RECEPTOR TYROSINE KINASES

Getting on TRK

Tumour-suppressor function is most often disrupted in cancer cells through inactivating mutations or epigenetic mechanisms such as DNA methylation. Andrew Mackay and colleagues have identified an alternative splicing mechanism that causes neuroblastoma cells to switch from expressing a growth-inhibiting form of the receptor tyrosine kinase TRKA to an oncogenic form that promotes tumour progression.

TRKA is a member of the neurotrophin receptor family that binds nerve growth factor (NGF) and is required for development of the central and peripheral nervous systems. NGF binding to this receptor activates mitogen-activated protein kinase (MAPK) signalling to induce differentiation and growth arrest of neural progenitor cells. Specific mutations in TRKA can transform cells and have been identified in a range of tumour types, and there is evidence to indicate that TRKA normally functions as a tumour suppressor.

In studying the role of TRKA activation in neuroblastoma cells, Mackay and colleagues identified a novel splice variant of TRKA, named TRKAIII. It encodes a membrane-associated form of the receptor that lacks three exons of functional importance. This isoform is expressed specifically in neural-crest-derived neuroblastic tumour cells, normal pluripotent neural stem cells and neural-crest progenitors. The authors showed that TRKAIII signals in the absence of ligand through the inositol phosphate–AKT signalling pathway, rather than the MAPK pathway.

The transgenic expression of TRKAIII transformed fibroblasts in culture and also protected a neuroblastoma cell line from doxorubicin-induced cell death. These TRKAIII-expressing neuroblastoma cells grew as large tumour-like spheroids in suspension culture and formed tumours more rapidly than non-TRKAIII-expressing neuroblastoma cells in nude mice. Furthermore, the TRKAIII-expressing tumours isolated from these mice were more vascularized, indicating that this signalling pathway can also induce angiogenesis. In studying its role in angiogenesis induction, the authors observed that hypoxia stimulated TRKAIII expression specifically in normal human neural stem cells, neural-crest-derived progenitor cells and in neural-crest-derived neuroblastic tumour cells, but not in other cell types. Mackay and colleagues therefore propose that TRKAIII normally protects non-differentiated neural stem cells or neural-crest progenitors from hypoxic or other stressful conditions during development. Its expression is lost following differentiation commitment, but conserved in neural-crest-derived neuroblastic tumour cells.

Further experiments are required to determine how this dormant isoform becomes re-expressed in neuroblastomas, as well as in other tumour types such as medullary thyroid cancer and pheochromocytomas. In examining human tumour samples, Mackay and colleagues observed that TRKAIII was highly expressed in late-stage neuroblastomas, supporting its propensity for tumour aggressiveness. So, expression of TRKAIII might be used in determining patient prognosis, and this isoform could be an important, tumour-specific, therapeutic target.

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References and links

ORIGINAL RESEARCH PAPER Tacconelli, A. *et al.* TrkA alternative splicing: a regulated tumor-promoting switch in human neuroblastoma. *Cancer Cell* **6**, 347–360 (2004)

FURTHER READING Brodeur, G. Neuroblastoma: biological insights into a clinical enigma. *Nature Rev. Cancer* **3**, 203–216 (2003)