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TUMOUR IMMUNOLOGY

NK cells bring in the troops

The presence of conventional type 1 dendritic cells (cDC1s) in tumours has been associated with enhanced antitumour immunity, but it has been unclear what promotes their infiltration. A recent study from Caetano Reis e Sousa and colleagues now shows that natural killer (NK) cells recruit cDC1s to the tumour microenvironment by producing the chemokines CCL5 and XCL1.

The same authors previously reported that tumours suppress cDC1-dependent $CD8^+$ T cell antitumour responses by producing prostaglandin E2 (PGE_2), and that deletion of the cyclooxygenase (COX) enzymes that are necessary for PGE_2 synthesis enhances antitumour immunity. They therefore compared cDC1 accumulation in the tumours of mice that were implanted with COX-deficient $BRAF^{V600E}$ melanoma cells or with control $BRAF^{V600E}$ melanoma cells. Similar overall numbers of $CD45^+$ cells and $CD11c^+MHCII^+$ cells were found in COX-deficient and control tumours four days after implantation, but accumulation of cDC1s was markedly increased in the COX-deficient tumours. Furthermore, cDC1s infiltrated deeper into COX-deficient tumours and often formed multicellular clusters. Enhanced cDC1 infiltration into COX-deficient tumours was also observed in other mouse models of breast cancer and colorectal cancer. BATF3-deficient mice (which lack cDC1 cells) were unable to suppress the growth of COX-deficient tumours, and this was associated with markedly reduced $CD8^+$ T cell infiltration, indicating the functional relevance of cDC1s for antitumour immunity.

An early increase in NK cell recruitment was also seen in COX-deficient tumours, with the distribution of intratumoural NK cells closely matching that of cDC1s. This suggested that NK cells may recruit cDC1s and, in agreement with this, genetic or antibody-mediated depletion of NK cells (but not other lymphocytes) decreased cDC1 accumulation in COX-deficient tumours. Moreover, antibody-mediated depletion of NK cells led to rapid growth of COX-deficient tumours in wild-type mice. The authors assessed the levels of various NK cell-derived chemokines and found that COX-deficient tumours contained markedly elevated levels of CCL5 protein and *Xcl1* mRNA. Intracellular flow cytometry analyses of cells from COX-deficient tumours four days after implantation showed that NK cells expressed CCL5 protein and *Xcl1* mRNA, while some rare tumour-infiltrating $CD8^+$ T cells expressed CCL5 but not *Xcl1*.

cDC1s express the CCL5 receptors CCR1 and CCR5 as well as XCR1, the receptor for XCL1, and the authors showed that they migrate towards these chemokines in transwell assays. Moreover, antibody-mediated blockade of CCL5 and XCL1 *in vivo* markedly reduced cDC1 accumulation in COX-deficient tumours. Further studies revealed that PGE_2 reduces NK cell survival within tumours and inhibits their production of CCL5 and XCL1, as well as impairing cDC1 responsiveness to these chemokines. Therefore, in mice, NK cells can promote antitumour immunity by recruiting cDC1s, and tumour-derived PGE_2 blocks this process.

The authors analysed data sets from human haematopoietic cells and found that human NK cells also express CCL5 and XCL1, as well as XCL2 (an XCL1 paralogue found in humans but not in mice). They used The Cancer Genome Atlas to assess whether these genes are expressed in human cancers and found a positive correlation between the expression of *XCL1*, *XCL2* and *CCL5* in data sets for cutaneous melanoma and several carcinomas. This chemokine gene expression signature further correlated positively with gene signatures of NK cells, cDC1s and $CD8^+$ T cells. Finally, the authors found that higher expression of NK cell and cDC1 signature genes in tumour samples was associated with increased patient survival from various skin, head and neck, breast and lung cancers.

These findings suggest that NK cells drive immunity to tumours by recruiting cDC1s that activate $CD8^+$ T cells and that tumour cell production of PGE_2 suppresses this antitumour pathway. The authors propose that strategies that drive cDC1 accumulation in tumours could enhance the efficacy of cancer immunotherapies.

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“higher expression of NK cell and cDC1 signature genes in tumour samples was associated with increased patient survival”

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