Mir-21–Sox2 axis delineates glioblastoma subtypes with prognostic impact

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Glioblastoma is the most aggressive human brain tumor. Although several molecular subtypes of glioblastoma are recognized, a robust molecular prognostic marker has yet to be identified. Here we report that the stemness regulator Sox2 is a new, clinically important target of microRNA-21 (miR-21) in glioblastoma, with implications for prognosis. Using the miR-21–Sox2 regulatory axis, about half of all glioblastoma tumors present in The Cancer Genome Atlas (TCGA) and in-house patient databases can be mathematically classified into high miR-21/low Sox2 (Class A) or low miR-21/high Sox2 (Class B) subtypes. This classification reflects phenotypically and molecularly distinct characteristics and is not captured by existing classifications. Supporting the distinct nature of the subtypes, gene set enrichment analysis of the TCGA dataset predicted that Class A and Class B tumors were significantly involved in immune/inflammatory response and in chromosome organization and nervous system development, respectively. Patients with Class B tumors had longer overall survival than those with Class A tumors. Analysis of both databases indicated that the Class A/Class B classification is a better predictor of patient survival than currently used parameters. Further, manipulation of miR-21–Sox2 levels in orthotopic mouse models supported the longer survival of the Class B subtype. The miR-21–Sox2 association was also found in mouse neural stem cells and in the mouse brain at different developmental stages, suggesting a role in normal development. Thus, this mechanism-based classification suggests the presence of two distinct populations of glioblastoma patients with distinguishable phenotypic characteristics and clinical outcomes.

Biography

Sadhan Majumder is a Professor of Genetics and Neuro-Oncology at MD Anderson Cancer Center, Houston, USA.

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