LETTER

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Therapeutic targeting of ependymoma as informed by oncogenic enhancer profiling

Stephen C. Mack[1,2,3,4]*, Kristian W. Pajtler[5,6,7]*, Lukas Chavez[5,6,8]*, Konstantin Okonechnikov[5,6], Kelsey C. Bertrand[1,2,9], Xiuxing Wang[3,4,10], Serap Erkek[5,6,11], Alexander Federation[12], Anne Song[3,4], Christine Lee[3,4], Xin Wang[13], Laura McDonald[13], James J. Morrow[14], Alina Saiakhova[14], Patrick Sin-Chan[13], Qiulian Wu[3,4,10], Kulandaimanuvel Antony Michaelraj[13], Tyler E. Miller[3,4,15], Christopher G. Hubert[3,4], Marina Ryzhova[16], Livia Garzia[13], Laura Donovan[13], Stephen Dombrowski[3,4,17], Daniel C. Factor[14], Betty Luu[13], Claudia L. L. Valentim[3,4], Ryan C. Gimple[3,4,10,15], Andrew Morton[3,4,14], Leo Kim[3,4,10], Briana C. Prager[3,4,10], John J. Y. Lee[13], Xiaochong Wu[13], Jennifer Zuccaro[13], Yuan Thompson[13], Borja L. Holgado[13], Jüri Reimand[18,19], Susan Q. Ke[3,4], Adam Tropper[3,4], Sisi Lai[3,4], Senthuran Vijayarajah[9,20], Sylvia Doan[21], Vaidehi Mahadev[3,4], Ana Fernandez Miñan[22], Susanne N. Gröbner[5,6], Matthias Lienhard[23], Marc Zapatka[24], Zhiqin Huang[24], Kenneth D. Aldape[25], Angel M. Carcaboso[26], Peter J. Houghton[27], Stephen T. Keir[28], Till Milde[5,7,29], Hendrik Witt[5,6,7], Yan Li[14], Chao-Jun Li[30], Xiu-Wu Bian[31], David T. W. Jones[5,6], Ian Scott[13], Sheila K. Singh[32], Annie Huang[13,33], Peter B. Dirks[13], Eric Bouffet[13,33], James E. Bradner[33], Vijay Ramaswamy[13,34], Nada Jabado[35], James T. Rutka[13], Paul A. Northcott[36], Mathieu Lupien[19], Peter Lichter[24], Andrey Korshunov[37,38], Peter C. Scacheri[14], Stefan M. Pfister[5,6,7], Marcel Kool[5,6]§, Michael D. Taylor[13]§ & Jeremy N. Rich[3,4,10,17]§

Genomic sequencing has driven precision-based oncology therapy; however, the genetic drivers of many malignancies remain unknown or non-targetable, so alternative approaches to the identification of therapeutic leads are necessary. Ependymomas are chemotherapy-resistant brain tumours, which, despite genomic sequencing, lack effective molecular targets. Intracranial ependymomas are segregated on the basis of anatomical location (supratentorial region or posterior fossa) and further divided into distinct molecular subgroups that reflect differences in the age of onset, gender predominance and response to therapy[1–3]. The most common and aggressive subgroup, posterior fossa ependymoma group A (PF-EPN-A), occurs in young children and appears to lack recurrent somatic mutations[2]. Conversely, posterior fossa ependymoma group B (PF-EPN-B) tumours display frequent large-scale copy number gains and losses but have favourable clinical outcomes[1,3]. More than 70% of supratentorial ependymomas are defined by highly recurrent gene fusions in the NF-κB subunit gene *RELA* (ST-EPN-RELA), and a smaller number involve fusion of the gene encoding the transcriptional activator YAP1 (ST-EPN-YAP1)[1,3,4]. Subependymomas, a distinct histologic variant, can also be found within the supratetorial and posterior fossa compartments, and account for the majority of tumours in the molecular subgroups ST-EPN-SE and PF-EPN-SE. Here we describe mapping of active chromatin landscapes in 42 primary ependymomas in two non-overlapping primary ependymoma cohorts, with the goal of identifying essential super-enhancer-associated genes on which tumour cells depend. Enhancer regions revealed putative oncogenes, molecular targets and pathways; inhibition of these targets with small molecule inhibitors or short hairpin RNA diminished the proliferation of patient-derived neurospheres and increased survival in mouse models of ependymomas. Through profiling of transcriptional enhancers, our study provides a framework for target and drug discovery in other cancers that lack known genetic drivers and are therefore difficult to treat.

To pinpoint genes that depend on enhancers for their role in tumour formation, we characterized regions of actively transcribed chromatin in 42 primary intracranial ependymomas using histone 3 lysine 27 acetylation chromatin immunoprecipitation and sequencing (H3K27ac

[1]Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA. [2]Department of Pediatric Hematolgy and Oncology, Texas Children's Cancer and Hematology Centers, Houston, Texas, USA. [3]Department of Stem Cell Biology and Regenerative Medicine, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio 44195, USA. [4]Department of Molecular Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio 44195, USA. [5]Hopp Children's Cancer Center at the NCT Heidelberg (KiTZ), 69120 Heidelberg, Germany. [6]Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany and German Cancer Consortium (DKTK), 69120 Heidelberg, Germany. [7]Department of Pediatric Oncology, Hematology and Immunology, Heidelberg University Hospital, 69120 Heidelberg, Germany. [8]Department of Medicine, Division of Medical Genetics, University of California – San Diego School of Medicine, La Jolla, California 92093, USA. [9]Department of Pediatrics, Cleveland Clinic, Cleveland, Ohio 44195, USA. [10]Department of Medicine, Division of Regenerative Medicine, University of California – San Diego School of Medicine, La Jolla, California, USA. [11]European Molecular Biology Laboratory, Genome Biology Unit, Heidelberg, Germany. [12]Department of Genomic Sciences, University of Washington, Seattle, Washington 355065, USA. [13]Division of Neurosurgery, Program in Developmental and Stem Cell Biology, Arthur and Sonia Labatt Brain Tumour Research Centre, Hospital for Sick Children, Toronto, Ontario M5G 1X8, Canada. [14]Department of Genetics and Genome Sciences, Case Western Reserve University, Cleveland, Ohio 44106, USA. [15]Department of Pathology, Case Western Reserve University, Cleveland, Ohio 44106, USA. [16]Department of Neuropathology, NN Burdenko Neurosurgical Institute, 4th Tverskaya-Yamskaya 16, Moscow 125047, Russia. [17]Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Cleveland Clinic Neurological Institute, Department of Neurosurgery, Cleveland Clinic, Cleveland, Ohio 44195, USA. [18]Computational Biology Program, Ontario Institute for Cancer Research, Toronto, Ontario M5G 0A3, Canada. [19]Department of Medical Biophysics, University of Toronto, Toronto, Ontario M5G 1L7, Canada. [20]Department of Pediatrics, Division of Critical Care, University of Utah School of Medicine, Salt Lake City, Utah, USA. [21]Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah, USA. [22]Centro Andaluz de Biología del Desarrollo, Consejo Superior de Investigaciones Científicas and Universidad Pablo de Olavide, Sevilla, Spain. [23]Department of Computational Molecular Biology, Max-Planck-Institute for Molecular Genetics, 14195 Berlin, Germany. [24]Division of Molecular Genetics, German Cancer Research Center (DKFZ), 69121 Heidelberg, Germany. [25]Department of Pathology, University Health Network, Toronto, Ontario M5G 1L7, Canada. [26]Preclinical Therapeutics and Drug Delivery Research Program, Fundacio Sant Joan de Deu, 08950 Barcelona, Spain. [27]Nationwide Children's Hospital, Center for Childhood Cancer and Blood Diseases, Columbus, Ohio. [28]Duke University Medical Center, Department of Surgery, Durham, North Carolina, USA. [29]Clinical Cooperation Unit Pediatric Oncology, German Cancer Research Center (DKFZ), INF 280, D-69120 Heidelberg, Germany. [30]MOE Key Laboratory of Model Animal for Disease Study, Model Animal Research Center, Nanjing University, National Resource Centre for Mutant Mice, Nanjing, China. [31]Institute of Pathology and Southwest Cancer Center, Southwest Hospital, The Third Military Medical University, and The Key Laboratory of Tumor Immunopathology, The Ministry of Education of China, Chongqing, China. [32]Department of Surgery, Division of Neurosurgery, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada. [33]Novartis Institutes for Biomedical Research, Cambridge, Massachusetts 02139, USA. [34]Division of Hematology and Oncology, Hospital for Sick Children, Toronto, Ontario M5G 1X8, Canada. [35]Departments of Paediatrics and Human Genetics, McGill University and the McGill University Health Centre Research Institute, Montreal, Quebec H3Z 2Z3, Canada. [36]Developmental Neurobiology, St Jude Children's Research Hospital, Memphis, Tennessee, USA. [37]Department of Neuropathology, University of Heidelberg, 69120 Heidelberg, Germany. [38]Clinical Cooperation Unit Neuropathology, German Cancer Research Center (DKFZ), 69121 Heidelberg, Germany.
*These authors contributed equally to this work.
§These authors jointly supervised this work.