Battling brain tumours – novel therapies to treat astrocytomas

Dr Peter J Houghton, from Greehey Children's Cancer Research Institute UT Health San Antonio, is exploring the molecular foundation of astrocytoma – a common type of primary brain tumour. By identifying proteins that could be potential therapeutic targets, the team aim to achieve their goal of developing effective treatments to fight against astrocytoma and reduce adverse secondary impacts of current therapies, such as ionising radiation.

The key mission of Greehey Children's Cancer Research Institute is to advance scientific knowledge and develop novel therapies relevant to paediatric cancer. Their director, Dr Peter Houghton, and his team work hard to further our understanding of sarcoma (a rare type of cancer). One of their current projects is focused on exploring the molecular mechanisms that underpin a different type of cancer, childhood 'astrocytomas'. They hope to develop novel therapies to treat this cancer.

Astrocytomas are the most common form of glioma – brain tumours which originate in glial cells. These cells are the most abundant in the central nervous system (CNS), with their role being to protect neurons (nerve cells). Astrocytes are a star-shaped type of glial cell which support and deliver nutrients to the neurons. Their function – aiding information processing and communication – is therefore essential within the CNS.

Approximately 35% of childhood brain tumours are astrocytomas, and survival rates often vary substantially depending on the severity of the tumour. Astrocytomas are 'graded' from one to four according to their growth rate. Low grade one to two tumours are classified as 'slow-growing' and usually affect a specific area with minimal spread. Surgical removal is usually sufficient to treat these tumours, with their likelihood to return also diminished as a result. However, higher grade astrocytomas (grade three to four) are fast-growing, and spread much more rapidly through the CNS. Unfortunately, these tumours tend to recur following treatment.

Generally, low-grade astrocytomas (LGA) are more common and can be treated using chemotherapy, radiotherapy, or a mixture of both. The five-year progression-free survival rate for chemotherapy plus radiotherapy is around 68%, which is significantly better than chemotherapy alone, and has a survival rate of 38%.

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However, many clinical challenges still remain. Current therapeutic options used to treat LGA, such as ionising radiation, can result in other long-term devastating disorders. These typically include visual defects, vasculopathy (blood vessel abnormalities) and an increased risk of transformation to a higher-grade astrocytoma. Because of this, Dr Houghton and his team have been inspired to develop safer, less costly treatments capable of effectively tackling these tumours.

LOW-GRADE ASTROCYTOMA DEVELOPMENT

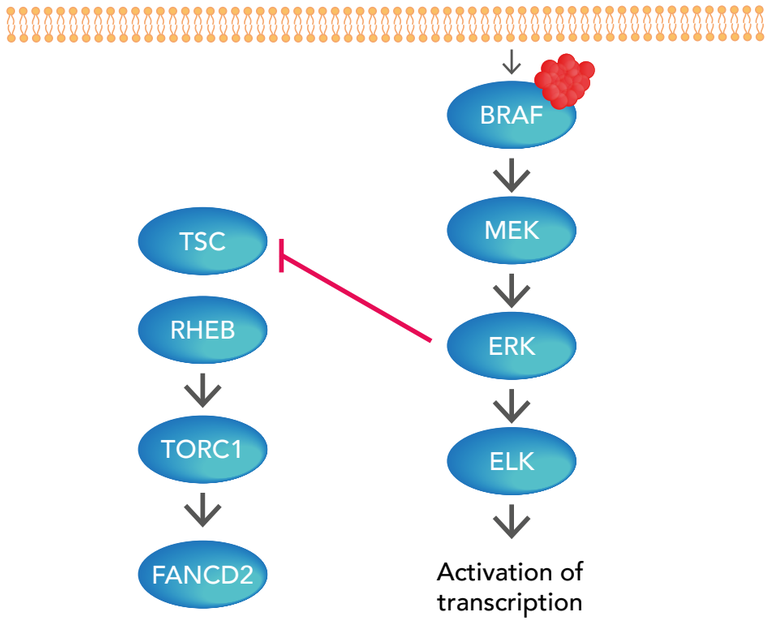
In-depth genotyping studies enabled the DNA sequences between many tumours to be compared, to determine genetic differences. Results indicated that LGA were associated with mutated versions of a gene called *BRAF*, resulting in its continuous activation. *BRAF* mutation was caused by either one of two things: i) gene duplication – whereby a segment of DNA is amplified and can result in the fusion of two genes (in this case, one of which is *BRAF*), or ii) point mutations – in which one nucleotide base is altered within the gene sequence.

CONSEQUENCES OF *BRAF* ACTIVATION

BRAF encodes a protein called B-Raf (a type of kinase) which is an essential component of the mitogen-activated protein kinase (MAPK) signalling pathway. This is an important form of cell communication, which ultimately controls cell growth and proliferation. For this to work, an extracellular signalling protein known as mitogen binds to cell membrane surface receptors. This then triggers a kinase cascade, in which phosphorylation by kinases (including B-raf) activates proteins downstream. Think of it as a chain of dominos with the activation of *BRAF* as the starting point.

To exemplify this, B-Raf activates MEK (mitogen-activated protein kinase kinase) which subsequently triggers the activation of MAP kinase. This enzyme phosphorylates a variety of proteins, including nuclear transcription factors, which control cellular processes. A vital part of any cell signalling pathway is its ability to be controlled i.e., it can be switched 'on' or 'off'. A continually activated *BRAF* gene (caused by mutation) means B-Raf is continually left 'on', which ultimately causes uncontrollable cell growth and, eventually, causes astrocytomas.

Signalling in *BRAF*-driven malignant cells is regulated mostly by independent extracellular ligands



INHIBITING THE MAPK PATHWAY

Identifying the key abnormal protein that causes LGA is an exciting step in the development of novel treatments. Various trials conducted by Dr Houghton and his team have showed that over-active B-Raf can be indirectly inhibited. A drug called selumetinib can directly suppress the MEK protein, which, in turn, represses cell proliferation and reduces the risk of cancerous spread. However, Dr Houghton is also interested in the other effects MEK inhibition can have, and is currently investigating whether these could benefit the development of LGA treatments.

In the context of *BRAF* mutations in LGA, MEK also regulates another important protein known as TORC1 (Target of Rapamycin), which is essential in maintaining cell integrity in terms of transcription, protein/lipid synthesis and nutrient transport. Of particular significance in this context, is the role of TORC1 as a regulator of the DNA damage repair protein Fanconi Anaemia Complementation Group D2 Protein (FANCD2).

Inhibiting MEK results in a chain of protein suppression, eventually leading to FANCD2 downregulation. Reduced FANCD2 activity has been shown to result in an increased sensitivity to ionising radiation (XRT) – a treatment typically used to treat LGA. This inspired Dr Houghton to explore whether MEK inhibition by selumetinib indirectly enhances sensitivity to XRT.

Mice with LGA tumours were administered selumetinib for four days to reduce FANCD2 levels, before beginning XRT treatment with a dose of 10 Gy. The results from this showed that 60% of mice remained tumour-free at the end of the study (160 days), therefore suggesting that a combination treatment of selumetinib and 10 Gy XRT is equivalent to 20 Gy XRT dose without selumetinib. High levels of XRT are extremely potent and can have a wide range of adverse consequences. Therefore, by using a combination of selumetinib and lower levels of XRT, radiation-induced detrimental secondary effects can be minimised.

Results indicated that around 23% of low-grade astrocytomas were associated with mutated versions of the *BRAF* gene, resulting in its continuous activation

Overall, Dr Houghton has highlighted the importance of using a synergistic approach to treat children with LGA. A combination therapy of drugs and XRT can greatly improve the likelihood of survival, and a reduction in radiation toxicity lowers the risk of patients developing debilitating secondary impacts. Although more studies need to be performed before this novel treatment can be put into practice, the research of Dr Houghton and his team could revolutionise how we treat cancer, and consequently, save countless lives.

Q&A

Why are astrocytomas such a common form of glioma?
The cause of astrocytomas is unknown. These tumours have alterations in the BRAF pathway mainly caused by a duplication of the *BRAF* gene with another gene *KIAA1549* that leads to activation of *BRAF* signalling that drives tumour formation.

What are the key differences between low- and high-grade astrocytomas?
'Low-grade' (LG) tumours are slow growing, and usually not invasive. LG tumours have a very small percentage of cells that are dividing. They are regarded as being non-malignant. High-grade tumours are rapidly dividing cells, invasive and highly malignant.

Why are LG astrocytomas more common in children than HG astrocytomas?
The reason is unknown.

How does a mutation in the BRAF gene result in low grade astrocytoma formation?
BRAF is an oncogene that drives a pathway that activates cell proliferation.

What are your research goals over the next five years?
With respect to low grade astrocytoma, to investigate approaches to reduce the dose of radiation required to control these tumours, as this will reduce the long-term sequelae of treatment (neurocognitive dysfunction etc.), and to build effective therapy using molecularly targeted agents in addition to the MEK inhibitors already identified.

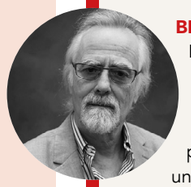
The Greehey Children's Cancer Research Institute.

Detail

RESEARCH OBJECTIVES
Dr Houghton's research aims to determine the mechanisms of tumour initiation and progression in children. He then aims to apply this knowledge to the identification of less toxic drugs with higher success rates.

FUNDING
National Institutes of Health (NIH)

COLLABORATORS
NCI PPTC http://www.ncipptc.org/



BIO
Dr Peter Houghton completed his Bachelor's degree at the University of Bradford in the UK, where he studied pharmacology. He then undertook a PhD at the Institute of Cancer Research at the University of London. He was also Chair of Molecular Pharmacology at St Jude Children's Research Hospital for 17 years.

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