IN BRIEF

DEVELOPMENT

A clonogenic bone marrow progenitor specific for macrophages and dendritic cells.

Fogg, D. K. *et al. Science* 1 Dec 2005 (doi:10.1126/science.1117729)

Although the origins of macrophages and dendritic cells (DCs) have been well studied, the lineage relationship between these cell types is unclear. Macrophages and DCs belong to the mononuclear-phagocyte system, and it has therefore been suggested that they arise from a common progenitor. To test this directly, Fogg *et al.* identified a mouse bone-marrow population that expresses both CX_3C-chemokine receptor 1 (CX_3CR1) and KIT but not lineage (Lin). Colonies arising from single $CX_3CR1^+KIT^+Lin^-$ cells contained macrophages and DCs but not other cell lineages: the presence of macrophage colony-stimulating factor (M-CSF) favoured macrophage development, whereas the presence of granulocyte/macrophage CSF favoured DC development. Moreover, *in vivo* transfer analysis of fluorescently labelled $CX_3CR1^+KIT^+Lin^-$ cells indicated that these progenitors could give rise to splenic DCs and other macrophage populations, such as brain microglial cells.

IMMUNE EVASION

Hepatitis C virus protease NS3/4A cleaves mitochondrial antiviral signaling protein off the mitochondria to evade innate immunity.

Li, X.-D. *et al. Proc. Natl Acad. Sci. USA* **102**, 17717–17722 (2005)

In this study, the authors identify the protein that is targeted by the hepatitis-C-virus-encoded serine protease NS3–NS4A, which enables the virus to establish chronic infection. In response to viral infection, retinoic-acid-induced gene I (RIG-I) recognizes viral double-stranded RNA and interacts with mitochondrial antiviral signalling protein (MAVS; also known as VISA and CARDIF), which triggers the expression of type I interferons (IFNs). However, Li *et al.* now show that NS3–NS4A colocalizes, binds and cleaves MAVS, resulting in the dislocation of MAVS from the mitochondria, thereby suppressing type I IFN expression. The cleavage site of MAVS requires Cys508, because mutation of this residue renders MAVS resistant to cleavage by NS3–NS4A. So, blocking of this host–pathogen interaction could be applied to the prevention or treatment of hepatitis C virus.

B-CELL RESPONSES

Cell surface recycling of internalized antigen permits dendritic cell priming of B cells.

Bergtold, A. *et al. Immunity* **23**, 503–514 (2005)

The ability of dendritic cells (DCs) to prime naive T cells is undisputed; by contrast, their ability to prime B cells is less well understood. In this study, Bergtold *et al.* show that DCs can endocytose antigen through the inhibitory Fc receptor for IgG (FcγRIIB) and recycle it to the cell surface for presentation to B cells. In contrast to antigen that is internalized by activating FcγRs, FcγRIIB-endocytosed antigen does not enter degradative vesicular compartments but instead is directed to recycling endosomes and reaches the cell surface as native antigen. Mice that were immunized with IgG-opsonized T-cell-independent antigen had increased humoral responses; this was not seen in FcγRIIB-deficient mice, indicating a mechanism of FcγRIIB-dependent antibody enhancement of T-cell-independent humoral responses *in vivo*.

TUMOUR IMMUNOLOGY

TGFβ suppresses cytotoxicity

One way in which tumour cells avoid the host tumour-specific T-cell response is by producing, or inducing host cells to produce, transforming growth factor-β (TGFβ). TGFβ has a broad range of immunosuppressive effects, but the specific mechanism by which it inhibits T-cell-mediated clearance of tumours is not known. Now, in a report published in *Cancer Cell*, it is shown that TGFβ inhibits the expression of effectors of cytotoxic T-lymphocyte (CTL)-mediated cytotoxicity.

Although TGFβ can inhibit the growth of tumour cells, as tumours progress they often become resistant to these growth-inhibitory effects, enabling the tumour to take advantage of the immunosuppressive properties of this cytokine. The importance of this was shown by the authors, as they found that (consistent with previous studies), in a mouse tumour model, systemic neutralization of TGFβ *in vivo* results in tumour clearance. Tumour clearance was associated with an increase in $CD8^+$ T-cell-mediated tumour-cell-specific cytotoxicity. Consistent with this, the gene-expression profiles of T cells activated *in vitro*, in the presence or absence of TGFβ, showed that the genes encoding perforin, granzyme A, granzyme B, interferon-γ (IFNγ) and CD95 ligand (CD95L, also known as FASL) — which are the effectors of CTL-mediated cytotoxicity — were downregulated in the presence of TGFβ. Further analysis showed that the intracellular concentration of each of these proteins was also decreased after *in vitro* activation of $CD8^+$ T cells in the presence of TGFβ, as was the ability of the CTLs to mediate target-cell lysis. Most importantly, in the mouse tumour model, in which systemic neutralization of TGFβ *in vivo* results in tumour clearance, tumour-specific $CD8^+$ T cells were shown to recover expression of perforin, granzyme A, granzyme B and IFNγ, but not CD95L, if TGFβ was neutralized *in vivo*.

This study indicates that TGFβ not only inhibits the clonal expansion of tumour-specific $CD8^+$ T cells, but also suppresses the ability of these cells to mediate cytotoxicity. These data led the authors to suggest that further understanding of the mechanisms by which TGFβ mediates these effects might provide new impetus to the development of therapies that inhibit TGFβ, because such therapies would not only target the immunosuppressive effects of TGFβ, but also target the pro-metastatic effects of this cytokine on tumour cells.

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ORIGINAL RESEARCH PAPER Thomas, D. A. & Massagué, J. TGF-β directly targets cytotoxic T cell functions during tumor evasion of immune surveillance. *Cancer Cell* **8**, 369–380 (2005)
FURTHER READING Trapani, J. A. The dual adverse effects of TGF-β secretion on tumor progression. *Cancer Cell* **8**, 349–350 (2005)

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