IMMUNOTHERAPY

Beneficial loss

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URLs

CD28
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=940

Cblb
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=208650

Atm
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=11920

Cytotoxic T lymphocytes (CTLs) mediate the host immune response against immunogenic tumours but, unfortunately, several hurdles limit their effective use as a cancer immunotherapy. For example, to be fully activated T cells require — besides T-cell receptor (TCR) activation — the co-stimulation of receptors such as CD28, but many tumours lack expression of ligands for CD28. Two groups now independently report that removing the E3 ubiquitin ligase *Cblb* (Casitas B-lineage lymphoma b), which makes T-cell activation independent of CD28 co-stimulation, protects mice against different types of transplanted and spontaneous tumours.

Jeffrey Chiang and colleagues studied in detail the effect of *Cblb* deletion on $CD8^+$ T cells, which mediate the anti-tumour immune response. Following TCR stimulation, $Cblb^{-/-}$ $CD8^+$ T cells showed increased proliferation and cytokine secretion compared with wild-type cells, without requiring CD28 co-stimulation. Proliferation and cytokine secretion were not reduced by transforming growth factor-β (TGFβ), which is often secreted by tumour cells and suppresses the CTL anti-tumour response. Interestingly, Stefanie Loeser and colleagues showed that $Cblb^{-/-}$ $CD8^+$ T cells are also partially resistant to suppression mediated by regulatory T cells, another mechanism that can prevent CTL tumour killing.

To test the effect of *Cblb* deletion on the anti-tumour response *in vivo*, Chiang and colleagues subcutaneously injected $Cblb^{-/-}$ mice with weakly immunogenic and highly immunogenic cells from a mouse thymoma that does not express co-stimulatory molecules. *Cblb* deletion prevented or attenuated tumour growth compared with wild-type mice, regardless of the intrinsic immunogenicity of the tumour. Tumour rejection seemed to be independent of CD28 because tumour growth was also suppressed in $Cblb^{-/-}$;$Cd28^{-/-}$ mice.

Similarly, Loeser and colleagues showed that $Cblb^{-/-}$ mice reject tumours derived from highly tumorigenic TC1 fibroblasts that express the E6 and E7 human papilloma virus 16 oncoproteins. Both groups confirmed that tumour rejection in $Cblb^{-/-}$ mice was mediated by $CD8^+$ T cells, and that adoptively transferred $CD8^+$ T cells from these animals induced the rejection of established tumours in recipient mice, although it has not yet been shown whether their cytotoxic activity is required.

So, does *Cblb* loss also reduce the development of spontaneous tumours? Chiang and colleagues crossed $Cblb^{-/-}$ mice with ataxia telangiectasia mutated (*Atm*) knockout mice, which develop thymic lymphomas at an early age. They found that ablating *Cblb* delayed or prevented the onset of lymphomas. Loeser and colleagues induced skin tumours in mice through UVB irradiation and found that $Cblb^{-/-}$ mice showed a strikingly reduced cancer susceptibility. Depletion of $CD8^+$ T cells from UVB-irradiated $Cblb^{-/-}$ mice that had previously not developed cancer caused the rapid onset of fast-growing tumours, ruling out the possibility that *Cblb* ablation might reduce tumorigenesis through other mechanisms.

Although *Cblb* inactivation in CTLs seems to be a promising strategy for cancer immunotherapy, potential side effects such as increased susceptibility to autoimmune disease could limit its use and should be considered.

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ORIGINAL RESEARCH PAPERS Chiang, J. Y., Jang, I. K., Hodes, R. & Gu, H. Ablation of *Cbl-b* provides protection against transplanted and spontaneous tumours. *J. Clin. Invest.* **117**, 1029–1036 (2007) | Loeser, S. *et al.* Spontaneous tumour rejection by *Cbl-b*-deficient $CD8^+$ T cells. *J. Exp. Med.* 2 April 2007 (doi: 10.1084/jem.20061699)