EXTRACELLULAR MATRIX

Sparcs turn into flames

Although cancer cells produce many factors that support their own proliferation and survival, it has been difficult to identify stromal factors that contribute to tumour progression. Sangaletti *et al.* show that stromal cells produce a secreted protein, acidic and rich in cysteine — Sparc — that helps organize the basement-membrane structure that is required for tumour progression.

Sparc is involved in tissue repair and remodelling, as it binds to components of the extracellular matrix such as fibrillar collagen and collagen type IV. It is expressed by various tumour and stromal cells, so Sangaletti *et al.* set out to learn more about its function. Mammary carcinoma cells that express high levels of Sparc grow into solid tumours in wild-type mice. These tumours have a well-structured stroma that comprises collagen type IV. In *Sparc*-null mice, however, the same tumours grew much more slowly. Tumours were smaller and less vascularized, contained necrotic areas and were devoid of collagen-type-IV-positive structures such as basement membranes of tumour lobules and blood vessels. So, Sparc production by the tumour environment, rather than the cancer cells themselves, is required for tumour progression.

But what host cells produce Sparc? Sangaletti *et al.* showed that when Sparc-expressing bone-marrow cells were transplanted into the null mice, tumours grew at the same rate as they did in wild-type mice. The transplanted bone-marrow-derived leukocytes localized to the tumours, where they expressed Sparc, allowing the tumour to develop a well-organized stromal compartment.

The authors propose that lack of Sparc production in the tumour environment prevents proper basement-membrane assembly, disrupting not only angiogenesis, but also removing a stromal 'shield' that protects the tumour from immune-cell infiltration.

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References and links

ORIGINAL RESEARCH PAPER Sangaletti, S. *et al.* Leukocytes, rather than tumor-produced SPARC, determines stroma and collagen type IV deposition in mammary carcinoma. *J. Exp. Med.* **198**, 1475–1485 (2003)

FURTHER READING Kalluri, R. Basement membranes: structure, assembly and role in tumour angiogenesis. *Nature Rev. Cancer* **3**, 422–433 (2003)

NANOTECHNOLOGY

Mapping progress

Biopsies of sentinel lymph nodes (SLNs) are used to determine whether tumour cells have begun to spread beyond the primary cancer site and whether lymphadectomy or systemic therapy is required. Locating which lymph node the cancer cells will drain to first — the SLN — using fluorescent dyes helps surgeons to biopsy the tissue quickly and efficiently. John Frangioni, Moungi Bawendi and colleagues now report a promising new approach for accurate SLN mapping, using nanotechnology.

Quantum dots (QDs) are fluorescent crystals that are typically less than 50 nm in diameter. These have potential for many biological applications; however, their development for bioimaging has been hampered by technical limitations. Frangioni's and Bawendi's groups previously developed QDs that fluoresce in the near-infrared (NIR) region of the spectrum to overcome the problem of poor sensitivity and poor resolution of visible QDs or conventional organic fluorescent dyes *in vivo*. For the current experiments, the dots were ~15.8 nm diameter — well within the range that is required for retention in the SLN. They were also coated with polydentate phosphine to make them water soluble.

The authors showed that NIR dots are stable even at high fluence rates, unlike conventional NIR fluorophores, which rapidly photobleach — in fact, NIR dots seem to photobrighten slightly. They are also stable in 100% serum at 37°C for more than 30 minutes, indicating that they will survive prolonged exposure to bodily fluids at core body temperature.

So, the main technical problems have been addressed, but do these NIR QDs migrate to SLNs *in vivo*? The authors first showed that the dots entered the lymphatic system and migrated quickly to the SLN when injected intradermally in mice, as confirmed by re-injection with the standard SLN mapping agent, isosulfan blue, and by histological examination. They then injected 400 pmol of NIR QDs intradermally into the thigh of five pigs, which are about the same size as humans. Real-time imaging allowed a surgeon to follow the lymphatic flow and quickly identify the SLN, so minimizing incision inaccuracies. Because the NIR QDs are stable and the fluorescence is intense, the surgeon could easily see the SLN throughout the biopsy procedure and could also inspect the surgical site to ensure total resection of the node.

The next important step will be to examine the toxicity of the NIR QDs, as they contain three metals, which in their uncomplexed elemental forms cause acute and chronic toxicity. The current experiments — with very low doses of the complexed metals — did not reveal any short-term toxicity.

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References and links

ORIGINAL RESEARCH PAPER Kim, S. *et al.* Near-infrared fluorescent type II quantum dots for sentinel lymph node mapping. *Nature Biotechnol.* 7 Dec 2003 (doi: 10.1038/nbt920)