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A newly identified transcriptional network for mesenchymal transformation of brain tumors: potential targets for therapeutic intervention

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Glioblastoma remains the ultimate challenge in neuro-oncology with dismal survival for the overwhelming majority of patients. Although historically viewed as a single pathological entity, recent insights suggest that at the molecular level glioblastomas can vary from patient to patient. The molecular pathology of these tumors is particularly important to consider, as molecular features may predict response to standard and experimental therapies. Recent work published in the journal **Nature** has shed more light on what specific molecular events are important to facilitating the mesenchymal phenotype of glioblastoma (Stella-Carro M. et. al. The transcriptional network for mesenchymal transformation of brain tumours, *Nature* Dec, 2009). Using reverse-engineering and an unbiased interrogation of a glioma-specific regulatory network investigators from Columbia University, NYU, and MD Anderson identified two transcription factors (C/EBP β and STAT3) as synergistic initiators and master regulators of mesenchymal transformation. Ectopic co-expression of C/EBP β 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 tumor aggressiveness. In human glioma, expression of C/EBP β and STAT3 correlates with mesenchymal differentiation and predicts poor clinical outcome. Collectively 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. The potential clinical applications of these findings are broad and include diagnostic stratification of the most aggressive forms of GBM as well as experimental therapeutics. Small molecule inhibitors of STAT3 have already been developed and tested in vitro against glioma. The next logical step will be to test the effectiveness of targeted inhibitors in vitro and in animal models, as a bridge to more effective adjuvant therapy for glioblastoma patients.

References

- Stella-Carro M, et al. The transcriptional network for mesenchymal transformation of brain tumours. *Nature*. Dec.2009

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Figure. Transcription factors (TFs) involved in activation of mesenchymal gene expression signature (MGES) targets are shown in pink, those involved in repression are in purple. MGES targets controlled by these TFs are in cyan. Overall, the six TFs control 74% of the genes in the mesenchymal signature of high-grade glioma.