Commentary

Uncovering first molecular mechanisms of secondary resistance against PD-1 blockade

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Checkpoint inhibition by anti-PD-1 antibodies alone or in combination with CTLA-4 blockers is the new paradigm in the treatment of metastatic melanoma (1,2). Response rates are high with about 40% in anti-PD-1 monotherapy and about 60% in combination with anti-CTLA-4 inhibitors (3). Initially, responses were assumed to be durable, but soon it became evident that even deeply responding patients with completely decreased metastases bear the potential to relapse even under continuously ongoing therapy (4,5). The molecular mechanisms of this acquired resistance remained unclear until now, when Zaretsky and coworkers from the group of Antoni Ribas succeeded to unravel some first molecular mechanisms helping to understand this complex clinical situation (6).

The authors performed an elaborate molecular workup of tumor tissues obtained from four melanoma patients treated with the PD-1 inhibitor pembrolizumab. They compared the results obtained by whole exome sequencing of tissue samples taken before the onset of pembrolizumab and at the time of secondary disease progression. Thereby, in three out of four patients genetic alterations in molecular pathways essential for interferon (IFN) signaling and antigen presentation were detected, which appeared under ongoing treatment and thus are likely to represent immune escape mechanisms evolving under the selective pressure of anti-PD-1 therapy.

It has been observed, that tumors without any T cell infiltrate before therapy achieve a dense CD8+ T cell infiltrate under ongoing anti-PD-1 treatment paralleled by a clinical response. Interestingly, in many tumors progressing at a later time point under ongoing therapy, these T cell infiltrates remain present. This observation indicates that the mechanisms attracting the T cells were still present, but their capacity to attack the tumor cells had developed new dysfunctionalities in terms of new immune escape mechanisms. These mechanisms could hypothetically be a dysfunction in the cytotoxic properties of the T cells, an inactivation of the T cells by cytokines and/or checkpoint molecules other than PD-1, a loss of tumor antigens, or a defect of the antigen processing and presentation machinery. The findings of Zaretsky and coworkers reveal the latter mechanism of a defective antigen processing and presentation as most relevant in melanoma with a secondary resistance to anti-PD1, as far as this can be estimated from the relatively low number of four patients analyzed.

In one of the four patients a frame-shift deletion was found in exon 1 of the beta-2-microglobulin (B2M) gene. B2M has an essential function supporting HLA class I molecules to stabilize their cell surface expression and to enable their capacity to present tumor-specific class I peptides. Loss-of-function mutations in B2M have already been described as a highly relevant strategy of tumor cells to escape from T cell-mediated immune responses by protecting the tumor cells from T cell recognition (7,8). Remarkably, in two of the four patients analyzed, loss-of-function mutations were detected in the genes encoding...
for interferon-receptor-associated Janus kinase 1 (JAK1) or Janus kinase 2 (JAK2), resulting in a lack of response to IFN gamma and its signaling cascade. Normally, IFN gamma pathway activation exerts anti-tumoral effects by a reduction of cell proliferation as well as an enhancement of antigen presentation and hereby tumor cell recognition by cell-mediated immune responses. The authors additionally performed functional assays showing that the tumor cells bearing JAK mutations were insensitive to IFN gamma as shown by a lack of phosphorylation of the signal transducer and activator of transcription 1 (STAT1), which is the key molecule in the IFN gamma signaling pathway.

Notably, Zaretsky and coworkers had to screen 78 metastatic melanoma patients treated with pembrolizumab at their institution to find four patients suitable for the intended molecular workup. Patients had to demonstrate an objective response under pembrolizumab therapy, which had to be confirmed four weeks later using RECIST criteria. Moreover, the patients had to show a late relapse under ongoing pembrolizumab after at least six months of documented clinical response. Finally, tumor tissue samples must have been available from before onset of pembrolizumab and from disease progression. This low rate of 5% of suitable patients with evaluable tumor materials although obtained at a university medical center indicates the need to strongly increase the frequency of diagnostic tumor biopsies taken from patients during their course of disease. Particularly in melanoma with its high rate of easily accessible metastases to the skin and lymph nodes, the procedure of sequential biopsy of these lesions should enter the routine clinical practice with the intent to gain molecular insights into the biology of the individual patient's tumor.

Taken together, the study of Zaretsky and coworkers demonstrated for the first time, that an immunotherapy with checkpoint inhibitors is able to induce genetic aberrations, translating into immune escape mechanisms in tumor cells which are thereafter clonally expanded by selective pressure, and hereby lead to a disease relapse in initially responding patients. In the present work only four patients could be analyzed. Thus, it can be assumed that after analysis of further suitable patient materials, in the near future a larger diversity of molecular mechanisms of secondary resistance to PD-1 inhibitors will be discovered.

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