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The transcriptional network for mesenchymal transformation of brain tumours.

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The inference of transcriptional networks that regulate transitions into physiological or pathological cellular states remains a central challenge in systems biology. A mesenchymal phenotype is the hallmark of tumour aggressiveness in human malignant glioma, but the regulatory programs responsible for implementing the associated molecular signature are largely unknown. Here we show that reverse-engineering and an unbiased interrogation of a glioma-specific regulatory network reveal the transcriptional module that activates expression of mesenchymal genes in malignant glioma. Two transcription factors (C/EBPbeta and STAT3) emerge as synergistic initiators and master regulators of mesenchymal transformation. Ectopic co-expression of C/EBPbeta and STAT3 reprograms neural stem cells along the aberrant mesenchymal lineage, whereas elimination of the two factors in glioma cells leads to collapse of the mesenchymal signature and reduces tumour aggressiveness. In human glioma, expression of C/EBPbeta and STAT3 correlates with mesenchymal differentiation and predicts poor clinical outcome. These results show that the activation of a small regulatory module is necessary and sufficient to initiate and maintain an aberrant phenotypic state in cancer cells.

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