The Effect of Targeted Inhibitors on Melanoma Tumor Immunity

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This research examines the effect of targeted inhibitors on melanoma tumor immunity. Background: While inhibitors/targeted therapies to driver oncogenes (mutated BRAF and MEK in the MAPK pathway) yield high response rates in melanoma patients, resistance and recurrence develop frequently. Immunotherapy, an alternative treatment option that inhibits immune checkpoints, offers a more durable response, but only to a subset of patients (10-35%). Therefore, the combination of both oncogene inhibitors and immunotherapy should be explored. To this end, surface proteins may illuminate how the melanoma could interact with the immune system when treated with targeted inhibitors. Research question: How do oncogene-signaling inhibitors (BRAFi and MEKi) affect expression of surface proteins instrumental in tumor immunity (PD-L1 and MHC)? Methods: two melanoma cell lines (BRAF V600E-mutant and BRAF-wildtype/NRAS-mutant) were treated with BRAFi and MEKi. After treatment, expression of (1) PD-L1 and MHC and (2) PD-L1 and phosphoERK were measured by flow cytometry. Data were analyzed with FlowJo and GraphPad Prism software. Results: When treated with BRAFi or MEKi, the BRAF-mutant melanoma exhibited decreased expression of PD-L1 and phosphoERK, demonstrating the effective shutoff of the MAPK pathway by the inhibitors. When the BRAF-wildtype/NRAS-mutant melanoma was treated with BRAFi, PD-L1 expression decreased, despite paradoxical activation (high phosphoERK expression) of the MAPK pathway. Application: Although further research is needed on how BRAF and MEK inhibitors affect PD-L1 expression in the BRAF-wildtype/NRAS-mutant melanoma, the study demonstrates that combining targeted inhibitors and immunotherapy is feasible in BRAF-mutant melanoma, which presents a novel treatment option.

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