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Bone morphogenetic proteins regulate tumorigenicity in human glioblastoma stem cells.

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Human glioblastomas appear to be established and expanded by cancer stem cells, which are endowed with tumour-initiating and perpetuating ability. We report that bone morphogenetic proteins (BMPs), amongst which BMP4 elicits the strongest effect, activate their cognate receptors (BMPRs) and trigger the Smad but not the MAP38 kinase signalling cascade in cells isolated from human glioblastomas (GBMs). This is followed by a reduction in proliferation and increased expression of differentiated neural markers, without affecting cell viability. The concomitant reduction in the clonogenic ability, both in the size of the CD133+ side population and in the growth kinetics of GBM cells, indicates that BMP4 triggers a reduction in the in vitro cancer stem cell (CSC) pool. Accordingly, transient ex vivo exposure to BMP4 abolishes the capacity of transplanted GBM cells to establish intracerebral GBMs. Most important, in vivo delivery of BMP4 effectively blocks the tumour growth and associated mortality which occur in 100% of control mice in less than 12 weeks, following intracerebral grafting of human GBM cells. These findings show that the BMP-BMPR signalling system, which controls the activity of normal brain stem cells, may also act as a key inhibitory regulator of cancer-initiating, GBM stem-like cells and identifies BMP4 as a novel, non-cytotoxic therapeutic effector, which may be used to prevent growth and recurrence of GBMs in humans.

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