TUMOUR IMMUNOLOGY

Natural killer cells spy greedy tumours

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A recent study in *Cell* identifies a new way in which natural killer (NK) cells sense and respond to tumours. Barrow *et al.* report that NK cells directly detect platelet-derived growth factor DD (PDGF-DD) by using the activating receptor Nkp44, and this interaction enables NK cells to limit tumour growth.

The human Nkp44 receptor is encoded by *NCR2* and has no mouse orthologue. It is expressed by activated NK cells, innate lymphoid cells (ILC1s and ILC3s) and plasmacytoid dendritic cells, but its physiological ligands are unknown. To address this, the authors constructed Nkp44–GFP reporter cells and screened more than 4,000 human and mouse proteins for potential Nkp44 ligands. The top 30 hits from this screen were assessed individually and PDGF-D identified as a putative Nkp44 ligand. PDGF-D is secreted as an inactive homodimer containing an atypical N-terminal CUB (C1r/C1s, UEGF and BMP1) domain; extracellular proteolytic processing of the CUB domain gives rise to active homodimeric PDGF-DD, which induces PDGF receptor β (PDGFR β) signalling. Both PDGF-D and PDGF-DD activated the Nkp44–GFP reporter cells, but an Nkp44–Fc fusion protein only bound to PDGF-DD. Therefore, proteolytically activated PDGF-DD, and not inactive PDGF-D, seems to be a bona fide ligand for Nkp44. The authors also

“an NK cell activating receptor can limit tumour cell growth through the recognition of a cellular growth factor”

tested some viral proteins and host nuclear proteins that had previously been suggested to be Nkp44 ligands, but these did not appear to bind Nkp44 in their systems.

PDGF-DD was found to induce ITAM signalling via Nkp44 in human NK cells, and its co-culture with IL-2-activated NK cells led to a dose-dependent upregulation of CD107a, which is associated with increased NK cell cytotoxicity and effector cytokine expression. Activation of Nkp44 by PDGF-DD was not in itself sufficient to drive NK cell-mediated lysis of target cells but induced robust secretion of IFN γ and TNF in IL-2-activated NK cells. Furthermore, PDGF-DD induced the upregulation of transcripts encoding other pro-inflammatory cytokines and chemokines in NK cells, as well as pro-inflammatory cytokine secretion by Nkp44-expressing ILC1s and ILC3s.

The authors next explored how PDGF-DD–Nkp44 interactions shape NK cell activity in tumours. TNF and IFN γ can induce cell-cycle arrest in tumours and, consistent with this, supernatant from PDGF-DD-stimulated NK cells induced growth arrest of human melanoma cell lines and altered their transcription profiles. Expression of *PDGFD* has been detected in multiple human tumours; strikingly, the authors found that expression of

NCR2 in tissues from patients with glioblastoma negatively correlated with the expression of cell-cycle genes and positively correlated with greater overall survival of patients. To directly test whether PDGF-DD promotes antitumour NK cell responses, the authors generated *NCR2*-transgenic (*NCR2*-tg) mice and subjected them to a B16-PDGFD metastatic tumour model (in which B16 melanoma cells were transfected with human *PDGFD*). Compared with non-transgenic controls, *NCR2*-tg mice had fewer lung metastases and developed smaller tumours; however, *NCR2*-tg mice formed more metastases if treated with anti-Nkp44. NK cells in tumour-free *NCR2*-tg mice did not express Nkp44 or the inhibitory checkpoint receptors PD1, TIGIT and CD96. However, Nkp44 and CD96 were expressed by NK cells in the lungs and lymph nodes of *NCR2*-tg mice that had been injected with B16-PDGFD cells. Notably, *NCR2*-tg mice treated with anti-CD96 developed fewer metastases following injection of B16-PDGFD cells compared with *NCR2*-tg mice treated with a control antibody or littermate controls injected with anti-CD96. Finally, the Nkp44–PDGF-DD axis also limited the growth of subcutaneous B16-PDGFD melanomas when NK cells were recruited to the tumours by intratumoural injection of CpG oligonucleotides.

This is the first study to show that an NK cell activating receptor can limit tumour cell growth through the recognition of a cellular growth factor. As polymorphisms in *PDGFD* have been linked to other human diseases, the authors propose that the Nkp44–PDGF-DD interaction may have other physiological roles beyond cancer control.

Yvonne Bordon

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