Neuro-Oncology 16:iii1–iii22, 2014.
doi:10.1093/neuonc/nou206.57

NEURO-ONCOLOGY

Monday, July 21, 2014

C11ORF95-RELA FUSIONS DRIVE ONCOGENIC NF-KB SIGNALING IN EPENDYMOMA

Richard Gilbertson, Matthew Parker, Kumarasamypet M. Mohankumar, Chandanamali Punchihewa, Ricardo Weinlich, James D. Dalton, Yongjin Li, Ryan Lee, Ruth G. Tatevossian, Timothy N. Phoenix, Radhika Thiruvenkatam, Elsie White, Bo Tang, Wilda Orisme, Kirti Gupta, Michael Rusch, Xiang Chen, Yuxin Li, Panduka Nagahawhatta, Erin Hedlund, David Finkelstein, Gang Wu, Sheila Shurtleff, John Easton, Kristy Boggs, Donald Yergeau, Bhavin Vadodaria, Heather L. Mulder, Jared Becksford, Pankaj Gupta, Robert Huether, Jing Ma, Guangchun Song, Amar Gajjar, Thomas Merchant, Frederick Boop, Amy A Smith, Li Ding, Charles Lu, Kerri Ochoa, David Zhao, Robert S. Fulton, Lucinda L. Fulton, Elaine R. Mardis, Richard K. Wilson, James R. Downing, Douglas R. Green, Jinghui Zhang, David W. Ellison, and Richard J. Gilbertson; St Jude Children's Research Hospital

BACKGROUND: The nuclear factor-kB (NF-kB) family of transcriptional regulators are central mediators of the cellular inflammatory response. Although constitutive NF-kB signaling is present in most human tumours, mutations in pathway members are rare, complicating efforts to understand and block aberrant NF-kB activity in cancer. METHODS: To identify additional genetic alterations that drive ependymoma, we sequenced the whole genomes (WGS) of 41 tumours and matched normal blood, and the transcriptomes (RNAseq) of 77 tumours. The transforming significance of alterations were tested in mouse NSCs that we showed previously to be cells of origin of ependymoma. RESULTS: Here, we show that more than two thirds of supratentorial ependymomas contain oncogenic fusions between RELA, the principal effector of canonical NF-kB signalling, and an uncharacterized gene, C11orf95. In each case, C11orf95-RELA fusions resulted from chromothripsis involving chromosome 11q13.1. C11orf95-RELA fusion proteins translocated spontaneously to the nucleus to activate NF-kB target genes, and rapidly transformed neural stem cells—the cell of origin of ependymoma—to form these tumours in mice. CONCLUSIONS: Our data identify the first highly recurrent genetic alteration of RELA in human cancer, and the C11orf95-RELA fusion protein as a potential therapeutic target in supratentorial ependymoma. SECONDARY CATEGORY: Neuropathology & Tumor Biomarkers.