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CANCER THERAPY Tumours switch to resist

ANTONI RIBAS and PAUL C. TUMEH

Department of Medicine, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles, California 90095-1782, USA

ANTONI RIBAS: aribas@mednet.ucla.edu

Abstract

Tumour cells can respond to targeted immune-cell therapies by losing proteins that mark them as being cancerous. Subverting this resistance mechanism may lead to more durable cancer-treatment strategies.

Decades of research have yielded methods for cancer treatment that can be more specifically tailored to a patient's cancer than broader strategies such as radiotherapy or chemotherapy. However, these methods — which include immunotherapy and therapies targeted at cancer-causing genes — are dogged by the problem of acquired resistance, in which many patients initially respond to the treatment but subsequently become unresponsive and experience relapse. Resistance is commonly thought to arise from the proliferation of a small proportion of resistant cells in a mixed tumour cell population. But on page 412 of this issue, Landsberg *et al.*¹ show, using a mouse model of melanoma, that resistance to a promising form of immunotherapy can develop when cancer cells change their protein-expression profile in response to treatment*.

Cancer immunotherapies are designed to initiate or boost a person's immune response to a tumour. One way of doing this is by adoptive cell transfer (ACT), in which patients receive transfusions of immune cells called T cells that target cancer-specific antigens (an antigen is a substance that elicits responses from the B cells and T cells of the immune system). By contrast, oncogene-targeted therapies work by reducing the function of certain mutated proteins that are overactivated in tumour cells. Although much progress has been made in determining why patients relapse with oncogene-targeted therapies, little is known about the mechanisms underlying acquired resistance in patients receiving ACT. However, there is generally a high initial response rate to ACT, so understanding what then happens to lead to resistance is a challenge worthy of investigation.

The most common sources of tumour-antigen-specific cells for ACT are tumour-infiltrating lymphocytes (TILs) or blood T cells that are isolated from the patient and modified before being reintroduced. In the case of TILs, which already have tumour specificity, this involves expanding the cell population and activating the cells. In therapies using blood T cells, which are initially not tumour specific, the cells' antigen receptors are first genetically engineered to recognize tumour antigens². Tumour responses tend to last longer in TIL-based ACT, probably because each TIL preparation might target several tumour antigens simultaneously³. However, TILs can be isolated from only a limited number of patients with melanoma, which hinders the application of this approach. Genetically engineered T cells

address this problem, because every patient has ample numbers of nonspecific T cells that can be harvested for this purpose. But although ACT based on genetically modified T cells results in a high frequency of positive initial responses, relapse often occurs a few months after the start of treatment⁴⁻⁶.

To study how this resistance arises, Landsberg *et al.* developed a mouse model of melanoma and an ACT protocol (using genetically modified T cells) that recapitulates the clinical course seen in people. The widely accepted view of how resistance to ACT therapy arises is that tumours contain small numbers of cells (called subclones) with genetic variations that give them a proliferative advantage in the face of the immune-cell attack. However, Landsberg and colleagues observed that the inflammatory response initiated by ACT caused a proportion of the melanoma cells to lose some of the antigens that defined the cells as being cancerous — a change that the authors describe as ‘dedifferentiation’ (Fig. 1). This is the key to their new hypothesis for tumour resistance: the T cells transferred in ACT are designed to target tumour-specific antigens, but precisely these antigens are lost by the tumour cells during treatment. The authors also identify the pro-inflammatory cell-signalling molecule tumour necrosis factor- α (TNF- α) as a crucial mediator of this cellular change, and show that the change is reversible, meaning that the cancer cells can reacquire expression of the antigens when the treatment is stopped and the inflammation resolves.

Although the cellular dedifferentiation described by Landsberg and colleagues is a new concept in cancer resistance, the idea fits well with previously proposed mechanisms of resistance to tumour-antigen-specific immunotherapy. For example, resistance has been observed after increased proliferation of subclones that did not express a tumour antigen that was being targeted by ACT, and also as a result of some or all cells in a tumour lacking key proteins in the cellular pathway by which antigens are ‘presented’ to T cells⁷. However, resistance to immunotherapy may also arise from changes in the transferred immune cells, rather than changes to the characteristics or relative abundance of cancer cells. For example, therapeutic T cells may lose their anti-tumour functions over time *in vivo*, owing to intrinsic changes in the T cells that shift their activity from cytotoxicity to an immune-tolerant state⁸ or through the effects of immune-suppressive cells in the tumour microenvironment, such as myeloid suppressor cells or regulatory T cells².

The mechanism of acquired resistance reported by Landsberg *et al.* has so far been observed only in their mouse model. But if similar effects are seen in patients, then the authors’ findings will open up avenues for improving ACT-based therapies. For example, because this resistance mechanism may be restricted to the loss of certain tumour antigens, concurrently targeting several antigens of different classes by transferring a mixed population of T cells might slow or prevent resistance. A similar effect may be achieved by preventing TNF- α expression by the transferred T cells, as this seems to be the key inflammatory molecule that induces antigen loss by the tumour cells. Alternatively, broadening the immune response by combining ACT with other immune-supporting agents, such as anti-CTLA4 or anti-PD-1 antibodies, might minimize the reliance of the therapy on recognizing a single antigen and thereby make it harder for the cancer cells to escape. Thus, by identifying a mechanism by which cancers adapt to evade ACT therapy, Landsberg and colleagues have provided the basis for several testable approaches to overcome this problem in patients.

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Figure 1. Escape by dedifferentiation

Cancer cells express certain antigens that are not expressed by non-cancerous cells (red colour on cells indicates antigen expression). Adoptive cell transfer is a type of immunotherapy in which immune cells called T cells with receptors that specifically recognize these defining antigens are transferred into patients, where they initiate an immune response that kills the cancer cells. Landsberg *et al.*¹ show that, in the process of cancer-cell killing, the tumour-infiltrating T cells release the inflammatory molecule TNF- α , which causes some of the tumour cells to stop expressing of some of their cancer-specific antigens. These 'dedifferentiated' cancer cells are no longer recognized by the T cells, resulting in resistance to the therapy and tumour regrowth.