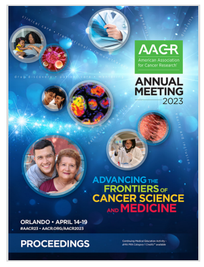
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Abstract

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Abstract 2261: Deciphering cross-resistance mechanisms associated to targeted therapies and immunotherapy in BRAF^{mut}melanoma: The role of tumor-associated macrophages and galectin-1 FREE

Florencia Veigas; Yamil Damian Mahmoud; Joaquin P. Merlo; Montana Manselle Cocco; Mora Massaro; Sabrina Gatto; Rosa Morales; Maria R. Girotti; Juan M. Perez-Saez; Gabriel A. Rabinovich

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Abstract

Both targeted therapies (TT) and immunotherapies have revolutionized the treatment of metastatic melanoma patients. Particularly, TT with BRAFi or BRAFi/MEKi leads to prompt but not durable responses in most patients due to the development of resistance within 1 year. Tumors refractory to TT derive little benefit from subsequent immunotherapy. Here we aim to elucidate how previous treatments with TT shape tumor-immune landscape and how it could be overcome therapeutically. Firstly, we analyzed the gene expression profile of a single-cell RNA-Seq dataset of 48 biopsies (16,291 cells) from melanoma patients before and during treatment with anti-PD1/anti-CTLA4. Our single-cell data analysis showed that macrophages and CD8^{+} T-cells of non-responders to immunotherapy upregulate a specific glycosylation-related signature unraveling a novel potential mechanism of resistance. Interestingly, we found a new subset of macrophages associated with resistance that arises during treatment. Macrophages of non-responders express high levels of galectin-1 (Gal-1), an immunosuppressive lectin implicated in tumor progression and immune escape, and display an M2-like phenotype regulated by the activation of specific transcription factors and signaling pathways including TGF-b, hypoxia, and VEGF. This observation was validated on bulk RNA-Seq datasets, where we observed that melanoma patients refractory to immunotherapy have a higher M2-macrophage infiltrate at baseline by MIXTURE (p-value<0.05). To study cross-resistance, we first analyzed by MIXTURE the immune microenvironment of melanoma patients treated with BRAFi or BRAFi/MEKi using 6 published transcriptomic datasets. We identified the prevalence of an immunosuppressive microenvironment significantly enriched in M2-macrophages in relapsed biopsies (p-value < 0.05) accompanied by low levels of T cells activation markers and dysregulation of the TGF-b/Gal-1 axis. Interestingly, we observed that the expression of Gal-1 is increased in human and mouse melanoma cell lines resistant to TT (p-value<0.05). To further elucidate the mechanisms underlying this effect and identify potential therapeutic targets, we developed an immunocompetent mouse model of resistance to BRAFi/MEKi in BRAFmut melanoma which mimics the M2 macrophage-centered immune profile observed in melanoma patients and the low response rates to immunotherapy at progression in TT-refractory tumors. Our preliminary findings suggest that Gal-1-glycan interactions could promote an immune evasive microenvironment in BRAFi/MEKi-resistant tumors, preventing subsequent response to immunotherapy. Hence, the Gal1-glycan axis arises as a potential actionable target for the development of combination therapies in non-responding melanoma patients.

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