TUMOUR IMMUNOLOGY

The new midfielders in the tumour microenvironment

Many tumours elicit an immunosuppressive microenvironment, whereby certain immune cells are recruited to suppress cytotoxic T lymphocyte (CTL) antitumour activity. Broz *et al.* investigated the tumour microenvironment with the aim of understanding how the different immune cells in it influence the CTL response.

The authors analysed the different tumour-infiltrating antigen-presenting cells (APCs) in a modified spontaneous breast tumour model — polyoma middle T antigen, engineered to express mCherry and ovalbumin (PyMTChOVA). Tumoural dendritic cells (DCs) were distinguished from macrophages based on $CD24^{hi}$ and $F4/80^{low}$ expression. Two populations of DCs, namely $CD11b^{+}$ and $CD103^{+}$ DCs (previously described in healthy tissues) were identified within breast tumours and were also found to exist in two mouse models of melanoma, as well as in multiple additional mouse tumours. Similarly, two populations of tumour-associated macrophages (TAMs) were also identified: $CD11c^{low}CD11b^{hi}$ TAMs and $CD11c^{hi}CD11b^{low}$ TAMs, which were also present in all tumour models analysed. These TAM and DC populations were also found in human metastatic melanoma biopsies. Consistent across all mouse and human samples was the rarity of the $CD11b^{+}$ and $CD103^{+}$ DC populations, with $CD103^{+}$ DCs being particularly sparse.

To further characterize these APCs, the authors analysed their gene expression profiles. The four populations could be clearly segregated, with the TAMs and $CD11b^{+}$ DCs sharing most of the macrophage-specific makers, and $CD103^{+}$ DCs showing the most distinct transcriptional profile. Among the genes most distinctly expressed were DC-defining transcription factors, such as interferon-regulatory factor 8 (*IRF8*; specific for $CD103^{+}$ DCs alone), zinc finger and BTB domain-containing protein 46 (*ZBTB46*; specific for both sets of DCs), and *IRF4* (enriched in $CD11b^{+}$ DCs). Knocking down the expression of these genes showed that the different tumoural APC populations rely on these transcription factors to different extents. In a PyMT ectopic breast tumour model, loss of *Irf8* specifically ablated $CD103^{+}$ DCs but did not affect TAMs. In the B78ChOVA model, deletion of *Irf4* resulted in the specific reduction of $CD11b^{+}$ DCs with little change in the other cell populations. Deletion of *Batf3* resulted in ablation of the $CD103^{+}$ DC population, with no effect on the numbers of $CD11b^{+}$ DCs or TAMs, showing that $CD103^{+}$ DCs represent a distinct lineage of APCs in the tumour.

The different gene expression profiles also revealed considerable differences among the populations with regards to APC function, such as antigen processing, presentation and co-stimulation, and suggested that $CD103^{+}$ DCs are particularly well poised for efficient antigen presentation to CTLs. The authors found that $CD103^{+}$ DCs were the only population of tumoural APCs that were capable of inducing robust T cell receptor (TCR) signalling as well as strong proliferation of established CTLs, indicating that $CD103^{+}$ DCs are superior cross-presenters of antigens to CTLs in the tumour microenvironment.

Further experiments showed that DCs and TAMs were located in different places within the tumour. Whereas $CD11b^{+}$ and $CD103^{+}$ DCs were mainly found in areas that were distal to the tumour lesion, TAMs were preferentially found at the tumour margins, where T cells are generally recruited. A very small proportion of $CD103^{+}$ DCs was also found at the tumour margins, where their interaction with T cells may occur.

Finally, the authors observed that regressing tumours had increased numbers of $CD103^{+}$ DCs, and mice that lack $CD103^{+}$ DCs (such as $Irf8^{-/-}$ mice) showed increased tumour growth. Importantly, they evaluated the expression of the genes that characterize $CD103^{+}$ DCs in data from all types of human cancers and found that the $CD103^{+}/CD103^{-}$ gene ratio strongly correlated with increased overall survival compared with other current prognosticators, including the total number of T cells.

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