the authors asked whether autocrine production of TGF-β has a role in the LPS-induced increase in SHIP expression. This was found to be the case, because TGF-β increased SHIP expression by SHIP-sufficient cells that were stimulated with LPS. In addition, neutralizing antibodies specific for TGF-β inhibited the increase in SHIP expression, thereby preventing the induction of endotoxin tolerance.

This study considerably advances our understanding of endotoxin tolerance.

Elaine Bell

References and links

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DENDRITIC CELLS

Guess who

What am I? I am recruited to tumours, where I form new blood vessels to supply nutrients for the growing mass. If your first guess is an endothelial cell or its precursor then think again, because new research published in *Nature Medicine* shows that dendritic cells (DCs) recruited to ovarian tumours, instead of stimulating an immune response, can become blood-vessel cells.

This surprising result arose from the observation that expression of β-defensin 29 (DEFB29) by ID8 mouse ovarian cancer cells markedly accelerated tumour growth when these cells were transplanted subcutaneously in mice, but only when the cells also co-expressed high levels of vascular endothelial growth factor (VEGF; also known as VEGF-A). ID8 VEGF$^+$DEFB29$^+$ tumours contained more blood vessels than ID8 VEGF$^+$ tumours, indicating that DEFB29 functions with VEGF to promote tumour angiogenesis.

Because β-defensins are known to be chemoattractive for DCs, the authors analysed expression of the DC marker CD11c in ID8 VEGF$^+$DEFB29$^+$ tumours. CD11c$^+$ cells were found in capillary-like structures and were shown to have an immature DC phenotype, but they were also found to express endothelial-cell markers, such as CD34 and VE-cadherin. These CD11c$^+$ cells were shown to be responsible for the increased tumour growth by comparing ID8 VEGF$^+$ cells transplanted alone or mixed with CD11c$^+$ cells from ID8 VEGF$^+$DEFB29$^+$ tumours. Further experiments showed that tumour-derived CD11c$^+$ cells can form blood-vessel-like structures *in vitro* and *in vivo*, without proliferation (ruling out the involvement of a stem-cell population), confirming that the CD11c$^+$ cells increase tumour growth through vasculogenesis. Interestingly, tumour-infiltrating CD11c$^+$ cells could present antigen to T cells when removed from the tumour milieu *in vitro*, showing that these cells can function as endothelial-like cells or DCs depending on the environment.

An environment containing high levels of VEGF and DEFB29 favours endothelial specialization, but what are the roles of these two factors? The addition of bone-marrow-derived CD11c$^+$ cells to ID8 VEGF$^+$ tumours resulted in levels of vascularization similar to those of ID8 VEGF$^+$DEFB29$^+$ tumours, confirming that DEFB29 is responsible for the initial recruitment of CD11c$^+$ cells to the tumour. DEFB29 could attract CD11c$^+$ immature DCs *in vitro* and *in vivo* through the chemokine receptor CCR6. However, addition of CD11c$^+$ cells did not increase the growth rate or vascularization of tumours expressing only low levels of VEGF, indicating that VEGF is required for conversion of these immature DCs to an endothelial phenotype. Antibody-mediated blockade of VEGF receptor 2 expressed by DCs prevented upregulation of the endothelial marker CD34 by CD11c$^+$ cells cultured in ID8 VEGF$^+$DEFB29$^+$ tumour-conditioned medium and inhibited the formation of capillary networks *in vivo*.

These findings indicate a new model of tumour angiogenesis in which DEFB29 recruits CD11c$^+$ immature DCs that have the potential to adopt endothelial characteristics in the presence of VEGF. The authors showed that this model is also applicable to human ovarian tumours, which express endogenous β-defensins, and it now needs to be determined whether this model applies to other tumour types. The effects of this angiogenesis pathway on the antitumour immune response also need further study. It seems that by promoting the endothelial specialization of immature DCs, the tumour might not only ensure a sufficient blood supply but also prevent these DCs from initiating an immune response against tumour antigens. In this case, therapeutic targeting of this pathway could both reduce tumour growth and promote immune attack.

Kirsty Minton

References and links

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