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Durable complete response in a patient with metastatic melanoma following adoptive transfer of autologous T cells recognizing 10 mutated tumor antigens

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Durable complete response rates of 20% have been observed in clinical trials of patients with metastatic melanoma employing adoptive cell transfer (ACT) of patient derived tumor infiltrating lymphocytes (TIL). Here we provide a detailed analysis of the response of TIL administered to a patient with metastatic melanoma who exhibited a complete response ongoing greater than 3 years. Using whole exome and RNA sequencing and bioinformatic analysis of the patient's matched tumor and normal gDNA we identified over 4,000 non-synonymous somatic mutation variants. We screened 745 somatically mutated genes using tandem minigene constructs expressing transcripts expressed in autologous tumor cells whose expression levels were greater than 0.1% of the levels of β- actin. These tandem minigenes were then transfected into autologous B cells and then analyzed for their ability to stimulate the administered T cells. Our results indicated that the autologous TIL distinctly recognized 10 somatically mutated gene products, each of which was recognized in the context of three different HLA class I restriction elements expressed by the patient's tumor. Detailed T cell clonal analysis revealed that 9 of the top 20 most prevalent clones present in the infused TIL, comprised over ¼ of total infused cells and recognized mutated antigens. These results further supported our efforts to identify and enrich mutation-reactive T cells for the treatment of patients with metastatic cancer.

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