HIGHLIGHTS

TUMOUR PROGRESSION

Destroy the environment!

Data supporting the vital role of the tumour microenvironment in cancer formation and progression have been accumulating for several years, but now Huang and co-workers have provided direct evidence that matrix metalloproteinase-9 (MMP-9) is a crucial molecule in this process. Huang *et al.* report in the 7 August issue of the *Journal of the National Cancer Institute* that expression of MMP-9 by host macrophages promotes growth and invasion of xenografted ovarian cancer cells in nude mice. These stromal constituents could provide a target for therapy in ovarian cancer.

Both ovarian cancer cells and stromal cells, such as macrophages, that are adjacent to and infiltrate the tumour, express *MMP9*. Progressive growth of ovarian cancer and the formation of ascites fluid are dependent on angiogenesis, and MMP-9 contributes to this process.

So, how did the authors show that MMP-9-positive macrophages had an important role in the progressive growth of human ovarian tumours? They implanted *MMP9*-expressing human ovarian tumour cells (SKOV3.ip1 or HEY-A8) into both wild-type and *Mmp9*-null mice. All of the mice that expressed *Mmp9* and were injected with human ovarian cancer cells developed peritoneal tumours, but the mice lacking the gene for Mmp-9 produced far fewer and smaller tumours, as well as less ascites fluid.

To infiltrate a tissue, macrophages must penetrate the extracellular matrix, and Huang *et al.* observed that wild-type mice had more peritoneal exudate macrophages than *Mmp9*-null mice, even when they had not been injected with human tumour cells. The macrophages that were present in *Mmp9*-null mice — whether or not they were injected with human ovarian cancer cells — had no detectable MMP-9 activity and had decreased potential to invade a filter that was coated with Matrigel matrix. Macrophage infiltration into human ovarian tumours is associated with the formation of blood vessels — tumours that developed in wild-type mice had a higher density of blood vessels than *Mmp9*-null mice, and had increased expression of the pro-angiogenic molecule vascular endothelial growth factor. Most tumour-infiltrating mouse cells in human ovarian tumours were positive for both MMP-9 and the macrophage-specific marker F4/80.

In addition, if *Mmp9*-null mice were reconstituted with spleen cells — a rich source of macrophages — from wild-type mice, the growth of peritoneal tumours derived from SKOV3.ip1 or HEY-A8 cells and the formation of ascites fluid was greatly enhanced, and the microvessel density in these tumours was significantly higher.

Liotta and Kohn comment in a linked Editorial that this paper from Isaiah Fidler's group is a seminal work and shows that the local microenvironment is "the driving force in stimulating or suppressing the invasive and malignant behaviours of cancer cells". MMP-9 and its source, the peritoneal macrophage, are potential selective targets for therapeutics in ovarian cancer. The first-generation MMP inhibitors target the active site of the enzyme, and results in the clinic have been disappointing — a stromal-therapy approach might be the next logical step.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Huang, S. *et al.* Contributions of stromal metalloproteinase-9 to angiogenesis and growth of human ovarian carcinoma in mice. *J. Natl Cancer Inst.* **94**, 1134–1142 (2002)

FURTHER READING Liotta, L. A. & Kohn, E. C. Stromal therapy: the next step in ovarian cancer. *J. Natl Cancer Inst*. **94**, 1113–1114 (2002) | Liotta, L. A. & Kohn, E. C. The microenvironment of the tumour–host interface. *Nature* **411**, 375–379 (2001)

WEB SITE

Isaiah Fidler's lab: http://utm-notes-db2.mdacc.tmc.edu/mdacc/Resrep.nsf/183e659df33a35188625662c0017b401/91e1e9fa1de4891486256731004ed70f?OpenDocument