Identifying RNA-binding Proteins as a Novel Class of Therapeutic Targets in Glioblastoma Cancer Stem-Like Cells

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Abstract: Increasing evidence has shown that cancer stem-like cells (CSC), analogues to multipotent stem cells, can reconstitute a heterogeneous tumor. Most importantly, several studies have now shown that the CSC population can often evade traditional anti-tumor therapies and become the driving force for relapse in cancer patients. Previous investigations of CSCs have mostly focused on the role of transcription factors and epigenetic regulators. More recently, key studies have demonstrated a major role of RNA-binding proteins (e.g. splicing factors) in regulating embryonic stem cell pluripotency and differentiation. In addition, significant oncogenic and tumor suppressor role of RNA-binding proteins during cancer development has been reported. However, the role of RNA-binding proteins and alternative splicing in CSCs has largely been unexplored. Here we propose an integrative approach combining computational, molecular and biochemical methodologies to identify the role key RNA-binding proteins play in regulating CSCs during oncogenesis.In studying this issue, we unexpectedly have observed that an RNA-binding protein, NOVA1, previously thought to be selectively expressed in neurons, is highly expressed in glioma CSCs, and confirmed its in vivo binding to multiple RNAs encoding “stemness” factors (e.g. SOX2). We will confirm and extend this observation by taking advantage of our access to surgical specimens to study the expression profile and function of RNA-binding proteins in fresh cell isolates from a range of glioblastoma specimens representative of the genomic heterogeneity of this tumor. This study aims at providing a novel CSC-focused strategy for the identification of therapeutic targets in the currently incurable glioblastoma.