Tumour cell teamwork

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Cell–cell connections by membrane tubes have been observed in many settings and are known to contribute to certain cellular processes *in vitro*, but their exact function in mammalian cells has remained unclear. A study in *Nature* reports that astrocytoma cells form a multicellular network interconnected by distinct tumour microtubes that drive invasion, mediate cell–cell communication, enable self-repair and confer radioresistance.

In nude mice transplanted with patient-derived astrocytoma cell lines and in a syngeneic astrocytoma model, Osswald *et al.* observed abundant tumour cell membrane protrusions with characteristics distinct from those of similar structures previously reported to mediate cell–cell communication in other settings. *In vivo* imaging revealed that these tumour microtubes projected from one astrocytoma cell to another, were present at the invasive tumour front and increased in length and frequency as tumours progressed.

New nuclei generated after astrocytoma cell division were shown to travel through

the tumour microtubes, further supporting their role in tumour dissemination. In addition, a proportion of tumour microtubes appeared to follow axons, consistent with the role of axons as leading structures for astrocytoma dissemination. But are tumour microtubes present in human astrocytomas?

Compared with human oligodendrogliomas, astrocytomas — which are more invasive — showed an increased abundance of tumour microtubes, and increased microtubule length was correlated with unfavourable prognosis. These data highlighted the clinicopathological relevance of tumour microtubes, leading the authors to further investigate their function.

In an allogeneic transplant model of astrocytoma, *in vivo* calcium imaging and electrophysiology of tumour microtube-connected astrocytoma cells revealed long-range bidirectional intercellular propagation of reproducible calcium waves, confirming that the tumour microtubes were physically connected over long distances. Intercellular calcium waves were significantly reduced in frequency and synchronicity by gap junction blockade, and the authors implicated connexin 43 (CX43; also known as gap junction protein $\alpha 1$) in this gap junction-mediated intercellular communication. In patient astrocytoma tissue, CX43 colocalized with the sites at which tumour microtubes came into physical contact, and *in vivo* knockdown of CX43 significantly reduced intercellular calcium signalling, tumour microtube formation and tumour size in the allogeneic transplant model.

Further experiments revealed intriguing characteristics of the tumour microtube network.

First, *in vivo* laser-induced ablation of network-connected astrocytoma cells was followed by movement of a new nucleus via tumour microtubes to the location of the ablated cells; this self-repair process was observed significantly less frequently after ablation of cells that were not part of the tumour microtube network. Second, network-connected astrocytoma cells were also protected from radiotherapy. Radioprotection correlated with increased microtube formation and intercellular calcium communication, and was reduced by CX43 knockdown.

Pathway analysis of gene expression data in The Cancer Genome Atlas revealed prominent activation of neurotrophin signalling in astrocytomas, and the authors went on to identify the downstream effector growth-associated protein GAP43 (also known as neuromodulin) as an important driver of tumour microtube formation. When transplanted, GAP43-deficient human astrocytoma cell lines showed significantly reduced invasiveness, microtube formation and intercellular calcium signalling *in vivo*. Mice transplanted with these cells had significantly smaller tumours and showed enhanced radiosensitivity. Conversely, overexpression of GAP43 enabled oligodendroglioma cells to become more invasive and more radioresistant.

These data demonstrate that when astrocytoma cells become part of a tumour microtube-connected multicellular network, they function in an ‘all for one and one for all’ manner that drives tumour progression and promotes self-preservation in response to damage. The tumour microtube network thus represents a target for antitumour therapies and/or adjuvant treatments that aim to enhance tumour radiosensitivity.

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