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[Brain](#). 2010 May 30. [Epub ahead of print]

Bone morphogenetic protein-7 release from endogenous neural precursor cells suppresses the tumourigenicity of stem-like glioblastoma cells.

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Abstract

Glioblastoma cells with stem-like properties control brain tumour growth and recurrence. Here, we show that endogenous neural precursor cells perform an anti-tumour response by specifically targeting stem-like brain tumour cells. In vitro, neural precursor cells predominantly express bone morphogenetic protein-7; bone morphogenetic protein-7 is constitutively released from neurospheres and induces canonical bone morphogenetic protein signalling in stem-like glioblastoma cells. Exposure of human and murine stem-like brain tumour cells to neurosphere-derived bone morphogenetic protein-7 induces tumour stem cell differentiation, attenuates stem-like marker expression and reduces self-renewal and the ability for tumour initiation. Neurosphere-derived or recombinant bone morphogenetic protein-7 reduces glioblastoma expansion from stem-like cells by down-regulating the transcription factor Olig2. In vivo, large numbers of bone morphogenetic protein-7-expressing neural precursors encircle brain tumours in young mice, induce canonical bone morphogenetic protein signalling in stem-like glioblastoma cells and can thereby attenuate tumour formation. This anti-tumour response is strongly reduced in older mice. Our results indicate that endogenous neural precursor cells protect the young brain from glioblastoma by releasing bone morphogenetic protein-7, which acts as a paracrine tumour suppressor that represses proliferation, self-renewal and tumour-initiation of stem-like glioblastoma cells.

PMID: 20513660 [PubMed - as supplied by publisher]

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