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DIPG-20. DELINEATING MEDIATORS OF ONCOGENESIS IN FOXR2-EXPRESSING DIFFUSE MIDLINE GLIOMAS

Jessica Tsai[1], Paloma Cejas[1], Marissa Coppola[1], Dayle Wang[1], Smruti Patel[1], David Wu[2], Phonepasong Arounleut[3], Xin Wei[3], Ningxuan Zhou[1], Sudeepa Syamala[1], Frank Dubois[1], Kristine Pelton[1], Jayne Vogelzang[1], Cecilia Sousa[1], Audrey Baguette[4], Xiaolong Chen[5], Alexandra Condurat[1], Sarah Dixon-Clarke[1], Kevin Zhou[1], Sophie Lu[1], Elizabeth Gonzalez[1], Madison Chacon[1], Jeromy Digiacomo[1], Rushil Kumbhani[1], Dana Novikov[1], Maria Tsoli[6], David Ziegler[6], Uta Dirksen[7], Natalie Jager[8], Gnana Prakash Balsubramanian[8], Christof Kramm[9], Michaela Nathrath[10], Stefan Bielack[11], Suzanne Baker[5], Jinghui Zhang[5], James McFarland[2], Gad Getz[2], Francois Aguet[2], Nada Jabado[4], Olaf Witt[8], Stefan Pfister[8], Keith Ligon[1], Volker Hovestadt[1], Claudia Kleinman[4], Henry Long[1], David Jones[8], Pratiti Bandopadhayay[1], Timothy Phoenix[3]; [1]Dana-Farber Cancer Institute, Boston, USA. [2]Broad Institute of MIT and Harvard, Cambridge, USA. [3]University of Cincinnati, Cincinnati, USA. [4]McGill University, Montreal, Canada. [5]St. Jude Children's Research Hospital, Memphis, USA. [6]Lowy Cancer Research Centre, Sydney, Australia. [7]University Hospital Essen, Essen, Germany. [8]German Cancer Research Center (DKFZ), Heidelberg, Germany. [9]University Medical Center Göttingen, Göttingen, Germany. [10]Klinikum Kassel, Kassel, Germany. [11]University Hospital Stuttgart, Stuttgart, Germany

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-proteomic 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.