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CNS CANCER

Wnt affects blood–brain barrier permeabilty

Medulloblastoma, the most common brain tumour in children, is typically divided into four genomic subtypes, which vary substantially in terms of treatment sensitivity and survival. Now, newly published research has revealed that Wnt-medulloblastoma, which is highly sensitive to treatment compared with SHH, group 3, or group 4 medulloblastomas, secretes Wnt antagonists that increase the permeability of the blood–brain barrier (BBB).

Using genetically modified mouse models, investigators observed significantly more haemorrhagic tumours, with much more dense and markedly more branched vascular networks in mice harbouring Wnt-medulloblastoma-like alterations (mWnt) than in mouse models of SHH (mSHH) or group 3 disease. Studies of these mice during embryonic development confirmed that these effects are not a developmental legacy, and occurr postnatally.

This increased vascularity was found to correlate with an increase in BBB permeability, as demonstrated following systemic injection of tetramethylrhodamine-dextran (TMR) a 70 kDa fluorescent dye, which accumulated to a significantly greater extent in the brains of mWnt, but than in those of mSHH mice.

The role of Wnt signalling in BBB permeability was investigated using implantation of one of two types of virally-transfected cells designed to either overcome the secretion of Wnt inhibitors in the mWnt mice, or to inhibit Wnt signalling in the mSHH mice. Restoration of Wnt signalling to the mWnt model, and inhibition of Wnt signalling in the mSHH model resulted in a significant reduction, and significant increase in BBB permeability in these models, respectively.

Confirming the clinical relevance of these findings, mWnt mice treated with vincristine had significantly longer overall survival durations than their untreated counterparts. Furthermore, mSHH mice did not respond to vincristine, suggesting that the treatment sensitivity of Wnt-medulloblastoma might be explained by increased BBB permability.

Peter Sidaway

> “… the treatment sensitivity of Wnt-medulloblastoma might be explained by increased BBB permability”

ORIGINAL ARTICLE Phoenix T. N. *et al.* Medulloblastoma genotype dictates blood brain barrier phenotype. *Cancer Cell* **29**, 1–15 (2016).