Immunotherapy Resistance by Inflammation-Induced Dedifferentiation

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ABSTRACT

A promising arsenal of targeted and immunotherapy treatments for metastatic melanoma has emerged over the last decade. With these therapies, we now face new mechanisms of tumor-acquired resistance. We report here a patient whose metastatic melanoma underwent dedifferentiation as a resistance mechanism to adoptive T-cell transfer therapy (ACT) to the MART1 antigen, a phenomenon that had been observed only in mouse studies to date. After an initial period of tumor regression, the patient presented in relapse with tumors lacking melanocytic antigens (MART1, gp100) and expressing an inflammation-induced neural crest marker (NGFR). We demonstrate using human melanoma cell lines that this resistance phenotype can be induced in vitro by treatment with MART1 T cell receptor–expressing T cells or with TNFα, and that the phenotype is reversible with withdrawal of inflammatory stimuli. This supports the hypothesis that acquired resistance to cancer immunotherapy can be mediated by inflammation-induced cancer dedifferentiation.

SIGNIFICANCE: We report a patient whose metastatic melanoma underwent inflammation-induced dedifferentiation as a resistance mechanism to ACT to the MART1 antigen. Our results suggest that future melanoma ACT protocols may benefit from the simultaneous targeting of multiple tumor antigens, modulating the inflammatory response, and inhibition of inflammatory dedifferentiation-inducing signals.

INTRODUCTION

Despite the high initial response rates of patients to T-cell receptor (TCR) engineered adoptive T-cell transfer therapy (ACT), most patients relapse within a few months (1–3). The prevailing hypotheses for how resistance to ACT develops in patients with melanoma are either that their T cells become ineffective, due to exhaustion or immune tolerance, or that a subset of tumor cells acquire a survival advantage, possibly by genetic alterations that increase proliferation or that result in the loss of presentation of the antigen targeted by ACT (4–9). In recent years, an alternative mechanism, inflammation-induced dedifferentiation of tumor cells to precursor cells of neural crest origin (10–12), has come to light from mouse studies and using human cell lines. Work by Landsberg and colleagues (11) in a mouse model demonstrated that ACT using T cells specific for the shared melanosomal antigen gp100 resulted in initial tumor responses followed by regrowth of cancer.
cells that had lost gp100 expression and dedifferentiated into a neural crest lineage. This tumor cell dedifferentiation was mediated by tumor necrosis factor alpha (TNFα) produced by the gp100 TCR transgenic T cells in response to gp100 antigen recognition.

The inflammatory cytokine-induced plasticity of tumor cells, with reversible loss of the tumor-targeting antigen (11, 13), may have widespread clinical implications on how best to target antigens in ACT. Here, we show clinical and pathologic findings from a patient who received MART1-specific ACT and developed resistance to therapy in association with a dedifferentiated tumor phenotype that lacked conventional melanocytic antigens.

RESULTS
Clinical Case Report

A 60-year-old man with multiple pigmented nevi over his body presented with metastatic melanoma and was enrolled in a clinical trial of MART1 TCR-engineered ACT immunotherapy in combination with MART1 peptide-pulsed dendritic cells (DC) and high-dose IL2, administered after a lymphodepleting conditioning regimen (Fig. 1A; NCT00910650). Two years prior, he had noted a mole on his back that had grown and bled occasionally; however, it spontaneously regressed over time. Three months prior to presentation, he noted a right posterior neck mass, and 1 month prior to presentation, he was admitted for abdominal pain and jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) revealed peripancreatic masses, and a fine-needle biopsy raised the possibility of melanoma. A whole-body PET/CT scan revealed multiple metastases in the lungs, head and tail of the pancreas, stomach wall, right lobe of the liver, and peritoneal and mesenteric regions (Fig. 1B). An incisional biopsy of the right posterior neck mass confirmed a MART1-positive metastatic melanoma. HLA typing of the patient revealed HLA-A*0201 positivity, making him a candidate for this clinical trial. This patient was treated before the approvals of immunotherapies that have shown improvement in overall survival in patients with advanced melanoma, such as ipilimumab, nivolumab, and pembrolizumab (14–16).

Per study protocol (Fig. 1A), the patient underwent a nonmyeloablative conditioning regimen of cyclophosphamide (60 mg/kg/day, days −7 and −6) given with mesna (60 mg/kg/day) followed by fludarabine (25 mg/m², days −5 to −1). On day 0, the patient received adoptive transfer of 1 × 10⁷ lymphocytes that had been retrovirally transduced with the F5 MART1 specific TCR. On days +1, +14, and +30, the patient received MART1 peptide-pulsed DC vaccines (1.8 × 10⁷, 1.8 × 10⁷, and 1.7 × 10⁷ cells, respectively). Between days +1 and +7, he received high-dose IL2 administered every 8 hours to tolerance. Over the course of the study, peripheral blood was collected at regular intervals for basic laboratory tests and immune monitoring, and he underwent baseline and on-therapy biopsies and PET/CT scans.

At the time of treatment, the patient presented with diffuse metastatic disease confirmed by incisional biopsy of his left neck lesion to be stage IVc melanoma with homogeneously positive MART1 (Melan-A) expression by IHC (Fig. 1B). The patient tolerated infusion of F5 TCR T cells, followed by IL2 treatments, and MART1 peptide-pulsed DC vaccines with the main adverse effect being a whole-body skin rash. The patient was able to return to work 1 month after infusion. An early follow-up PET/CT scan at 35 days after infusion demonstrated a dramatic decrease in [18F]fluoro-2-deoxy-D-glucose (FDG) uptake in the vast majority of the patient’s baseline lesions, with increased uptake in seven lesions and the presence of two new lesions with mild FDG uptake (Fig. 1C; new lesions marked with black arrows and biopsied lesion marked with a red arrow). A subsequent PET/CT scan at 84 days after infusion demonstrated objective responses on most baseline lesions by RECIST. However, there were also several new and increasingly FDG-avid lesions (Fig. 1D); biopsied lesion marked with a red arrow) concerning for progression of disease including on his right anterior chest, liver, and paraspinal, paraaortic, and mesenteric regions, among others. The right anterior chest and wall lesion was biopsied at that time for further investigation of his progressing disease. The patient’s progression-free survival was 3 months, and his overall survival was 5 months.

Loss of MART1 Antigen in Regressing and Relapsed Tumors

The initial biopsy of the patient’s left neck lesion (Fig. 1B, red arrow) showed an atypical malignant epithelioid neoplasm that was consistent with melanoma. IHC staining was performed and showed strong, diffuse S100 and melanocytic antigen expression, including MART1, gp100, and tyrosinase (Fig. 1E). One month after infusion of the F5 TCR T cells, the same left neck lesion was biopsied but showed a heterogeneous pattern of MART1 staining with multifocal areas of low or absent MART1 expression (Fig. 1F). S100 staining showed no difference in intensity and distribution of expression when compared with the initial biopsy; however, gp100 and tyrosinase staining patterns mimicked the multifocal MART1 pattern (Fig. 1F). At the time of progression, an anterior chest lesion biopsy revealed the complete absence of MART1 expression, along with absence of gp100 and tyrosinase, but again a normal S100 staining pattern (Fig. 1G). The global loss of melanocytic antigens, as opposed to just MART1, suggested a phenotype switch (13) within the progressing tumor.

Figure 1. Progressive tumors after ACT demonstrate loss of melanocytic antigens. A, Overall treatment course for this patient. The patient was treatment naïve at the time of initiation of the ACT protocol. The patient underwent leukopheresis, and peripheral blood mononuclear cells (PBMC) were used to manufacture T cells for ACT and DCs for use in a MART1 peptide-pulsed DC vaccine. The patient underwent nonmyeloablative conditioning with cyclophosphamide and fludarabine started at day −7 prior to ACT. He received the DC vaccine on days +1, +14, and +30 after ACT. Several follow-up PET/CT scans were performed, initially showing disease regression at day +35 and eventual progression by day +84. B–D, PET/CT scans of the patient are shown at baseline before ACT, (C) during tumor regression on day +35 of ACT, and (D) during tumor progression on day +84 of ACT. Red arrows indicate biopsied tumors and black arrows indicate progressing lesions at day +35. E–G, IHC of the patient’s tumor for expression of S100, MART1, CD8, gp100, and tyrosinase at (E) baseline before ACT, (F) during tumor regression, and (G) during tumor progression. A heterogeneous, multifocal loss of MART1 and gp100 is seen during tumor regression, with complete loss of these melanocytic antigens at the time of tumor progression.
Immunotherapy Resistance by Dedifferentiation

**A**

Leukopheresis → PBMCs → Activation with anti-CD3 and IL2 → Activated CTLs → MSGV1-F5AF2AB retroviral transduction (×2) → F5 TCR CTLs

- **3 Months prior to ACT:** New right neck mass
- **2 Years prior to ACT:** Spontaneous resolution of a bleeding mole
- **1 Month prior to ACT:** ERCP showing peripancreatic masses and FNA concerning for melanoma
- **Day −7:** Beginning of nonmyeloablative conditioning
- **Day −1:** DC vaccine
- **Day +1 to +7:** High-dose IL2
- **Day +14:** DC vaccine
- **Day +30:** DC vaccine
- **Day +84:** PET/CT showing several new FDG-avid lesions

**B**

Left neck baseline lesion before F5 TCR ACT

**C**

Left neck regressing lesion Day +35 post-F5 TCR ACT

**D**

Right anterior chest progressing lesion Day +84 post-F5 TCR ACT

**E**

S100 MART1 gp100 Tyrosinase

**F**

S100 MART1 gp100 Tyrosinase

**G**

S100 MART1 gp100 Tyrosinase

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**Research Brief**

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Prior to ACT, the majority of CD8 CTLs were observed at the periphery of the tumor with few CD8 CTLs present in the central regions of the tumor parenchyma (Figs. 1E and 2A). At 35 days after infusion of F5 TCR T cells, a prominent but multifocal lymphocytic infiltrate was observed within the tumor, largely at the periphery with moderate infiltration of the center of the tumor (Figs. 1F and 2B). At the time of relapse, the anterior chest biopsy revealed a predominance of CD8 CTLs diffusely in all areas of the tumor (Figs. 1F and 2C). The expression of NGFR was low in pretreated tumor biopsies (Figs. 1E and 2A). However, increased multifocal expression of NGFR was observed in the tumor 35 days after infusion of F5 TCR T cells (Figs. 1F and 2B). Importantly, the expression of NGFR was negatively correlated with expression of MART1 and gp100 within the tumor and was observed predominantly in regions of increased CD8 CTL infiltration, thus suggesting that its expression was linked to regions of the tumor with increased inflammatory mediators (Figs. 1F and 2B). In the progressing tumor this phenomenon was even more apparent, as the vast majority of the tumor cells did not express MART1 and had strong NGFR expression with heavy infiltration of CD8 CTLs (Figs. 1G and 2C).

**F5 TCR T Cells Induce Dedifferentiation in Human Melanoma Cell Lines**

To determine if F5 TCR-transduced T cells are sufficient to induce dedifferentiation of human melanoma cells *in vitro*, we cultured the human melanoma cell line M397 with conditioned media from the coculture of F5 TCR T cells with M397.
cells. We were unable to derive cell lines from the patient’s biopsy samples; thus, the M397 line was chosen due to its HLA-A2 positivity and expression of MART1. M397 cells cultured with conditioned media generated from coculture with F5 TCR transduced T cells demonstrated decreased surface expression of MART1 and upregulation of NGFR (Fig. 3A). No effect was seen on M397 cells that remained untreated or that were treated with conditioned media from untransduced T cells (Fig. 3A), thus suggesting that conditioned media from F5 TCR T cells are sufficient to induce dedifferentiation of human melanoma cells.

A report in preclinical models had suggested that inflammation-induced dedifferentiation in mouse models of melanoma and in human cell lines is mediated by TNFα (11). To test if F5 TCR T cells produce TNFα upon antigen encounter, we performed intracellular staining of F5 TCR T cells

Figure 3. F5 TCR T cells induce dedifferentiation of human melanoma cell lines. A, M397 cells were left untreated or cultured for 3 days with conditioned media obtained from coculture of either untransduced or F5 TCR T cells with M397 cells. Flow cytometry was subsequently performed for surface expression of MART1 and NGFR. B, Untransduced or F5 TCR T cells were cocultured with M397 cells for 6 hours. Flow cytometry was subsequently performed with intracellular staining for TNFα. SSC, saline sodium citrate.
TNFα Induces Reversible Dedifferentiation and Markers of ACT Resistance in Human Melanoma

To verify TNFα-induced dedifferentiation in human melanoma cell lines, we treated 8 previously described patient-derived MART1-expressing melanoma cell lines (17) with either TNFα or DMSO for 3 days, and analyzed them for surface expression of MART1 and NGFR (Fig. 4A and B). Consistent with previous findings, we found that TNFα treatment led to dedifferentiation characterized by decreased surface MART1 expression and upregulation of NGFR (Fig. 4A and B). To better understand the molecular mechanism underlying this phenotypic transformation, we performed RNA sequencing of three different melanoma cell lines, M229, M263, and M297, treated with either TNFα or DMSO for 3 days. Gene set enrichment analysis (GSEA) of differentially expressed genes between TNFα- and DMSO-treated cells (Supplementary Tables S1 and S2) revealed that TNFα-treated cells were enriched for genes characteristic of the TNFα inflammatory response [normalized enrichment score (NES) = 2.21, FDR < 0.001], epithelial-to-mesenchymal transition (EMT; NES = 1.92, FDR < 0.001) and neural crest stem cells (NES = 1.49, FDR = 0.016; Fig. 4C). Moreover, genes involved in the microphthalmia-associated transcription factor (MITF) pathway (18), including melanocytic antigens such as MART1, tyrosinase, and PMEL (same as gp100), were enriched in DMSO samples and downregulated in TNFα-treated cells (NES = −2.38, FDR < 0.001; Fig. 4C; Supplementary Table S1). Interestingly, TNFα treatment also led to the enrichment of several pathways characteristic of the innate anti–PD-1 resistance (IPRES) gene signature (ref. 19; Supplementary Table S2). This included enrichment of genes involved in EMT, angiogenesis, and hypoxia, among others (Supplementary Table S2), which is reflective of a more invasive melanoma phenotype and that has been associated with increased NGFR expression (20, 21).

Among the differentially expressed genes with TNFα treatment of our melanoma cell lines were LIF and IL8, both of which are known to promote EMT and tumor resistance (22, 23), thus suggesting that autocrine signaling through these proteins may play a role in tumor dedifferentiation. We thus measured the secretion of IL8 and LIF in the supernatant of M397 cells treated with TNFα or cocultured with untransduced or F5 TCR T cells. Both TNFα and F5 TCR T-cell treatment of M397 cells resulted in increased IL8 and LIF secretion (Supplementary Fig. S1A). However, neither IL8 nor LIF treatment of M397 cells was sufficient to induce dedifferentiation (Supplementary Fig. S1B), thus suggesting that the melanoma resistance phenotype observed in this study is a direct effect of TNFα or may be mediated by factors other than IL8 and LIF.

To test the reversibility of inflammation-induced dedifferentiation in our melanoma cell lines, we treated M397 cells for 3 days with TNFα and subsequently removed the inflammatory media for 7 days (Fig. 4D). Withdrawal of inflammatory media resulted in increased surface MART1 expression and loss of NGFR expression (Fig. 4D), thus suggesting that inflammation-induced dedifferentiation is reversible and that persistent TNFα exposure is required to maintain this phenotypic state.

DISCUSSION

We report a case of melanoma dedifferentiation as a mechanism of immune escape in a patient treated with cancer immunotherapy, a phenomenon previously described only in mouse models and human cell lines (11, 13, 20). The notion of phenotypic switching of melanoma is consistent with our current model of melanoma resistance; that is, we see the loss of the target antigen, in this case MART1, in progressing tumors, which is a phenomenon frequently encountered by pathologists. The global loss of melanocytic markers, including gp100 and tyrosinase, in conjunction with the expression of the inflammation-induced neural crest marker NGFR, suggests that the tumor cells acquired a dedifferentiated state that is reflective of earlier stages of embryologic development of melanocytes, cells that originally arise from within the neural crest. Although it has been suggested that the plasticity of melanoma cells is reversible in mouse models (11), this cannot readily be tested in human patients. Our in vitro data using human melanoma cell lines suggest, however, that the same phenomenon may apply to humans, with cells dedifferentiating in the setting of inflammation with the possibility of redifferentiating after inflammation resolves.

Our RNA-sequencing analysis of melanoma cell lines treated with TNFα suggests that the pathways of inflammation-induced dedifferentiation may overlap with those of innate anti–PD-1 resistance (Supplementary Table S2). In particular, the enrichment of genes involved in EMT may reflect a more invasive phenotype. This has parallels to resistance patterns observed with BRAF inhibition and may suggest that the concept of phenotypic switching applies more broadly as a resistance mechanism to other modes of melanoma therapy (13, 18, 20, 21, 24, 25). In particular, several hypotheses suggest that the expression of MITF serves as a rheostat for melanoma cell phenotypes, with high levels of MITF promoting differentiation, moderate levels promoting proliferation, and low levels promoting invasiveness (26). MITF is a critical factor for expression of melanocyte pigment genes, and loss of MITF and MART1 (18) with elevated expression of AXL receptor tyrosine kinase and NGFR (20, 21, 27) has been implicated in switching of melanoma cells from a proliferative to an invasive phenotype. Given that invasive cells are more resistant to BRAF inhibition (28), this phenotypic switching may serve as a mechanism to develop resistance to such inhibitors. Single-cell studies of human melanomas at different stages of treatment have revealed that most tumors contain heterogeneous subsets of low and high MITF-expressing cells, with the relative composition of such cells shifting toward low MITF-expressing cells in BRAF or MEK inhibitor-treated patients (27).

This case report suggests that inflammation-induced dedifferentiation of melanoma cells may play a role in evading ACT in a subgroup of patients. In the clinical trial, 13 patients were evaluable for tumor response and 9 patients (69%) showed evidence of tumor regression; however, they all had disease...
TNFα treatment induces a reversible dedifferentiation of several BRAFV600-mutant melanoma cell lines. A, M229 and M262 BRAFV600-mutant cell lines were treated with DMSO or TNFα (1,000 U/mL) for 3 days. The surface expression of MART1 and NGFR at the end of this period was quantified using flow cytometry. B, Normalized median fluorescence intensities of MART1 and NGFR expression by flow cytometry in several BRAFV600-mutant melanoma cell lines treated with DMSO or TNFα for 3 days. Red and blue boxes highlight increased and decreased expression with TNFα treatment, respectively. C, GSEA of differentially expressed genes between melanoma cell lines treated with TNFα or DMSO for 3 days. An enrichment of genes characteristic of TNFα signaling, EMT, and neural crest stem cells was seen in TNFα-treated cells, and an enrichment of genes involved in the MITF pathway was seen in DMSO-treated cells. D, M397 cells were left untreated or treated for 3 days with TNFα. Inflammatory media were then replaced with fresh culture media for 7 days, and cells were subsequently analyzed by flow cytometry for surface expression of MART1 and NGFR.

progression within 6 months (29), similar to other TCR-engineered ACT trials (30). There were 4 patients with biopsies at progression, and only this case had evidence of dedifferentiation. This highlights the critical need for more studies investigating the underlying mechanisms of ACT resistance in human patients. These data are important in suggesting that future ACT protocols may benefit from the simultaneous targeting of multiple tumor antigens using mixed T-cell populations and from broadening of the response by concurrent administration of checkpoint inhibitors, so that dedifferentiation and loss of critical melanocytic antigens such as MART1 and gp100 do not contribute to
treatment resistance. In addition, concurrent reduction of the T cell–induced inflammatory milieu that is associated with elevated NGFR expression may also enhance therapeutic efficacy.

METHODS

Study Design

This was a pilot clinical trial for patients with metastatic melanoma (Clinicaltrials.gov number NCT00910650; refs. 31–33). The study protocol and its amendments were approved by the University of California, Los Angeles, Institutional Review Board. The patient provided written informed consent.

Manufacture of Cell Products

The patient underwent leukapheresis to collect peripheral blood mononuclear cells (PBMC). T cells and DCs were manufactured as previously described (31–33). Briefly, PBMCs were activated using anti-CD3 antibodies (OKT3) and IL2 to enrich for T cells and retrovirally infected with the MSGV1-F5AF2AB vector. Cells were infected fresh. DCs were produced by ex vivo differentiation of PBMCs using granulocyte/monocyte colony stimulating factor and IL4 and pulsed with the MART126-35 anchor–modified immunodominant peptide in the HLA-A2.1 allele (29). Full details are provided in the Supplementary Appendix.

Tumor Pathology and IHC

Formalin-fixed paraffin-embedded baseline and on-therapy biopsies were cut and stained with hematoxylin and eosin, anti-S100, anti-Melan-A, anti-CD8, and anti-NGFR antibodies at the UCLA Anatomic Pathology Immunohistochemistry and Histology Laboratory as previously described (34).

Cell Culture, In Vitro Stimulation, and Flow Cytometry

Human melanoma cell lines were cultured as previously described (17). For in vitro dedifferentiation experiments, MART1-specific T cells and untransduced T cells were cocultured with M397 cells, and supernatant was obtained after 24 hours. The conditioned media were diluted 1:1 in fresh culture media for use in subsequent cultures. One million M397 cells were then seeded and treated with TNFα (1,000 IU/mL), conditioned media from MART1 F5 TCR-transduced T cells, conditioned media from mock untransduced T cells, or no treatment for 3 days. To test the reversibility of dedifferentiation, the treatment media were removed from some replicates on day 3 and replaced with fresh culture media for 7 days. All cells were stained with anti-NGFR and anti-MART1 fluorescein conjugated antibodies for analysis by flow cytometry. Intracellular staining was performed using anti-TNFα antibodies after fixation using the Fixation/Permeabilization Solution Kit (BD Biosciences). Samples were analyzed using an LSR-II flow cytometer (BD Biosciences), and the data were analyzed using FlowJo software (TreeStar, Inc.). Full details of all in vitro assays are provided in the Supplementary Appendix.

Bulk RNA Sequencing and Analysis

RNA was extracted for three melanoma cell lines treated with either DMSO or TNFα and processed for library preparation. Samples were sequenced by 50-bp single-end sequencing on an Illumina HiSeq 2500 sequencer. Reads were mapped using TopHat2 v2.0.9 (35), and gene expression was quantified using Cufflinks v2.2.1 and Cuffnorm (36). GSEA was used to assess enrichment across several gene sets on the Molecular Signatures Database (MSigDB) and the pathways for IPRES (19). Full details are provided in the Supplementary Appendix.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions


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