

Letter

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Bone morphogenetic proteins inhibit the tumorigenic potential of human brain tumour-initiating cells

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Transformed, oncogenic precursors, possessing both defining neural-stem-cell properties and the ability to initiate intracerebral tumours, have been identified in human brain cancers¹. Here we report that bone morphogenetic proteins (BMPs), amongst which BMP4 elicits the strongest effect, trigger a significant reduction in the stem-like, tumour-initiating precursors of human glioblastomas (GBMs). Transient *in vitro* exposure to BMP4 abolishes the capacity of transplanted GBM cells to establish intracerebral GBMs. Most importantly, *in vivo* delivery of BMP4 effectively blocks the tumour growth and associated mortality that occur in 100% of mice after intracerebral grafting of human GBM cells. We demonstrate that BMPs activate their cognate receptors (BMPRs) and trigger the Smad signalling cascade in cells isolated from human glioblastomas (GBMs). This is followed by a reduction in proliferation, and increased expression of markers of neural differentiation, with no effect on cell viability. The concomitant reduction in clonogenic ability, in the size of the CD133⁺ population and in the growth kinetics of GBM cells indicates that BMP4 reduces the tumour-initiating cell pool of GBMs. These findings show that the BMP–BMPR signalling system—which controls the activity of normal brain stem cells^{2,3}—may also act as a key inhibitory regulator of tumour-initiating, stem-like cells from GBMs and the results also identify BMP4 as a novel, non-cytotoxic therapeutic effector, which may be used to prevent growth and recurrence of GBMs in humans.

Top

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