CANCER GENETICS

A killing combination

Induction of an inflammatory response within the cervix following human papillomavirus (HPV) infection might lead to an increased risk of cervical cancer — this is the conclusion of a new study by Mary Carrington and colleagues. Natural killer (NK) cells are an important component of the innate immune response against viruses and tumours, and their activation is thought to depend partly on the balance between inhibitory and activating receptors such as the killer immunoglobulin-like receptors (KIRs). KIRs engage specific human leukocyte antigen (HLA) class I proteins on target cells, and the considerable range of possible KIR and HLA haplotypes means that there is huge scope for variation in KIR–HLA interactions. Carrington *et al.* show that certain combinations of KIRs and HLA class I proteins are associated with a higher risk of developing cervical cancer.

The authors began by examining the frequencies of HLA class I alleles among people with and without cervical cancer. They found that some HLA allelic groups that are known to be high-affinity ligands for inhibitory KIRs — HLA *Cw* group 2 and HLA *Bw4* alleles — are associated with a reduced risk of the disease.

They also found that some activating KIRs — such as KIR3DS1 — are expressed at a higher frequency by people who have cervical cancer than people who do not. Furthermore, when the authors examined the effects of KIR3DS1 together with HLA *Cw* group 2 and *Bw4* alleles, they found a gradient of susceptibility to cervical cancer.

However, protection against cervical cancer does not come without a cost — resistance against one disease can confer susceptibility to another. Combinations of KIR and HLA genes that promote NK activation are already known to be linked to increased resistance against viral diseases, but epidemiological data show that KIR/HLA genotypes associated with viral protection are also associated with susceptibility to autoimmune diseases.

Carrington and colleagues point out that lesions in women with oncogenic HPV are often associated with concomitant inflammation of the cervix, and they suggest that NK activation might promote cancer development by contributing to local inflammation. However, although inflammation has been associated with some other cancers, further studies are needed to clarify the relationship between inflammation, transformation and the role of NK cells.

Jenny Bangham

References and links

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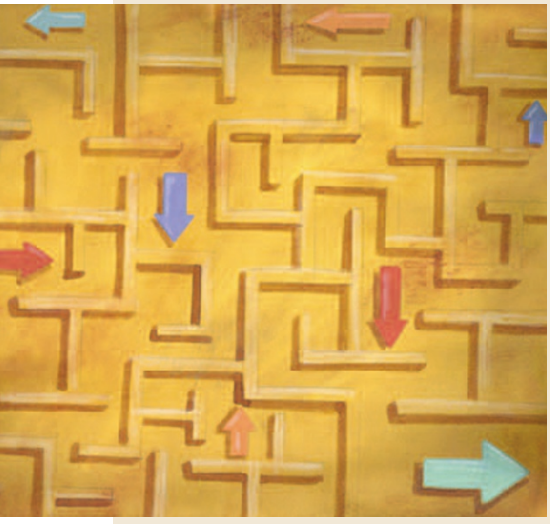
TUMORIGENESIS

Route master

Matrix metalloproteinases (MMPs), which include membrane type 1 (MT1)-MMP, are mainly known for their hydrolysis of extracellular matrix (ECM) components. But recently it has become apparent that they have a much wider substrate repertoire. Stephen Weiss and colleagues show that MT1-MMP can modify signal transduction through platelet-derived growth factor B (PDGFB) and its receptor PDGFRβ to regulate development of the microvasculature.



The integrity of vascular walls depends on the interaction between the outer sheath of mural cells and the inner endothelial cells. PDGFB-mediated signal transduction regulates mural-cell function, and is modulated by the interactions of PDGFB with PDGFRβ and various accessory factors. This prompted Weiss and colleagues to investigate a previous report that the expression of MT1-MMP specifically in mural cells is associated with the recruitment of these cells to developing vasculature.

Histological analysis showed that the aortae of young *MT1-MMP*$^{-/-}$ mice were defective; but in culture, *MT1-MMP*$^{-/-}$ and *MT1-MMP*$^{+/+}$ mural cells were visually indistinguishable. However, treating the *MT1-MMP*$^{-/-}$ cells with various growth factors revealed defects in their growth and chemotactic responses, but only when PDGFB was used to stimulate the cells.

The levels of PDGFB and PDGFRβ proteins and the extent of their phosphorylation was comparable in wild-type and *MT1-MMP*$^{-/-}$ cells. Moreover, MT1-MMP was found to bind PDGFRβ, both with and without PDGFB. However, the normal PDGFB signalling responses, such as increased active extracellular signal-regulated kinase 1/2 and AKT levels and changes in actin polymerization, were significantly reduced or absent in *MT1-MMP*$^{-/-}$ cells.

The responses of *MT1-MMP*$^{-/-}$ cells to PDGFB could be restored by the retroviral expression of wild-type MT1-MMP, but not of catalytically inactive MT1-MMP. Furthermore, in COS-1 cells (where MT1-MMP and PDGFRβ are usually undetectable) only co-expression of MT1-MMP and PDGFRβ could produce an optimal signalling response to PDGFB. So, catalytically active MT1-MMP is an important component of the PDGFB–PDGFRβ signalling complex.

Furthermore, the vascular morphology of *MT1-MMP*$^{-/-}$ mice seems to phenocopy that of PDGFRβ mutants. Similarly, tissue explants from *MT1-MMP*$^{-/-}$ mice mirror the wound-healing responses of *Pdgfrβ*$^{-/-}$ cells from chimeric *Pdgfrβ*$^{-/-}$*Pdgfrβ*$^{+/+}$ mice.

So in mural cells, MT1-MMP is necessary for the propagation of signalling through PDGFB–PDGFRβ. This pathway is crucial in stabilizing the vasculature of growing tumours, so the discovery that MT1-MMP is required for this process has uncovered a potential target for therapeutics that could be used to control tumour vascularization.

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References and links

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