METASTASIS

No way out?

Semaphorin 3F (SEMA3F), one of a family of axonal guidance regulators, was first identified on part of a chromosome commonly deleted in lung cancer, indicating that it might also be a tumour suppressor. Michael Klagsbrun, Diane Bielenberg and colleagues now report that SEMA3F inhibits melanoma metastatic spread and angiogenesis — effectively leaving a tumour no way of progressing and rendering it benign.

Many tumour cell types express SEMA3F, but highly metastatic tumours downregulate it. Klagsbrun and colleagues took a highly metastatic human melanoma cell line (SM) that expressed high levels of the SEMA3F receptor neuropilin 2 (NRP2) and showed that transfection of these cells with SEMA3F decreased adhesion and motility in culture — both necessary features of a metastatic phenotype.

So, does SEMA3F expression inhibit metastasis *in vivo*? When either SM control cells or SM/SEMA3F cells were injected into nude mice tumorigenicity was 100%, but only those injected with SM cell clones developed large lymph-node and lung metastases. The authors confirmed this lack of metastatic ability of the SM/SEMA3F cells using several approaches; for example, fluorescently labelled tumour cells injected into mice resulted in no occult spontaneous metastases. The authors observed that the SM/SEMA3F tumours were encapsulated and had well-defined borders composed of fibroblasts and collagen matrix, whereas the SM tumours showed massive keratinocyte hyperplasia overlying the tumour and were not encapsulated.

Next, the authors compared the tumour vasculature in mouse models. The blood vessels in SM/SEMA3F tumours were smaller, less branched and were less than half in number than those in SM tumours. Examining the stained cryosections of the tumours and surrounding skin carefully, the authors noticed that blood vessels seemed to be blocked from invading the tumour. Could SEMA3F be repelling the blood vessels in a similar way to that in which SEMA3F repels growing axons from ganglia? Klagsbrun, Bielenberg and colleagues found that when SM/SEMA3F tumour cells were added to cultures of endothelial cells (EC) expressing NRP2, large zones of cell clearance appeared. If the tumour cells lacked SEMA3F or the ECs lacked NRP2 no clearance was observed. Time-lapse video clearly showed that chemorepulsion of the ECs by the tumour cells was an active process.

So, SEMA3F inhibits metastatic growth in many ways, mediated through its functional receptor NRP2 on both melanoma cells and endothelial cells. The authors are now investigating the expression of SEMA3F in primary melanoma and matched melanoma metastatic tissue from patients.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Bielenberg, D. R. *et al.* Semaphorin 3F, a chemorepulsant for endothelial cells, induces a poorly vascularized, encapsulated, nonmetastatic tumor phenotype. *J. Clin. Invest.* **114**, 1260–1271 (2004)

FURTHER INFORMATION

Supplemental time-lapse movie: http://www.jci.org/cgi/content/full/114/9/1260/DC1

TRIAL WATCH

Learning from kinase-inhibitor trials

Results of a Phase II trial with the mitogen-activated protein kinase kinase (MEK) inhibitor CI-1040 are disappointing, but lessons have been learnt for the design of a Phase I/II study with a second-generation MEK inhibitor, PD-0325901.

The RAS–RAF–MEK–ERK pathway is constitutively active in many solid tumours. CI-1040 showed promise in a Phase I trial of 78 heavily pretreated patients — it was well tolerated and 30% achieved stable disease, there was one partial response, and a 50% or greater decrease in ERK expression seen after treatment.

The Phase II study included 67 patients with breast, colon, non-small-cell lung cancer and pancreatic cancer, most of whom had received no or only one previous treatment regimen. However, only 8 patients (12%) achieved stable disease lasting a median of 4.4 months and no objective responses were seen. The trial relied on assessing archived tumour specimens for ERK expression, and showed a mildly predictive association between ERK expression and probability of achieving stable disease.

PD-0325901 has more than 50-fold increased potency against MEK, an improved oral bioavailability and longer duration of target suppression. The ongoing Phase I/II trial includes pre- and post-treatment assessment of target levels, which will be related to both pharmacokinetics and treatment outcome.

ORIGINAL RESEARCH PAPER Rinehart, J. *et al.* Multicenter phase II study of the oral MEK inhibitor, CI-1040, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. *J. Clin. Oncol.* 13 Oct 2004 (doi:10.1200/JCO.2004.01.185)

Trends in Phase I trials

In the past decade cancer drugs under development have become more targeted and clinical research is more scrutinized. The impact of these changes on the risks and benefits to patients participating in Phase I cancer trials has now been investigated.

Roberts *et al.* included Phase I trials submitted to American Society of Clinical Oncology meetings 1991–2002, which had been subsequently published in peer-reviewed journals. They focused on trials of single agents in patients with advanced solid tumours, which had not been approved by the United States Food and Drug Administration at the time of submission. 213 studies including 6,474 patients were included.

The overall toxic death rate was 0.54% and the overall objective response rate was 3.8% — similar to that found in systematic reviews published in the 1990s. The toxic death rate decreased over time from 1.1% 1991–1994 to 0.06% 1999–2002. Response rates also decreased with time — from 6.2% 1991–1994 to 2.5% 1999–2002.

The authors suggest that the reduction in risk might be due to the targeted, less toxic nature of newer cancer drugs, and greater regulation of enrolment and scrutiny of safety in clinical research. However, publication bias could have significantly skewed the results, as negative research is less likely to be published. In addition, abstracts presented recently might not be published yet, so might have been prematurely excluded from the analysis.

The authors note that the trend for decreased response rate was skewed downwards by excluding haematological malignancies, in which impressive Phase I results have been reported recently. The results could also have been affected by excluding end points appropriate for newer drugs, such as stable disease or time to progression.

This study and the discussion surrounding it have important implications for both policy decisions and trial design.

ORIGINAL RESEARCH PAPER Roberts, T. G. *et al*. Trends in the risks and benefits to patients with cancer participating in phase I clinical trials. *JAMA* **292**, 2130–2139 (2004)