IN THE NEWS

A hot combination

The use of heated chemotherapy combined with surgery is more effective than conventional approaches in treating cancers that have spread to the abdomen. This is the conclusion of four studies carried out by investigators from Wake Forest University Baptist Medical Center (Winston-Salem, North Carolina). The results were presented at the Society of Oncology Surgeons national meeting in early March.

Investigators looked at the use of surgery with intraperitoneal hyperthermic chemotherapy (IPHC) for the treatment of cancers that had disseminated from the bowel, ovaries or appendix to the peritoneum (the lining of the abdominal cavity). Mesotheliomas originating in the abdomen were also studied. The use of heated drugs "…potentiates the effect of chemotherapy and decreases tumor resistance to chemotherapy", stated Perry Shen, who led one of the studies (*Reuters Health*, 7 March 2005).

In one study, six patients with peritoneal carcinomas secondary to small-bowel cancer, in addition to undergoing surgery to debulk the tumour, were treated with IPHC. Median survival of these patients was 45.1 months, compared with 3.1 months for conventionally treated patients. Although further studies are needed, these results indicate that surgery plus IPHC "...seems to be an effective and attractive option in a very difficult situation", remarked Perry Shen (www.newswise.com, 9 March 2005).

Treatments were not comprehensively successful — high-grade peritoneal tumours that had spread from the appendix showed no beneficial effect with IPHC. On balance though, as John Toy, of Cancer Research UK, comments, the results "…certainly look encouraging" (http://news.bbc.co.uk/, 8 March 2005).

Oliver Childs

METASTASIS

A fish by any other name…

The SRC substrate TKS5/FISH is a scaffolding protein that is known to localize to podosomes in transformed cells. Now, Seals and colleagues have identifed a role for TKS5/FISH in podosome formation, extracellular-matrix degradation and the invasive behaviour of some human cancer cells.

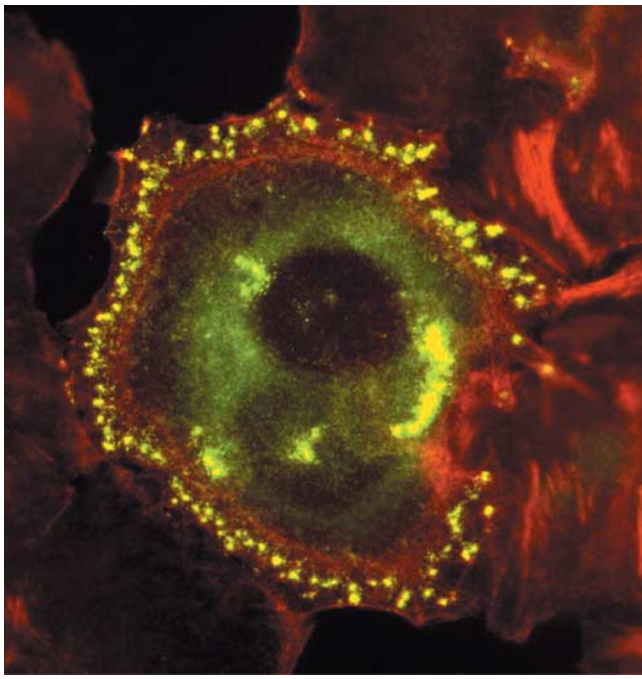
Having previously shown that TKS5/FISH relocates from the cytoplasm to podosomes in SRC-transformed cells, Seals and colleagues set out to show whether TKS5/FISH was involved in the formation or function of podosomes.

Initially, the authors used short interfering (si)RNA technology to knockdown the expression of TKS5/FISH in SRC-transformed NIH3T3 cells (Src3T3 cells). They showed that reducing TKS5/FISH expression caused Src3T3 cells to have a larger, flatter morphology, and fewer podosomes, than cells with normal TKS5/FISH expression. Furthermore, microinjecting the TKS5/FISH-knockdown cells with cDNA for the human homologue of TKS5/FISH (which was unaffected by the siRNA) restored podosome formation compared with uninjected cells. So, TKS5/FISH is rate limiting for podosome formation.

The authors then showed that TKS5/FISH-knockdown cells were unable to efficiently degrade extracellular-matrix proteins — a function that is important for cell invasion in cancer — whereas normal Src3T3 cells degraded matrix proteins in discrete spots that coincide with podosomes. The microinjection of human *TKS5/FISH* cDNA restored this ability in TKS5/FISH-knockdown cells. Similarly, the TKS5/FISH-knockdown cells showed reduced invasiveness in comparison with normal Src3T3 cells, although their basic motility did not seem to be affected. So, it seems that TKS5/FISH is required for podosome formation, matrix-protein degradation and invasiveness in this cell line.

Seals and colleagues then looked at the role of TKS5/FISH in human cancer cells. Cell lines from less invasive cancers showed much lower levels of TKS5/FISH protein expression than did cells from highly invasive cancers. However, *TKS5/FISH* mRNA levels did not always correlate with invasiveness, indicating that the control of TKS5/FISH expression might also occur at the protein level.

In comparison with the equivalent normal tissue samples, an increased amount of TKS5/FISH expression was detected in metastatic breast and skin tissue samples by immunohistochemistry. And, similar to the results with Src3T3 cells, TKS5/FISH seemed to be required for optimal invasiveness and matrix degradation in human cancer cell lines.



The image depicts T47D breast cancer cells. The centre cell is microinjected with plasmids expressing SRC and TKS5/FISH. This results in the formation of podosomes. Red staining, F-actin; green staining, TKS5/FISH. Image courtesy of Lia Tesfay, Van Andel Research Institute, Michigan, USA.

Furthermore, the addition of protease inhibitors to the matrix-invasion assays showed that TKS5/FISH is required for protease-mediated matrix invasion. Finally, using a poorly invasive cancer cell line that normally has low levels of TKS5/FISH expression, the authors showed that overexpression of TKS5/FISH was able to promote podosome formation in the presence of active SRC.

Seals and colleagues suggest that these findings support the case for further investigation of TKS5/FISH and its binding proteins. And they are hopeful that the ability to induce podosome formation using TKS5/FISH expression will help dissect the pathways that are involved in podosome formation, with a view to identifying both markers of invasive disease and potential therapeutic targets. They also suggest that the original clone name, TKS5, is used to identify this protein to avoid any potential problems with database searching.

Lesley Cunliffe

References and links

ORIGINAL RESEARCH PAPER Seals, D. F. *et al*. The adaptor protein Tks5/Fish is required for podosome formation and function, and for the protease driven invasion of cancer cells. *Cancer Cell* **7**, 155–165 (2005)