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Article *in* Neuro-Oncology · November 2014

DOI: 10.1093/neuonc/nou268.18

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Neuro-Oncology 16:v169–v174, 2014.
doi:10.1093/neuonc/nou268

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Abstracts

PM-18. EGFR-STAT3 ACTIVATES β-CATENIN SIGNALING TO DRIVE NEUROFIBROMA INITIATION IN NF1, AND PLAYS A ROLE IN TUMOR MAINTENANCE

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To identify genes and signaling pathways that drive peripheral nerve tumor initiation and growth beyond the Ras-MAPK pathway we used unbiased insertional mutagenesis screening. We identified Stat3 as a potential driver of Neurofibromatosis type 1 neurofibroma. Targeted genetic deletion of Stat3 in Schwann cell precursors (SCPs) and Schwann cells (SCs) largely prevented neurofibroma formation, and self-renewal of tumor initiating cells. Genetic gain- and loss-of-function identified EGFR as the major upstream regulator of P-Stat3 in mouse and human neurofibroma SCP and in neurofibroma initiation; IL-6 reinforced EGFR/Jak/Stat signaling. Preclinical tests of a Jak2/Stat3 inhibitor reduced established neurofibroma growth, supporting an additional role for Stat3 in benign nerve tumor maintenance. Unexpectedly, downstream of Stat3, we identified β-catenin, and β-catenin expression rescued phenotypic effects of Stat3 loss in SCPs. Phosphorylated STAT3 (Y705) and β-catenin were strongly correlated in NF1 human plexiform neurofibromas. The data support testing of JAK/STAT inhibition and Wnt/ β-catenin pathway inhibition in neurofibroma therapeutic trials. Supported by: NIH R01 NS28840 to N.R. and NIH P50 NS057531 to N.R. and D.L.), a DAMD New Investigator Award (W81XWH-11-1-0259) and an Ohio State University Comprehensive Cancer Center Pelotonia Idea Grant (to J.W.). The American Cancer Society (IRG-67-003-44) supported J.R.F.