Deciphering the genetic evolution of T-cell resistance in melanoma

Antje Sucker and Annette Paschen*

Department of Dermatology; University Hospital; University Duisburg-Essen and German Cancer Consortium (DKTK); Essen, Germany

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Introduction

Specific killing of melanoma cells by autologous CD8⁺ T cells has been demonstrated in numerous in vitro studies over the last 2 decades and recent clinical trials have provided evidence of effective in vivo antitumor T-cell activity. In a subgroup of melanoma patients, objective and durable clinical responses have been achieved upon adoptive transfer of ex vivo expanded tumor-infiltrating T lymphocytes and treatment with immunomodulatory antibodies.1,2 Thus, immunotherapy in melanoma holds great clinical promise, although mechanisms of intrinsic or acquired resistance to T–cell-based therapy are active in the majority of patients and need to be deciphered for further improvement of treatment regimens.

CD8⁺ T cells recognize peptide epitopes from tumor antigens in the context of human leukocyte antigen (HLA) class I molecules. In general, melanoma patients generate CD8⁺ T-cell responses toward multiple tumor antigens. Interestingly, the expressed somatic tumor mutations can function as neoantigens,3 giving rise to new antigenic peptide epitopes that increase melanoma immunogenicity. On the other hand, a number of specific somatic mutations directly interfere with T-cell recognition of melanomas. As such, mutational inactivation of the B2M gene has been demonstrated to generate a T–cell-resistant HLA class I-negative melanoma phenotype.4,5 The B2M gene encodes an essential component of all trimERIC HLA class I antigen complexes, consisting of an antigenic peptide, a HLA heavy chain, and the constant β2m light chain.

Melanoma cells, particularly those from sun-exposed tumors, are characterized by a high mutation load.6 Although a few mutations have been identified as shared “melanoma drivers,” the majority of the genetic alterations is “private.” This leads to marked tumor heterogeneity, both between and within patients, that further increases during disease progression. Due to the impact of genetic alterations on melanoma immunogenicity, it is conceivable that a tumor will give rise to different lineages of distinct immunogenicity. So far, the evolution of heterogeneity in melanoma immunogenicity, and in particular the development of T-cell resistance, is poorly understood.

Recently, we studied the immunogenicity of tumor cells from 3 consecutive metastases of a melanoma patient (Ma-Mel-48a) collected over a period of 1 year in the course of progressive stage IV disease.7 From excised tumor tissues, we established melanoma cell lines that were studied, at first, for their immunophenotypes. Of the 3 cell lines, only 2, Ma-Mel-48a (established from a skin metastasis, July 2002) and Ma-Mel-48b (established from a lymph node lesion, January 2003) expressed HLA class I molecules whereas the Ma-Mel-48c cells (established from a lymph node metastasis, July 2003) were HLA class I-negative. These cellular phenotypes were also detected in the corresponding cryopreserved tumor tissues. Studying the capacity of the HLA class I-positive Ma-Mel-48a and Ma-Mel-48b cells to stimulate autologous CD8⁺ T cells, we found Ma-Mel-48a cells to be strong stimulators whereas the Ma-Mel-48b cells had only low T-cell-stimulatory capacity. The gradual decrease of melanoma immunogenicity culminated in the HLA class I-negative T–cell-resistant phenotype of Ma-Mel-48c cells that was caused by a lack of B2M expression.

Molecular analyses found 2 genetic alterations to be responsible for the evolution of β2m deficiency in Ma-Mel-48c cells – a deletion on chromosome 15q where the B2M gene maps (Chr. 15q21.1) and an inactivating B2M gene mutation. Notably, the same deletion on chromosome 15q was already present in the Ma-Mel-48a and Ma-Mel-48b cells, indicating that the chromosomal aberration, associated with a B2M allele loss, occurred early in the course of disease.

This chronology of genetic alterations was also detected in tumor cells from consecutive metastases of the patient Ma-Mel-100.7 The cell lines Ma-Mel-100a and Ma-Mel-100b, established from distinct lymph node lesions in April 2004 and May 2005, respectively, were both of a HLA class I-negative phenotype. In these
Previously, the Ferrone group detected β2m loss in several recurrent melanoma metastases from patients receiving immunotherapy, suggesting that the activity of tumor-antigen-specific T cells favored the outgrowth of HLA class I-negative melanoma lesions. Interestingly, a recent mouse model study by Matsushita et al. pointed to neo-antigen-specific T cells as important players in this so-called T-cell-mediated cancer immunoeediting process. It remains to be determined whether this can be translated to the human situation. Furthermore, it remains to be analyzed whether β2m-deficient metastases are present among the recurrent lesions from patients receiving adoptive T-cell therapy or treatment with immunomodulatory antibodies. In summary, we postulate that melanoma cells can genetically evolve to avoid being recognized by CD8+ T cells and propose that the screening of metastases for specific genetic alterations prior to and during immunotherapy could be relevant to predicting clinical responses.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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