exposure to IFN-γ causes the selection of IFN-γ-resistant or non-sense tumors that can promote resistance to ICB.[2 3] However, the detailed mechanism of how IFN-γ contributes to tumor progression and what the immune cells interplay by IFN-γ are still unclear.

Methods Melanoma cell line YUMM1.7 overexpressing ovalbumin (YUMM1.7-OVA) and the adoptively transferring OT-I T cells (OVA-specific T cell receptor (TCR) transgenic T cells) were applied for tumor mouse model. In addition, we used genetic depletion of IFN-γR1 on YUMM1.7-OVA by CRISPR-Cas9 to mimic the tumor cells that lost IFN-γ sensing to evaluate the T cells exhaustion. In the above mouse model, we combined IFN-γ genetic deletion mice or antibody blockade to investigate the action of IFN-γ in coordinating CD8+, CD4+ T cells and cDCs.

Results We found that tumor cells with a loss-of-function on IFN-γ sensing contained a high concentration of IFN-γ in the tumor microenvironment (TME) associated with the increased exhaustion in CD8+ T cells. To elucidate whether the exposure of IFN-γ promotes T cell exhaustion, we found that genetic ablation of IFN-γ or antibody blockade robustly increased tumor-specific CD8+ T cells, but did not increase the percentage of TCF-1+ progenitor and PD-1+ TIM3+ CD8+ T cells. Surprisingly, we further revealed that in response to IFN-γ blockade, cDC2 instructed CD4+ T cells to restrict the formation of TCF-1+ progenitor CD8+ T cells via the IL-4/IL-13 cytokine axis.

Conclusions Altogether, our findings suggest that bypassing IFN-γ signaling, type 2 immune responses orchestrated by cDC2 and IL-4/-13-producing CD4+ T cells can cooperatively modulate the differentiation of tumor-specific progenitor CD8+ T cells. Our study reveals an intricate correlation of cDCs and CD4+ T cells signature in shaping non-IFN-γ-driven CD8+ T cells expansion that provides the possibility to boost anti-tumor T cell response by blocking IFN-γ as a therapeutic approach in tumors with acquired resistance on sensing IFN-γ.

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Ethics Approval All mice were housed and bred in the animal facility of the University of Lausanne. All mice experiments were undertaken in accordance with the guidelines of ethical regulation for the mice strain under approved protocols at University of Lausanne (VD3309).

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