TUMOUR IMMUNOLOGY

Beneficial loss

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URLs

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

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

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

Cytotoxic T lymphocytes (CTLs) are key mediators of the host response against tumours, but, unfortunately, several hurdles limit their effective use in cancer immunotherapy. For example, to be fully activated, T cells require signals through both the T-cell receptor (TCR) and co-stimulatory receptors such as CD28, but many tumours lack expression of ligands for CD28. Two groups now independently report that deleting the gene encoding the E3 ubiquitin ligase Casitas B-lineage lymphoma B (CBL-B), which results in T-cell activation independent of CD28 co-stimulation, protects mice against different types of transplanted and spontaneous tumour.

Previous work showed that *Cblb*$^{-/-}$ T cells can be activated independently of CD28 signalling, and this prompted Chiang *et al.* to study in detail the effect of CBL-B depletion on the activity of CTLs. Following TCR stimulation, *Cblb*$^{-/-}$ CD8^{+} T cells, compared with wild-type cells, had increased proliferation and cytokine secretion 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 results in the suppression of the CTL antitumour response. Interestingly, Loeser and colleagues showed that *Cblb*$^{-/-}$ CD8^{+} T cells are also partially resistant to suppression mediated by regulatory T cells.

To test the effect of *Cblb* deletion on the antitumour response *in vivo*, Chiang and colleagues injected *Cblb*$^{-/-}$ mice subcutaneously with weakly immunogenic and highly immunogenic cells from a mouse thymoma that does not express co-stimulatory molecules. Compared with wild-type mice, the lack of *Cblb* in these mice prevented or attenuated tumour growth, regardless of the intrinsic immunogenicity of the tumour. Tumour rejection proved to be independent of CD28 co-stimulation, as 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, expressing the E6 and E7 human papilloma virus 16 oncoproteins. Both groups showed that tumour rejection in *Cblb*$^{-/-}$ mice was indeed mediated by CD8^{+} T cells and that adoptively transferred CD8^{+} T cells from these animals induced rejection of established tumours in recipient mice, although it is not clear whether their cytotoxic activity is required.

So, does CBL-B deficiency 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 deleting *Cblb* delayed or prevented the onset of lymphomas in these mice. Loeser and colleagues induced skin tumours in mice through UVB irradiation and found that *Cblb*$^{-/-}$ mice showed a strikingly reduced cancer susceptibility compared with control animals. Depletion of CD8^{+} T cells from the UVB-exposed *Cblb*$^{-/-}$ mice that had not previously developed cancer caused the rapid onset of fast-growing tumours, which rules out the possibility that CBL-B might reduce tumorigenesis through other mechanisms.

Although ablation of *Cblb* 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. *et al.* Ablation of *Cbl-b* provides protection against transplanted and spontaneous tumors. *J. Clin. Invest.* **117**, 1029–1036 (2007) | Loeser, S. *et al.* Spontaneous tumor rejection by *Cbl-b*-deficient CD8^{+} T cells. *J. Exp. Med.* 2 April 2007 (doi:10.1084/jem.20061699)