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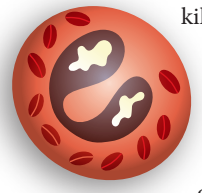
GRANULOCYTES

# Eosinophils enable the antitumour T cell response



Tumour-associated eosinophilia is frequently observed in patients with cancer, and eosinophils can directly kill tumour cells *in vitro*. However, intratumoral eosinophils have been associated with both good and bad prognoses in human studies, and mouse models have not shown a direct effect of eosinophils on tumour growth. Instead, this study shows that eosinophils are crucial accessory cells in the antitumour immune response that enable the infiltration of $CD8^+$ T cells.

In mice with MO4 melanoma tumours, the depletion of regulatory T ($T_{Reg}$) cells resulted in tumour rejection that was associated with the infiltration of activated $CD8^+$ T cells and of eosinophils. Eosinophil depletion using a Siglec-F-specific antibody significantly inhibited tumour rejection after $T_{Reg}$ cell depletion and decreased mouse survival. This effect of eosinophil depletion was associated with a decreased number of activated $CD8^+$ T cells in the tumour.

In the absence of eosinophils, there was a significant impairment of the upregulated expression of various pro-inflammatory genes in the tumour microenvironment induced by the depletion of $T_{Reg}$ cells. In particular, expression of the chemokine genes encoding CCL5, CXCL9 and CXCL10 was reduced by eosinophil depletion. Eosinophils sorted from $T_{Reg}$ cell-depleted tumours produced large amounts of these chemokines, which are potent chemoattractants for $CD8^+$ T cells, leading the authors to suggest that tumour-associated eosinophils promote T cell chemoattraction. In support of this model, kinetic studies of tumours showed that eosinophil infiltration precedes infiltration of $CD8^+$ T cells.

In addition to chemokine production, tumour-associated eosinophils were shown to promote vascular normalization of the tumour — the conversion of a small number of dilated, tortuous blood vessels to a larger number of smaller vessels — which is associated with decreased leakiness, improved perfusion and decreased hypoxia, all of which increase T cell infiltration and activity.

Macrophages sorted from MO4 tumours after the co-transfer of eosinophils and $CD8^+$ T cells were mainly $CD206^{low}$MHC class $II^{hi}$ M1-like macrophages, compared with the $CD206^{hi}$MHC class $II^{low}$ M2-like macrophages found in untreated tumours. As M2-like macrophages produce tumour-angiogenesis factors such as vascular endothelial growth factor — the expression levels of which were significantly lower in macrophages from eosinophil- and T cell-treated tumours compared with untreated tumours — the authors suggest that M1 skewing of tumour-associated macrophages by eosinophils might explain the observed vessel normalization.

The restricted access of effector T cells into tumours is a major limitation to successful immunotherapy, so the authors investigated whether eosinophils could improve the efficacy of adoptive T cell transfer. The transfer of tumour-specific $CD8^+$ T cells together with activated eosinophils led to greater inhibition of tumour growth and increased survival of mice compared with transfer of T cells alone in two mouse tumour models. The positive effect of eosinophils on tumour rejection could be prevented by antibody-mediated blockade of CCL5, CXCL9 and CXCL10.

The authors conclude that eosinophils, which are probably attracted to naturally occurring tumours by necrotic damage, have an important role in supporting cytotoxic T cell infiltration. In this context, the authors note that it is of particular interest that an increased number of eosinophils has been reported in patients with melanoma during immunotherapy with ipilimumab. It remains to be seen whether these eosinophils contribute to the therapeutic success of this drug.

*Kirsty Minton*

S.Bradbrook/NPG

> “eosinophils could improve the efficacy of adoptive T cell transfer”

**ORIGINAL RESEARCH PAPER** Carretero, R. *et al.* Eosinophils orchestrate cancer rejection by normalizing tumor vessels and enhancing infiltration of $CD8^+$ T cells. *Nature Immunol.* http://dx.doi.org/10.1038/ni.3159 (2015)