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IMMUNOTHERAPY

Killing with natural killers, naturally

Natural killer cells (NK cells) are cytotoxic lymphocytes that, once activated, can respond rapidly to viral infection or tumour formation, triggering apoptosis of the infected or cancerous cells. However, NK cells that lack expression of the E3 ubiquitin ligase *Cbl-b* (casitas B-lineage lymphoma-b) can reject tumours spontaneously and now, Josef Penninger and colleagues, have shown that they can also reject metastasis.

The authors used a mouse model that lacked *Cbl-b* or in which CBL-B E3 ligase function was inactivated. The absence of *Cbl-b* potentiated the anti-metastatic activity of NK cells, as mice injected with melanoma cells showed a reduced number of metastases in the lung. Moreover, loss of *Cbl-b* in transgenic mice that develop metastatic breast tumours significantly suppressed the growth of mammary tumours and metastases in the lung. These mice also showed a marked accumulation of NK cells within the metastatic foci.

The authors then carried out *in vitro* ubiquitylation reactions on 9,000 human proteins, and identified cell surface TAM tyrosine kinase receptors as main ubiquitylation substrates for CBL-B. They then went on to investigate if modulation of the CBL-B–TAM pathway could be used for antitumour immunotherapy. To that end, they developed a highly selective TAM kinase inhibitor, LDC1267. Using different mouse models and different routes of administration, *in vivo* therapy with LDC1267 consistently reduced melanoma and mammary tumour metastases in lung and liver in a NK cell-dependent manner without any serious toxic effects.

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Original article Paolino, M. *et al*. The E3 ligase Cbl-b and TAM receptors regulate cancer metastasis via natural killer cells. *Nature* doi:10.1038/nature12998