Acquired Immune Resistance Follows Complete Tumor Regression without Loss of Target Antigens or IFN gamma Signaling

Cancer immunotherapy can result in durable tumor regressions in some patients. However, patients who initially respond often experience tumor progression. Here, we report mechanistic evidence of tumoral immune escape in an exemplary clinical case: a patient with metastatic melanoma who developed disease recurrence following an initial, unequivocal radiologic complete regression after T-cell-based immunotherapy. Functional cytotoxic T-cell responses, including responses to one mutant neoantigen, were amplified effectively with therapy and generated durable immunologic memory. However, these immune responses, including apparently effective surveillance of the tumor mutanome, did not prevent recurrence. Alterations of the MHC class I antigen-processing and presentation machinery (APM) in resistant cancer cells, but not antigen loss or impaired IFN gamma signaling, led to impaired recognition by tumor-specific CD8(+) T cells. Our results suggest that future immunotherapy combinations should take into account targeting cancer cells with intact and impaired MHC class I-related APM. Loss of target antigens or impaired IFN gamma signaling does not appear to be mandatory for tumor relapse after a complete radiologic regression. Personalized studies to uncover mechanisms leading to disease recurrence within each individual patient are warranted.

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