Injecting *mitfa-BRAF*^{V600E} into embryos homozygous for a mutation in *TP53* resulted in about 6% of the fish developing malignant melanomas by 4 months of age. The melanoma cells expressed melanin and were morphologically similar to human melanoma cells. The cells spread rapidly following transplant into wild-type zebrafish (unlike cells from the f-nevi), and 89% of them showed chromosomal abnormalities similar to those seen in human melanomas.

With this zebrafish model of melanoma, Patton *et al.* demonstrate that it is feasible to use these animals to explore the genetic interactions that cause malignant phenotypes, and provide evidence that BRAF mutations do indeed underlie this disease.

Helen Dell

References and links

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METASTASIS

Moving PARts

Protease-activated receptors (PARs) are G-protein-coupled receptors that act as sensors of extracellular protease gradients, allowing cells to react to the proteolytic microenvironment during tissue remodelling in development, inflammation and angiogenesis, and also in cancer. Athan Kuliopulos and colleagues set out to investigate the role of PARs during cancer invasion and metastasis, and, in doing so, have uncovered a new PAR protease and a novel link between invading cells and the extracellular matrix.

The authors focused on PAR1, an oncogene that has long been thought to be involved in the invasion and metastasis of melanomas and cancers of the breast, colon, lung, pancreas and prostate. PAR1 responds to a select group of serine proteases that includes thrombin, plasmin, Xa and activated protein C. These cleave the PAR1 extracellular domain and induce transmembrane signalling, but, curiously, none of these proteases are crucial for the invasive properties of PAR1-dependent breast cancer cells.

Kuliopulos and colleagues started by investigating the role of PAR1 during the invasive interaction between breast cancer cells and the stroma. They showed that the migration of breast cancer cells towards fibroblast-derived media does require 'proteolysable' PAR1; cells transfected with 'proteolytically dead' PAR1 are unable to migrate.

The authors then confirmed that PAR1 is a highly tumorigenic and invasogenic factor *in vivo*, by transfecting MCF-7 cells — which resemble early breast cancer cells — with PAR1 and injecting them into the mammary fat pads of nude mice. They also carried out the converse experiment, using small interfering RNA to knock down levels of PAR1 in the highly tumorigenic cell line MDA-MB-231, markedly reducing migration and invasion. So if PAR1 confers invasive and migration properties on breast cancer cells, which protease is activating it?

The authors tested a range of proteases and protease inhibitors for their ability to affect the migration of PAR1-expressing breast cancer cells *in vitro*. To their surprise, the only stromal protease that was found to induce migration was matrix metalloproteinase 1 (MMP1). They went on to show that MMP1 that is secreted by fibroblasts cleaves PAR1, providing the first demonstration of direct activation of a G-protein-coupled receptor by an MMP. It has previously been shown that MMPs are expressed by stromal fibroblasts and inflammatory cells that are recruited to tumours, and MMP1 is a marker of poor prognosis in breast, colorectal and oesophageal tumours. These results, together with the findings of Kuliopulos and co-workers, indicate that breast cancer cells can use fibroblast-derived MMP1 and PAR1 as a chemotactic signal to invade surrounding stromal tissues.

The researchers note that several MMP inhibitors have been tested in Phase III clinical trials to treat diverse cancers, but patients have suffered from joint toxicity that is thought to be due to MMP1 inhibition. Their investigations of PAR1 or MMP1 as therapeutic targets showed that inhibiting either target *in vivo* substantially reduced tumour growth, invasion and vascularity, so PAR1 could be used as a downstream target for therapies that aim to block MMP1.

Jenny Bangham

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