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CANCER IMMUNOTHERAPY

The right shape

Targeting antigens expressed specifically on the cell surface of cancer cells with monoclonal antibodies (mAbs) or chimeric antigen receptor (CAR)-expressing T cells has become a successful approach in cancer therapy. Most of the cancer-specific antigens shared by multiple tumours are likely to have already been identified by transcriptome or proteome analyses, and finding new antigens is difficult given their great diversity within and between individual tumours. However, tumour neoantigens that are formed by post-translational modifications — such as glycosylation or conformational changes — might have been missed in these transcriptomic and proteomic analyses.

To explore whether these antigens could be potential targets, Hosen *et al.* screened more than 10,000 mAb clones for their binding to multiple

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myeloma (MM) cell lines and to bone marrow cells from patients with MM. The authors found that one such mAb, MMG49, bound specifically to MM cells, but not to normal peripheral blood mononuclear cells (PBMCs). The MMG49 epitope was then found in the N-terminal region of integrin $\beta 7$, which is inaccessible in the resting conformation of the integrin but exposed in the active conformation. Although no mutations of integrin $\beta 7$ were detected in MM cells, these cells have high expression and constitutive activation of integrin $\beta 7$, in contrast to other cell types, including normal integrin $\beta 7^+$ leukocytes, in which the integrin is found in the resting conformation, which explains the observed specificity of MMG49.

As the density of the MMG49 epitope on MM cells was not high enough to induce cytotoxicity

by using the mAb, the authors decided to design an MMG49-based CAR, which enables targeting of antigens present at low densities, by combining the single-chain variable fragment from MMG49 and the CD28 and CD3- ζ signalling domains. Subsequently, T lymphocytes were transduced with the MMG49 CAR and expanded *in vitro*. MMG49-CAR T cells were activated, secreted the cytokines interferon- γ and interleukin-2 and showed cytotoxic activity when co-cultured with either cells that expressed MMG49 or primary MM cells derived from patients, but not in the presence of normal PBMCs or haematopoietic progenitor cells.

Finally, the authors tested the anti-tumour activity of the MMG49-CAR T cells *in vivo*, in a xenograft model of MM. Infusion of MMG49-CAR T cells reduced the tumour burden and prolonged survival compared with treatment with CD19-CAR T cells without toxicity to normal haematopoietic cells.

These results not only identify the active conformation of integrin $\beta 7$ as a potential therapeutic target in MM but also suggest an alternative approach of finding immunotherapeutic targets in cell-surface proteins that undergo conformational changes, even if the expression of the proteins themselves is not cancer specific. “[The next] breakthrough in CAR T cell therapy should be its application for solid tumours, but appropriate target antigens are needed for it. We have already started searching for cancer-specific conformational epitopes in solid tumours” concludes Hosen.

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ORIGINAL ARTICLE Hosen, N. *et al.* The activated conformation of integrin $\beta 7$ is a novel multiple myeloma-specific target for CAR T cell therapy. *Nat. Med.* <http://dx.doi.org/10.1038/nm.4431> (2017)