IMMUNOTHERAPY

Adapt and survive

“ACT should include a mix of cytotoxic T cells that recognize melanocyte-specific and non-melanocyte-specific antigens.”

A few patients with melanoma have been successfully treated with adoptive cell transfer therapies (ACTs), which involve the transfusion into patients of cytotoxic T cells engineered to recognize melanoma-specific antigens. However, resistance to this treatment is common and is thought to arise through the outgrowth of pre-existing melanoma clones that no longer express the targeted antigen. A new mouse model of melanoma ACT indicates that dedifferentiation of melanoma cells, driven by an inflammatory response, might also have a role in resistance.

Use of a chemical protocol to treat mice that overexpress hepatocyte growth factor (HGF) in a background of disrupted cell cycle regulation results in the development of macroscopic melanomas. Thomas Tüting and colleagues treated these mice with activated, syngeneic cytotoxic T cells that recognize the GP100 melanoma antigen, using a regimen similar to that used in humans. The treated melanomas regressed, but relapse occurred in many of the treated mice. Amelanotic regions were common in some of the tumours that grew back after prolonged remission, as was the loss of GP100 expression. Such changes were associated with the infiltration of immune-suppressive myeloid cells and increased expression levels of several inflammatory cytokines.

To better understand what is driving this relapse, the authors established a melanoma cell line from these mice and transplanted it into syngeneic mice so that only one melanoma arose per mouse. These melanomas responded similarly to ACT and relapse was again common. The authors examined the parental melanoma cells and six relapsed melanoma cell lines. Although the relapsed cell lines were all amelanotic and no longer expressed GP100, transplantation of one of these lines into syngeneic mice resulted in the re-expression of GP100, and these mice once again responded to ACT. Relapse in these mice was also associated with an inflammatory response and loss of GP100 expression. Thus, the authors hypothesized that the T cell-mediated immune response within the tumours can also lead to

the reduced expression of GP100 and therapeutic resistance.

Whole-genome mRNA expression analyses in parental, relapsed and re-transplanted melanomas indicated that the resistant melanoma cells downregulated melanocytic differentiation genes and upregulated mesenchyme-related genes. Further experiments *in vitro* indicated that the expression of tumour necrosis factor (TNF) by activated immune cells was mostly responsible for this shift of melanoma cells towards a more dedifferentiated phenotype characterized by loss of GP100 expression and upregulation of nerve growth factor receptor (NGFR) typical for precursors of the neural crest lineage from which melanocytes develop. After withdrawal of TNF, dedifferentiated melanoma cells reverted to a mixed population of differentiated, GP100-expressing melanoma cells and dedifferentiated, NGFR-expressing melanoma cells. A similar population equilibrium was established in dedifferentiated melanoma cell lines injected into syngeneic mice. These results indicate that the differentiation status of melanoma cells can be altered in response to signals emanating from the tumour microenvironment.

The authors established that human melanoma cell lines behave similarly to the mouse melanomas in response to TNF and, importantly, they showed that although TNF induces the downregulation of melanocyte-specific antigens it has no effect on other antigens expressed by melanoma cells. Thus, the authors propose that ACT should include a mix of cytotoxic T cells that recognize melanocyte-specific and non-melanocyte-specific antigens.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Landsberg, J. et al. Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation. *Nature* 10 Oct 2012 (doi:10.1038/nature11538)

DIGITAL VISION