

MOLECULAR INTERACTION NETWORK BASED DISCOVERY OF MASTER REGULATOR GENES

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KEYNOTE SPEAKER FOR

“MOLECULAR BIOINFORMATICS FOR DISEASE”

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The identification of genes acting synergistically as master regulators of physiologic and pathologic cellular phenotypes is a key open problem in systems biology. Here we use a molecular interaction based approach to identify the repertoire of transcription factors (TFs) of a master regulatory module responsible for synergistic activation of a tumor-specific signature. Specifically, we used the ARACNe algorithm and other computational tools to infer regulatory interactions responsible for initiating and maintaining the mesenchymal phenotype of Glioblastoma Multiforme (GBM), previously associated with the poorest disease prognosis. Expression of mesenchymal genes is a hallmark of aggressiveness but the upstream regulators of the signature are unknown. Starting from the unbiased analysis of all TFs, we identify a highly interconnected module of six TFs jointly regulating >75% of the genes in the signature. Two TFs (Stat3 and C/EBPb), in particular, display features of initiators and master regulators of module activity. Biochemical validation confirms that the TFs in the module bind to the inferred promoters *in vivo* and ectopic expression of the master TFs activates expression of the mesenchymal signature. These effects are sufficient to trigger mesenchymal transformation of neural stem cells, which become highly tumorigenic *in vivo*, and promote migration and invasion. Conversely, silencing of Stat3 and C/EBPb in human glioma cells leads to collapse of the mesenchymal signature and reduction of tumor aggressiveness. Our results reveal that activation of a small transcriptional module is necessary and sufficient to induce a mesenchymal phenotype in malignant brain tumors.