



T-cell recognition of non-mutated tumor antigens in healthy individuals: connecting endogenous immunity and tumor dormancy

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Abstract

The concept of a dual functional programme of the immune system to destroy malignant cells but also to edit their immunogenic profile, considerably improved our understanding of the process of tumor evolution in the context of a continuum of interactions between tumor cells and immune lymphocytes. Such an endogenous antitumor immunity throughout the period of cancer development established the concept of cancer immunomodulation which is practically based on a process of selection of more clonal tumors which are manageable by the immune system and constitute the equilibrium phase of immunoediting. The duration of this phase is very important, because the immune system keeps the tumor in a dormant state via cell interactions which establish a balanced state of tumor immunosurveillance versus tumor immune evasion. Depending on the quality and quantity of antitumor immune reactivity and the effectiveness of resistance mechanisms employed by the tumor cells to counteract this immune attack, the equilibrium phase may have shorter or longer duration. Notwithstanding its natural course, the equilibrium phase should be considered as a part of tumor evolutionary process guided by genetic as well as epigenetic changes which in turn activate endogenous cellular immunity to certain levels capable of controlling tumor growth rates and maintain tumor dormancy.

Keywords Tumor dormancy · Melanoma antigens · T-cell recognition · Endogenous immunity · Neoantigens · PIVAC 17

Introduction

There is now accumulating evidence, suggesting that the cellular and molecular events which keep the balance between tumor dormancy and immune surveillance after the elimination phase of immunoediting, regulate epigenetic changes in tumor cell biology as well as the time of their appearance ultimately leading to tumor escape [1–3]. However, tumor

dormancy may also include early metastases, preceding the equilibrium phase, via disseminated tumor cells before the primary tumor becomes clinically detectable. Such early disseminated tumor cells are also kept in a dormant state via endogenous antitumor immunity. Thus, tumor dormancy should be considered as a part of neoplastic disease in cancer patients undergoing complete responses upon treatment. Moreover, it may also represent a situation of malignant disease in, apparently, healthy individuals who have developed robust endogenous antitumor immunologic responses. Therefore, it will be of paramount importance to detect cellular components comprising the main actors of the immunologic pathways comprising the endogenous antitumor immunity and acting as predictive biomarkers of cancer dormancy.

A recently published paper by Przybyla et al. [4] reports for the first time on the identification of melanoma-specific T lymphocytes in healthy individuals displaying strong reactivity against 15-mer synthetic peptides covering the entire sequence of melanoma antigens Tyrosinase–MAGEA3–Melan-A/Mart-1–Pmel 17gp100–and NY-ESO-1. The data from this paper strongly support

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This paper comments on an Original Article entitled Natural T cell autoreactivity to melanoma antigens: clonally expanded melanoma-antigen specific CD8+ memory T cells can be detected in healthy humans by Anna Przybyla et al.

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the notion that this kind of immunity may represent (i) an endogenous antitumor immunity preserving tumor (melanoma) dormancy in these apparently healthy donors, or (ii) a natural autoreactivity against melanocytes protecting against the development of malignant melanoma. This was signified by three different means: (a) by the high frequencies of these melanoma-specific T cells resembling the frequencies of clonally expanded memory T lymphocytes; (b) by their active functional status through the production of IFN γ upon stimulation with the pool of melanoma peptides, further supporting their role as memory T cells which had displayed immune reactivity *in vivo* resulting in their clonal expansion; and (c) by their absence in melanoma patients.

The data by Przybyla et al. [4] also bring back an issue that has been abandoned in the scientific domain, namely, that of the role of non-mutated melanoma antigens to trigger robust T-cell-mediated immunity. During the past few years the role of neoantigens arising from tumor-specific non-synonymous somatic mutations has attracted much attention as a major factor guiding antitumor T-cell reactivity during immunotherapies. In particular, successful immune checkpoint blockade-based immunotherapies are related to the presence of clonally expressed tumor-specific neoantigens [5] and this has led to their recognition as predictive biomarkers. Moreover, neoantigens are promising for the development of novel therapies to promote antitumor reactivity of T cells specifically recognizing them in the context of MHC class I and class II molecules [6]. Because neoantigens represent a distinct class of tumor antigens encoded by mutated genes, these are recognized as non-self-antigens by a non-tolerized T-cell receptor repertoire, presumably of high affinity, resulting in robust antitumor reactivity. On a theoretical background, this could provide a reasonable explanation for justifying their dominant role, over non-mutated tumor self-antigens, not only as key components for endogenous antitumor responses, but also as therapeutic targets. However, there are some issues which seem to challenge this view. First of all, melanoma is an immunogenic tumor with high mutational load but also overexpressing non-mutated self-antigens which enables continuous interactions with the immune system. As a result, in melanoma, besides reports describing T-cell responses against patient-specific neoantigens [7, 6], there are ample studies showing endogenous reactivity of CD8+ T cells against non-mutated shared antigens [8–11]. In addition, such an endogenous antimelanoma immunity was associated with clinical responses to immune checkpoint blockade [9, 10]. Moreover, the study by Weide et al. [11] convincingly demonstrated the prognostic value of memory endogenous T-cell reactivity to melanoma self-antigens in patients with advanced melanoma, and reported an association between clinical outcome and the presence of NY-ESO-1 T-cell responses after ipilimumab-based immunotherapy in metastatic melanoma patients [12].

On the other hand, the process of discovering immunogenic mutant peptides is rather complex and cumbersome requiring whole exome sequencing, RNA-sequencing, and mass spectrometry combined with algorithms predicting binding of the identified peptides to MHC molecules. Then, from the thousands of exome and transcript coding variations only a small number of such epitopes will be validated as immunogenic [13] to be further validated as therapeutic targets. Another issue which challenges the dominant role of neoantigens as predictive biomarkers is related to the activation of melanoma-intrinsic oncogenic pathways resulting in the lack of tumor infiltration by T cells. For instance, activation of the WNT/ β -catenin-signaling pathway was predictive for clinical responses in metastatic melanoma patients to anti-PD1 therapy independent of their mutational load [14, 15]. But also in the case of T-cell infiltrated tumors, immune editing will eliminate the majority of strongly immunogenic tumor cells bearing neoantigens, thereby weakening the endogenous antitumor T-cell reactivity.

The data presented by Przybyla et al. [4] reinvigorate the role of melanoma non-mutated self-antigens as key players of endogenous anti-melanoma immunity. Their finding that healthy donors harbor increased frequencies of circulating melanoma self-antigen-reactive CD8+ T cells may be explained by postulating, as the authors suggest melanocyte activation in the context of skin inflammation during sunburns which supports natural CD8+ T-cell autoreactivity. They also speculate that the immunobiological role of these autoreactive T cells will be to protect against the development of melanoma. The alternative would be to suggest that these findings predict immune responses favoring melanoma dormancy. To this end, Masoud Manjili has recently proposed [16] that cellular malignancies are manifested as early disseminated tumor cells which can be kept by immune lymphocytes in a dormant state for long periods of time without clinical evidence of primary tumors. Thus, immunotherapeutic targeting of dormant tumor cells would be an option for avoiding the generation of primary tumors followed by tumor relapses. Consequently, the major barrier that dormant tumor cells must overcome is of immunologic origin and in this scenario the type of cytotoxic T cells described in the study by Przybyla et al. [4] recognizing tumor self-antigens, is of paramount importance.

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Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest regarding this article.

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