Année de publication : 2021

Patryk Skowron, Hamza Farooq, Florence M G Cavalli, A Sorana Morrissy, Michelle Ly, Liam D Hendrikse, Evan Y Wang, Haig Djambazian, Helen Zhu, Karen L Mungall, Quang M Trinh, Tina Zheng, Shizhong Dai, Ana S Guerreiro Stucklin, Maria C Vladoiu, Vernon Fong, Borja L Holgado, Carolina Nor, Xiaochong Wu, Diala Abd-Rabbo, Pierre Bérubé, Yu Chang Wang, Betty Luu, Raul A Suarez, Avesta Rastan, Aaron H Gillmor, John J Y Lee, Xiao Yun Zhang, Craig Daniels, Peter Dirks, David Malkin, Eric Bouffet, Uri Tabori, James Loukides, François P Doz, Franck Bourdeaut, Olivier O Delattre, Julien Masliah-Planchon, Olivier Ayrault, Seung-Ki Kim, David Meyronet, Wieslawa A Grajkowska, Carlos G Carlotti, Carmen de Torres, Jaume Mora, Charles G Eberhart, Erwin G Van Meir, Toshihiro Kumabe, Pim J French, Johan M Kros, Nada Jabado, Boleslaw Lach, Ian F Pollack, Ronald L Hamilton, Amulya A Nageswara Rao, Caterina Giannini, James M Olson, László Bognár, Almos Klekner, Karel Zitterbart, Joanna J Phillips, Reid C Thompson, Michael K Cooper, Joshua B Rubin, Linda M Liau, Miklós Garami, Peter Hauser, Kay Ka Wai Li, Ho-Keung Ng, Wai Sang Poon, G Yancey Gillespie, Jennifer A Chan, Shin Jung, Roger E McLendon, Eric M Thompson, David Zagzag, Rajeev Vibhakar, Young Shin Ra, Maria Luisa Garre, Ulrich Schüller, Tomoko Shofuda, Claudia C Faria, Enrique López-Aguilar, Gelareh Zadeh, Chi-Chung Hui, Vijay Ramaswamy, Swneke D Bailey, Steven J Jones, Andrew J Mungall, Richard A Moore, John A Calarco, Lincoln D Stein, Gary D Bader, Jüri Reimand, Jiannis Ragoussis, William A Weiss, Marco A Marra, Hiromichi Suzuki, Michael D Taylor (2021 Mar 20)

The transcriptional landscape of Shh medulloblastoma.

Nature communications : 1749 : DOI : 10.1038/s41467-021-21883-0

Résumé

Sonic hedgehog medulloblastoma encompasses a clinically and molecularly diverse group of cancers of the developing central nervous system. Here, we use unbiased sequencing of the transcriptome across a large cohort of 250 tumors to reveal differences among molecular subtypes of the disease, and demonstrate the previously unappreciated importance of non-coding RNA transcripts. We identify alterations within the cAMP dependent pathway (GNAS, PRKAR1A) which converge on GLI2 activity and show that 18% of tumors have a genetic event that directly targets the abundance and/or stability of MYCN. Furthermore, we discover an extensive network of fusions in focally amplified regions encompassing GLI2, and several loss-of-function fusions in tumor suppressor genes PTCH1, SUFU and NCOR1. Molecular convergence on a subset of genes by nucleotide variants, copy number aberrations, and gene fusions highlight the key roles of specific pathways in the pathogenesis of Sonic hedgehog medulloblastoma and open up opportunities for therapeutic intervention.

Année de publication : 2020

Kulandaimanuvel Antony Michealraj, Sachin A Kumar, Leo J Y Kim, Florence M G Cavalli, David

Przelicki, John B Wojcik, Alberto Delaidelli, Andrea Bajic, Olivier Saulnier, Graham MacLeod, Ravi N Vellanki, Maria C Vladoiu, Paul Guilhamon, Winnie Ong, John J Y Lee, Yanqing Jiang, Borja L Holgado, Alex Rasnitsyn, Ahmad A Malik, Ricky Tsai, Cory M Richman, Kyle Juraschka, Joonas Haapasalo, Evan Y Wang, Pasqualino De Antonellis, Hiromichi Suzuki, Hamza Farooq, Polina Balin, Kaitlin Kharas, Randy Van Ommeren, Olga Sirbu, Avesta Rastan, Stacey L Krumholtz, Michelle Ly, Moloud Ahmadi, Geneviève Deblois, Dilakshan Srikanthan, Betty Luu, James Loukides, Xiaochong Wu, Livia Garzia, Vijay Ramaswamy, Evgeny Kanshin, María Sánchez-Osuna, Ibrahim El-Hamamy, Fiona J Coutinho, Panagiotis Prinos, Sheila Singh, Laura K Donovan, Craig Daniels, Daniel Schramek, Mike Tyers, Samuel Weiss, Lincoln D Stein, Mathieu Lupien, Bradly G Wouters, Benjamin A Garcia, Cheryl H Arrowsmith, Poul H Sorensen, Stephane Angers, Nada Jabado, Peter B Dirks, Stephen C Mack, Sameer Agnihotri, Jeremy N Rich, Michael D Taylor (2020 May 24)
Metabolic Regulation of the Epigenome Drives Lethal Infantile Ependymoma.
Cell : 1329-1345.e24 : DOI : S0092-8674(20)30553-5

Résumé

Posterior fossa A (PFA) ependymomas are lethal malignancies of the hindbrain in infants and toddlers. Lacking highly recurrent somatic mutations, PFA ependymomas are proposed to be epigenetically driven tumors for which model systems are lacking. Here we demonstrate that PFA ependymomas are maintained under hypoxia, associated with restricted availability of specific metabolites to diminish histone methylation, and increase histone demethylation and acetylation at histone 3 lysine 27 (H3K27). PFA ependymomas initiate from a cell lineage in the first trimester of human development that resides in restricted oxygen. Unlike other ependymomas, transient exposure of PFA cells to ambient oxygen induces irreversible cellular toxicity. PFA tumors exhibit a low basal level of H3K27me3, and, paradoxically, inhibition of H3K27 methylation specifically disrupts PFA tumor growth. Targeting metabolism and/or the epigenome presents a unique opportunity for rational therapy for infants with PFA ependymoma.

Année de publication : 2019

Maria C Vladoiu, Ibrahim El-Hamamy, Laura K Donovan, Hamza Farooq, Borja L Holgado, Yogi Sundaravadanam, Vijay Ramaswamy, Liam D Hendrikse, Sachin Kumar, Stephen C Mack, John J Y Lee, Vernon Fong, Kyle Juraschka, David Przelicki, Antony Michealraj, Patryk Skowron, Betty Luu, Hiromichi Suzuki, A Sorana Morrissy, Florence M G Cavalli, Livia Garzia, Craig Daniels, Xiaochong Wu, Maleeha A Qazi, Sheila K Singh, Jennifer A Chan, Marco A Marra, David Malkin, Peter Dirks, Lawrence Heisler, Trevor Pugh, Karen Ng, Faiyaz Notta, Eric M Thompson, Claudia L Kleinman, Alexandra L Joyner, Nada Jabado, Lincoln Stein, Michael D Taylor (2019 May 3)
Childhood cerebellar tumours mirror conserved fetal transcriptional programs.
Nature : 67-73 : DOI : 10.1038/s41586-019-1158-7

Résumé

Study of the origin and development of cerebellar tumours has been hampered by the complexity and heterogeneity of cerebellar cells that change over the course of development. Here we use single-cell transcriptomics to study more than 60,000 cells from the developing mouse cerebellum and show that different molecular subgroups of childhood cerebellar tumours mirror the transcription of cells from distinct, temporally restricted cerebellar lineages. The Sonic Hedgehog medulloblastoma subgroup transcriptionally mirrors the granule cell hierarchy as expected, while group 3 medulloblastoma resembles Nestin stem cells, group 4 medulloblastoma resembles unipolar brush cells, and PFA/PFB ependymoma and cerebellar pilocytic astrocytoma resemble the prenatal gliogenic progenitor cells. Furthermore, single-cell transcriptomics of human childhood cerebellar tumours demonstrates that many bulk tumours contain a mixed population of cells with divergent differentiation. Our data highlight cerebellar tumours as a disorder of early brain development and provide a proximate explanation for the peak incidence of cerebellar tumours in early childhood.

Année de publication : 2018

Florence M G Cavalli, Jens-Martin Hübner, Tanvi Sharma, Betty Luu, Martin Sill, Michal Zapotocky, Stephen C Mack, Hendrik Witt, Tong Lin, David J H Shih, Ben Ho, Mariarita Santi, Lyndsey Emery, Juliette Hukin, Christopher Dunham, Roger E McLendon, Eric S Lipp, Sridharan Gururangan, Andrew Grossbach, Pim French, Johan M Kros, Marie-Lise C van Veelen, Amulya A Nageswara Rao, Caterina Giannini, Sarah Leary, Shin Jung, Claudia C Faria, Jaume Mora, Ulrich Schüller, Marta M Alonso, Jennifer A Chan, Almos Klekner, Lola B Chambless, Eugene I Hwang, Maura Massimino, Charles G Eberhart, Matthias A Karajannis, Benjamin Lu, Linda M Liau, Massimo Zollo, Veronica Ferrucci, Carlos Carlotti, Daniela P C Tirapelli, Uri Tabori, Eric Bouffet, Marina Ryzhova, David W Ellison, Thomas E Merchant, Mark R Gilbert, Terri S Armstrong, Andrey Korshunov, Stefan M Pfister, Michael D Taylor, Kenneth Aldape, Kristian W Pajtler, Marcel Kool, Vijay Ramaswamy (2018 Jul 19)

Heterogeneity within the PF-EPN-B ependymoma subgroup.

Acta neuropathologica : 227-237 : DOI : 10.1007/s00401-018-1888-x

Résumé

Posterior fossa ependymoma comprise three distinct molecular variants, termed PF-EPN-A (PFA), PF-EPN-B (PFB), and PF-EPN-SE (subependymoma). Clinically, they are very disparate and PFB tumors are currently being considered for a trial of radiation avoidance. However, to move forward, unraveling the heterogeneity within PFB would be highly desirable. To discern the molecular heterogeneity within PFB, we performed an integrated analysis consisting of DNA methylation profiling, copy-number profiling, gene expression profiling, and clinical correlation across a cohort of 212 primary posterior fossa PFB tumors. Unsupervised spectral clustering and t-SNE analysis of genome-wide methylation data revealed five distinct subtypes of PFB tumors, termed PFB1-5, with distinct demographics, copy-number

alterations, and gene expression profiles. All PFB subtypes were distinct from PFA and posterior fossa subependymomas. Of the five subtypes, PFB4 and PFB5 are more discrete, consisting of younger and older patients, respectively, with a strong female-gender enrichment in PFB5 (age: $p = 0.011$, gender: $p = 0.04$). Broad copy-number aberrations were common; however, many events such as chromosome 2 loss, 5 gain, and 17 loss were enriched in specific subtypes and 1q gain was enriched in PFB1. Late relapses were common across all five subtypes, but deaths were uncommon and present in only two subtypes (PFB1 and PFB3). Unlike the case in PFA ependymoma, 1q gain was not a robust marker of poor progression-free survival; however, chromosome 13q loss may represent a novel marker for risk stratification across the spectrum of PFB subtypes. Similar to PFA ependymoma, there exists a significant intertumoral heterogeneity within PFB, with distinct molecular subtypes identified. Even when accounting for this heterogeneity, extent of resection remains the strongest predictor of poor outcome. However, this biological heterogeneity must be accounted for in future preclinical modeling and personalized therapies.

Année de publication : 2017

Florence M G Cavalli, Marc Remke, Ladislav Rampasek, John Peacock, David J H Shih, Betty Luu, Livia Garzia, Jonathon Torchia, Carolina Nor, A Sorana Morrissy, Sameer Agnihotri, Yuan Yao Thompson, Claudia M Kuzan-Fischer, Hamza Farooq, Keren Isaev, Craig Daniels, Byung-Kyu Cho, Seung-Ki Kim, Kyu-Chang Wang, Ji Yeoun Lee, Wieslawa A Grajkowska, Marta Perek-Polnik, Alexandre Vasiljevic, Cecile Faure-Conter, Anne Jouvet, Caterina Giannini, Amulya A Nageswara Rao, Kay Ka Wai Li, Ho-Keung Ng, Charles G Eberhart, Ian F Pollack, Ronald L Hamilton, G Yancey Gillespie, James M Olson, Sarah Leary, William A Weiss, Boleslaw Lach, Lola B Chambless, Reid C Thompson, Michael K Cooper, Rajeev Vibhakar, Peter Hauser, Marie-Lise C van Veelen, Johan M Kros, Pim J French, Young Shin Ra, Toshihiro Kumabe, Enrique López-Aguilar, Karel Zitterbart, Jaroslav Sterba, Gaetano Finocchiaro, Maura Massimino, Erwin G Van Meir, Satoru Osuka, Tomoko Shofuda, Almos Klekner, Massimo Zollo, Jeffrey R Leonard, Joshua B Rubin, Nada Jabado, Steffen Albrecht, Jaume Mora, Timothy E Van Meter, Shin Jung, Andrew S Moore, Andrew R Hallahan, Jennifer A Chan, Daniela P C Tirapelli, Carlos G Carlotti, Maryam Fouladi, José Pimentel, Claudia C Faria, Ali G Saad, Luca Massimi, Linda M Liau, Helen Wheeler, Hideo Nakamura, Samer K Elbabaa, Mario Perezpeña-Diazconti, Fernando Chico Ponce de León, Shenandoah Robinson, Michal Zapotocky, Alvaro Lassaletta, Annie Huang, Cynthia E Hawkins, Uri Tabori, Eric Bouffet, Ute Bartels, Peter B Dirks, James T Rutka, Gary D Bader, Jüri Reimand, Anna Goldenberg, Vijay Ramaswamy, Michael D Taylor (2017 Jun 14)

Intertumoral Heterogeneity within Medulloblastoma Subgroups.

Cancer cell : 737-754.e6 : DOI : S1535-6108(17)30201-5

Résumé

While molecular subgrouping has revolutionized medulloblastoma classification, the extent of heterogeneity within subgroups is unknown. Similarity network fusion (SNF) applied to

genome-wide DNA methylation and gene expression data across 763 primary samples identifies very homogeneous clusters of patients, supporting the presence of medulloblastoma subtypes. After integration of somatic copy-number alterations, and clinical features specific to each cluster, we identify 12 different subtypes of medulloblastoma. Integrative analysis using SNF further delineates group 3 from group 4 medulloblastoma, which is not as readily apparent through analyses of individual data types. Two clear subtypes of infants with Sonic Hedgehog medulloblastoma with disparate outcomes and biology are identified. Medulloblastoma subtypes identified through integrative clustering have important implications for stratification of future clinical trials.

A Sorana Morrissy, Florence M G Cavalli, Marc Remke, Vijay Ramaswamy, David J H Shih, Borja L Holgado, Hamza Farooq, Laura K Donovan, Livia Garzia, Sameer Agnihotri, Erin N Kiehna, Eloi Mercier, Chelsea Mayoh, Simon Papillon-Cavanagh, Hamid Nikbakht, Tenzin Gayden, Jonathon Torchia, Daniel Picard, Diana M Merino, Maria Vladoiu, Betty Luu, Xiaochong Wu, Craig Daniels, Stuart Horswell, Yuan Yao Thompson, Volker Hovestadt, Paul A Northcott, David T W Jones, John Peacock, Xin Wang, Stephen C Mack, Jüri Reimand, Steffen Albrecht, Adam M Fontebasso, Nina Thiessen, Yisu Li, Jacqueline E Schein, Darlene Lee, Rebecca Carlsen, Michael Mayo, Kane Tse, Angela Tam, Noreen Dhalla, Adrian Ally, Eric Chuah, Young Cheng, Patrick Plettner, Haiyan I Li, Richard D Corbett, Tina Wong, William Long, James Loukides, Pawel Buczkowicz, Cynthia E Hawkins, Uri Tabori, Brian R Rood, John S Myseros, Roger J Packer, Andrey Korshunov, Peter Lichter, Marcel Kool, Stefan M Pfister, Ulrich Schüller, Peter Dirks, Annie Huang, Eric Bouffet, James T Rutka, Gary D Bader, Charles Swanton, Yusanne Ma, Richard A Moore, Andrew J Mungall, Jacek Majewski, Steven J M Jones, Sunit Das, David Malkin, Nada Jabado, Marco A Marra, Michael D Taylor (2017 Apr 11)

Spatial heterogeneity in medulloblastoma.

Nature genetics : 780-788 : DOI : 10.1038/ng.3838

Résumé

Spatial heterogeneity of transcriptional and genetic markers between physically isolated biopsies of a single tumor poses major barriers to the identification of biomarkers and the development of targeted therapies that will be effective against the entire tumor. We analyzed the spatial heterogeneity of multiregional biopsies from 35 patients, using a combination of transcriptomic and genomic profiles. Medulloblastomas (MBs), but not high-grade gliomas (HGGs), demonstrated spatially homogeneous transcriptomes, which allowed for accurate subgrouping of tumors from a single biopsy. Conversely, somatic mutations that affect genes suitable for targeted therapeutics demonstrated high levels of spatial heterogeneity in MB, malignant glioma, and renal cell carcinoma (RCC). Actionable targets found in a single MB biopsy were seldom clonal across the entire tumor, which brings the efficacy of monotherapies against a single target into question. Clinical trials of targeted therapies for MB should first ensure the spatially ubiquitous nature of the target mutation.