FOXR2-EXPRESSING DIFFUSE MIDLINE GLIOMAS


BACKGROUND: Diffuse midline gliomas (DMGs) are a universally fatal brain tumor of childhood. While histone mutations are a critical tumor initiating event, they are insufficient to drive gliomagenesis. Histone mutations co-occur with somatic alterations in other pathways including TP53, MAPK, and MYC signaling. However, the mechanisms through which these pathways are activated have not been fully elucidated. METHODS: We applied an integrative approach using transcriptomics, epigenetics, proteomics, in vitro cancer models, and in vivo mouse models to systematically evaluate how FOXR2 mediates gliomagenesis. RESULTS: We have recently found that a subset of DMGs aberrantly express FOXR2, a forkhead transcription factor. FOXR2 is both sufficient to enhance tumor formation, and necessary for FOXR2-expressing DMGs. While FOXR2 indeed enhances MYC protein stability, FOXR2 exerts oncogenesis through MYC-independent functions and specifically hijacks E26-transformation specific (ETS) transcriptional circuits and FOXR2 DNA-binding is highly enriched at ETS motifs. We have performed proteomic and phospho-proteomics analysis of FOXR2-expressing human neural stem cells to identify proteins and phospho-sites that are highly enriched in FOXR2-expressing cells. CONCLUSION: Taken together, this study elucidates how FOXR2 interacts with ETS transcription factors to mediate oncogenesis in FOXR2-expressing diffuse midline gliomas.