Année de publication : 2020

S Melloul, J-F Mosnier, J Masliah-Planchon, C Lepage, K Le Malicot, J-M Gornet, J Edeline, D Dansette, P Texereau, O Delattre, P Laurent Puig, J Taieb, J-F Emile (2020 Feb 22)

Loss of SMARCB1 expression in colon carcinoma.

Cancer biomarkers : section A of Disease markers : 399-406 : DOI : 10.3233/CBM-190287

Résumé

SMARCB1 is a tumor suppressor gene, which is part of SWI/SNF complex involved in transcriptional regulation. Recently, loss of SMARCB1 expression has been reported in gastrointestinal carcinomas. Our purpose was to evaluate the incidence and prognostic value of SMARCB1 loss in colon carcinoma (CC). Patients with stage III CC (n= 1695), and a second cohort of 23 patients with poorly differentiated CC were analyzed. Immunohistochemistry for SMARCB1 was performed on tissue microarrays, and cases with loss of expression were controlled on whole sections. Loss of SMARCB1 was compared with the clinico-pathological and molecular characteristics, and the prognostic value was evaluated. Loss of SMARCB1 was identified in 12 of 1695 (0.7%) patients with stage III CC. Whole section controls showed a complete loss in only one of these cases, corresponding to a medullary carcinoma. SMARCB1 loss was not associated with histological grade, tumor size nor survival. In the cohort of poorly differentiated CC, we detected 2/23 (8.7%) cases with loss of SMARCB1; one was rhabdoid while the other had medullary and mucinous histology. These 2 cases were deficient for MisMatched Repair (dMMR) and mutated for BRAF. SMARCB1 loss is rare in stage III CC, but appears more frequent in poorly differentiated CC.

Marie-Ming Aynaud, Olivier Mirabeau, Nadege Gruel, Sandrine Grossetête, Valentina Boeva, Simon Durand, Didier Surdez, Olivier Saulnier, Sakina Zaïdi, Svetlana Gribkova, Aziz Fouché, Ulykbek Kairov, Virginie Raynal, Franck Tirode, Thomas G P Grünewald, Mylene Bohec, Sylvain Baulande, Isabelle Janoueix-Lerosey, Jean-Philippe Vert, Emmanuel Barillot, Olivier Delattre, Andrei Zinovyev (2020 Feb 13)

Transcriptional Programs Define Intratumoral Heterogeneity of Ewing Sarcoma at Single-Cell Resolution.

Cell reports : 1767-1779.e6 : DOI : 10.1016/j.celrep.2020.01.049

Résumé

EWSR1-FLI1, the chimeric oncogene specific for Ewing sarcoma (EwS), induces a cascade of signaling events leading to cell transformation. However, it remains elusive how genetically homogeneous EwS cells can drive the heterogeneity of transcriptional programs. Here, we combine independent component analysis of single-cell RNA sequencing data from diverse cell types and model systems with time-resolved mapping of EWSR1-FLI1 binding sites and of open chromatin regions to characterize dynamic cellular processes associated with EWSR1-FLI1 activity. We thus define an exquisitely specific and direct enhancer-driven EWSR1-FLI1 program. In EwS tumors, cell proliferation and strong oxidative phosphorylation

metabolism are associated with a well-defined range of EWSR1-FLI1 activity. In contrast, a subpopulation of cells from below and above the intermediary EWSR1-FLI1 activity is characterized by increased hypoxia. Overall, our study reveals sources of intratumoral heterogeneity within EwS tumors.

Manuel Rodrigues, Khadija Ait Rais, Flore Salviat, Nathalie Algret, Fatoumata Simaga, Raymond Barnhill, Sophie Gardrat, Vincent Servois, Pascale Mariani, Sophie Piperno-Neumann, Sergio Roman-Roman, Olivier Delattre, Nathalie Cassoux, Alexia Savignoni, Marc-Henri Stern, Gaëlle Pierron (2020 Jan 3)

Association of Partial Chromosome 3 Deletion in Uveal Melanomas With Metastasis-Free Survival.

JAMA ophthalmology : DOI : 10.1001/jamaophthalmol.2019.5403

Résumé

Studies on uveal melanomas (UMs) have demonstrated the prognostic value of 8q gain and monosomy 3, but the prognosis of UMs with partial deletion of chromosome 3 remains to be defined.

Johannes Ommer, Joanna L Selfe, Marco Wachtel, Eleanor M O'Brien, Dominik Laubscher, Michaela Roemmele, Stephanie Kasper, Olivier Delattre, Didier Surdez, Gemma Petts, Anna Kelsey, Janet Shipley, Beat W Schäfer (2020 Jan 1)

Aurora A Kinase Inhibition Destabilizes PAX3-FOXO1 and MYCN and Synergizes with Navitoclax to Induce Rhabdomyosarcoma Cell Death.

Cancer research : 832-842 : DOI : 10.1158/0008-5472.CAN-19-1479

Résumé

The clinically aggressive alveolar rhabdomyosarcoma (RMS) subtype is characterized by expression of the oncogenic fusion protein PAX3-FOXO1, which is critical for tumorigenesis and cell survival. Here, we studied the mechanism of cell death induced by loss of PAX3-FOXO1 expression and identified a novel pharmacologic combination therapy that interferes with PAX3-FOXO1 biology at different levels. Depletion of PAX3-FOXO1 in fusion-positive (FP)-RMS cells induced intrinsic apoptosis in a NOXA-dependent manner. This was pharmacologically mimicked by the BH3 mimetic navitoclax, identified as top compound in a screen from 208 targeted compounds. In a parallel approach, and to identify drugs that alter the stability of PAX3-FOXO1 protein, the same drug library was screened and fusion protein levels were directly measured as a read-out. This revealed that inhibition of Aurora kinase A most efficiently negatively affected PAX3-FOXO1 protein levels. Interestingly, this occurred through a novel specific phosphorylation event in and binding to the fusion protein. Aurora kinase A inhibition also destabilized MYCN, which is both a functionally important oncogene and transcriptional target of PAX3-FOXO1. Combined treatment with an Aurora kinase A inhibitor and navitoclax in FP-RMS cell lines and patient-derived xenografts synergistically

induced cell death and significantly slowed tumor growth. These studies identify a novel functional interaction of Aurora kinase A with both PAX3-FOXO1 and its effector MYCN, and reveal new opportunities for targeted combination treatment of FP-RMS. SIGNIFICANCE: These findings show that Aurora kinase A and Bcl-2 family proteins are potential targets for FP-RMS.

Année de publication : 2019

Amaury Leruste, Jimena Tosello, Rodrigo Nalio Ramos, Arnault Tauzède-Espariat, Solène Brohard, Zhi-Yan Han, Kevin Beccaria, Mamy Andrianteranagna, Pamela Caudana, Jovan Nikolic, Céline Chauvin, Leticia Laura Niborski, Valeria Manriquez, Wilfrid Richer, Julien Masliah-Planchon, Sandrine Grossetête-Lalami, Mylene Bohec, Sonia Lameiras, Sylvain Baulande, Celio Pouponnot, Aurore Coulomb, Louise Galmiche, Didier Surdez, Nicolas Servant, Julie Helft, Christine Sedlik, Stéphanie Puget, Philippe Benaroch, Olivier Delattre, Joshua J Waterfall, Eliane Piaggio, Franck Bourdeaut (2019 Nov 12)

Clonally Expanded T Cells Reveal Immunogenicity of Rhabdoid Tumors.

Cancer cell : 597-612.e8 : DOI : S1535-6108(19)30482-9

Résumé

Rhabdoid tumors (RTs) are genomically simple pediatric cancers driven by the biallelic inactivation of SMARCB1, leading to SWI/SNF chromatin remodeler complex deficiency. Comprehensive evaluation of the immune infiltrates of human and mice RTs, including immunohistochemistry, bulk RNA sequencing and DNA methylation profiling studies showed a high rate of tumors infiltrated by T and myeloid cells. Single-cell RNA (scRNA) and T cell receptor sequencing highlighted the heterogeneity of these cells and revealed therapeutically targetable exhausted effector and clonally expanded tissue resident memory CD8 T subpopulations, likely representing tumor-specific cells. Checkpoint blockade therapy in an experimental RT model induced the regression of established tumors and durable immune responses. Finally, we show that one mechanism mediating RTs immunogenicity involves SMARCB1-dependent re-expression of endogenous retroviruses and interferon-signaling activation.

Amal M El-Naggar, Syam Prakash Somasekharan, Yemin Wang, Hongwei Cheng, Gian Luca Negri, Melvin Pan, Xue Qi Wang, Alberto Delaidelli, Bo Rafn, Jordan Cran, Fan Zhang, Haifeng Zhang, Shane Colborne, Martin Gleave, Anna Mandinova, Nancy Kedersha, Christopher S Hughes, Didier Surdez, Olivier Delattre, Yuzhuo Wang, David G Huntsman, Gregg B Morin, Poul H Sorensen (2019 Nov 1)

Class I HDAC inhibitors enhance YB-1 acetylation and oxidative stress to block sarcoma metastasis.

EMBO reports : e48375 : DOI : 10.15252/embr.201948375

Résumé

Outcomes for metastatic Ewing sarcoma and osteosarcoma are dismal and have not changed for decades. Oxidative stress attenuates melanoma metastasis, and melanoma cells must reduce oxidative stress to metastasize. We explored this in sarcomas by screening for oxidative stress sensitizers, which identified the class I HDAC inhibitor MS-275 as enhancing vulnerability to reactive oxygen species (ROS) in sarcoma cells. Mechanistically, MS-275 inhibits YB-1 deacetylation, decreasing its binding to 5′-UTRs of NFE2L2 encoding the antioxidant factor NRF2, thereby reducing NFE2L2 translation and synthesis of NRF2 to increase cellular ROS. By global acetylomics, MS-275 promotes rapid acetylation of the YB-1 RNA-binding protein at lysine-81, blocking binding and translational activation of NFE2L2, as well as known YB-1 mRNA targets, HIF1A, and the stress granule nucleator, G3BP1. MS-275 dramatically reduces sarcoma metastasis in vivo, but an MS-275-resistant YB-1K81-to-alanine mutant restores metastatic capacity and NRF2, HIF1α, and G3BP1 synthesis in MS-275-treated mice. These studies describe a novel function for MS-275 through enhanced YB-1 acetylation, thus inhibiting YB-1 translational control of key cytoprotective factors and its pro-metastatic activity.

Swati Srivastava, Nishanth Belugali Nataraj, Arunachalam Sekar, Soma Ghosh, Chamutal Bornstein, Diana Drago-Garcia, Lee Roth, Donatella Romaniello, Ilaria Marrocco, Eyal David, Yuval Gilad, Mattia Lauriola, Ron Rotkopf, Adi Kimchi, Yuya Haga, Yasuo Tsutsumi, Olivier Mirabeau, Didier Surdez, Andrei Zinovyev, Olivier Delattre, Heinrich Kovar, Ido Amit, Yosef Yarden (2019 Oct 3)

ETS Proteins Bind with Glucocorticoid Receptors: Relevance for Treatment of Ewing Sarcoma.

Cell reports : 104-117.e4 : DOI : S2211-1247(19)31150-7

Résumé

The glucocorticoid receptor (GR) acts as a ubiquitous cortisol-dependent transcription factor (TF). To identify co-factors, we used protein-fragment complementation assays and found that GR recognizes FLI1 and additional ETS family proteins, TFs relaying proliferation and/or migration signals. Following steroid-dependent translocation of FLI1 and GR to the nucleus, the FLI1-specific domain (FLS) binds with GR and strongly enhances GR's transcriptional activity. This interaction has functional consequences in Ewing sarcoma (ES), childhood and adolescence bone malignancies driven by fusions between EWSR1 and FLI1. In vitro, GR knockdown inhibited the migration and proliferation of ES cells, and in animal models, antagonizing GR (or lowering cortisol) retarded both tumor growth and metastasis from bone to lung. Taken together, our findings offer mechanistic rationale for repurposing GR-targeting drugs for the treatment of patients with ES.

Julian Musa, Florencia Cidre-Aranaz, Marie-Ming Aynaud, Martin F Orth, Maximilian M L Knott, Olivier Mirabeau, Gal Mazor, Mor Varon, Tilman L B Hölting, Sandrine Grossetête, Moritz

Gartlgruber, Didier Surdez, Julia S Gerke, Shunya Ohmura, Aruna Marchetto, Marlene Dallmayer, Michaela C Baldauf, Stefanie Stein, Giuseppina Sannino, Jing Li, Laura Romero-Pérez, Frank Westermann, Wolfgang Hartmann, Uta Dirksen, Melissa Gymrek, Nathaniel D Anderson, Adam Shlien, Barak Rotblat, Thomas Kirchner, Olivier Delattre, Thomas G P Grünewald (2019 Sep 13)
Cooperation of cancer drivers with regulatory germline variants shapes clinical outcomes.
Nature communications : 4128 : DOI : 10.1038/s41467-019-12071-2

Résumé

Pediatric malignancies including Ewing sarcoma (EwS) feature a paucity of somatic alterations except for pathognomonic driver-mutations that cannot explain overt variations in clinical outcome. Here, we demonstrate in EwS how cooperation of dominant oncogenes and regulatory germline variants determine tumor growth, patient survival and drug response. Binding of the oncogenic EWSR1-FLI1 fusion transcription factor to a polymorphic enhancer-like DNA element controls expression of the transcription factor MYBL2 mediating these phenotypes. Whole-genome and RNA sequencing reveals that variability at this locus is inherited via the germline and is associated with variable inter-tumoral MYBL2 expression. High MYBL2 levels sensitize EwS cells for inhibition of its upstream activating kinase CDK2 in vitro and in vivo, suggesting MYBL2 as a putative biomarker for anti-CDK2-therapy. Collectively, we establish cooperation of somatic mutations and regulatory germline variants as a major determinant of tumor progression and highlight the importance of integrating the regulatory genome in precision medicine.

Simon Durand, Cécile Pierre-Eugène, Olivier Mirabeau, Caroline Louis-Brennetot, Valérie Combaret, Léo Colmet-Daage, Orphée Blanchard, Angela Bellini, Estelle Daudigeos-Dubus, Virginie Raynal, Gudrun Schleiermacher, Sylvain Baulande, Olivier Delattre, Isabelle Janoueix-Lerosey (2019 Aug 28)
ALK mutation dynamics and clonal evolution in a neuroblastoma model exhibiting two ALK mutations.
Oncotarget : 4937-4950 : DOI : 10.18632/oncotarget.27119

Résumé

The gene is a major oncogene of neuroblastoma cases exhibiting ALK activating mutations. Here, we characterized two neuroblastoma cell lines established from a stage 4 patient at diagnosis either from the primary tumor (PT) or from the bone marrow (BM). Both cell lines exhibited similar genomic profiles. All cells in the BM-derived cell line exhibited an ALK F1174L mutation, whereas this mutation was present in only 5% of the cells in the earliest passages of the PT-derived cell line. The BM-derived cell line presented with a higher proliferation rate and injections in Nude mice resulted in tumor formation only for the BM-derived cell line. Next, we observed that the F1174L mutation frequency in the PT-derived cell line increased with successive passages. Further Whole Exome Sequencing revealed a second ALK mutation, L1196M, in this cell line. Digital droplet PCR documented that the

allele fractions of both mutations changed upon passages, and that the F1174L mutation reached 50% in late passages, indicating clonal evolution. treatment of the PT-derived cell line exhibiting the F1174L and L1196M mutations with the alectinib inhibitor resulted in an enrichment of the L1196M mutation. Using xenografts, we documented a better efficacy of alectinib compared to crizotinib on tumor growth and an enrichment of the L1196M mutation at the end of both treatments. Finally, single-cell RNA-seq analysis was consistent with both mutations resulting in ALK activation. Altogether, this study provides novel insights into ALK mutation dynamics in a neuroblastoma model harbouring two ALK mutations.

Laura Romero-Pérez, Didier Surdez, Erika Brunet, Olivier Delattre, Thomas G P Grünewald (2019 Aug 19)

STAG Mutations in Cancer.

Trends in cancer : 506-520 : DOI : S2405-8033(19)30138-4

Résumé

Stromal Antigen 1 and 2 (STAG1/2) are key subunits of the cohesin complex that mediate sister chromatid cohesion, DNA repair, transcriptional regulation, and genome topology. Genetic alterations comprising any of the 11 cohesin-associated genes possibly occur in up to 26% of patients included in The Cancer Genome Atlas (TCGA) studies. STAG2 shows the highest number of putative driver truncating mutations. We provide a comprehensive review of the function of STAG1/2 in human physiology and disease and an integrative analysis of available omics data on STAG alterations in a wide array of cancers, comprising 53 691 patients and 1067 cell lines. Lastly, we discuss opportunities for therapeutic intervention.

Angela Bellini, Nadia Bessoltane-Bentahar, Jaydutt Bhalshankar, Nathalie Clement, Virginie Raynal, Sylvain Baulande, Virginie Bernard, Adrien Danzon, Mathieu Chicard, Léo Colmet-Daage, Gaelle Pierron, Laura Le Roux, Julien Masliah Planchon, Valérie Combaret, Eve Lapouble, Nadège Corradini, Estelle Thebaud, Marion Gambart, Dominique Valteau-Couanet, Jean Michon, Caroline Louis-Brennetot, Isabelle Janoueix-Lerosey, Anne-Sophie Defachelles, Franck Bourdeaut, Olivier Delattre, Gudrun Schleiermacher (2019 Apr 25)

Study of chromatin remodeling genes implicates SMARCA4 as a putative player in oncogenesis in neuroblastoma.

International journal of cancer : DOI : 10.1002/ijc.32361

Résumé

In neuroblastoma (NB), genetic alterations in chromatin remodeling (CRGs) and epigenetic modifier genes (EMGs) have been described. We sought to determine their frequency and clinical impact. Whole exome (WES)/whole genome sequencing (WGS) data and targeted sequencing (TSCA®) of exonic regions of 33 CRGs/EMGs were analyzed in tumor samples from 283 NB patients, with constitutional material available for 55 patients. The frequency of CRG/EMG variations in NB cases was then compared to the Genome Aggregation Database

(gnomAD). The sequencing revealed SNVs/small InDels or focal CNAs of CRGs/EMGs in 20% (56/283) of all cases, occurring at a somatic level in 4 (7.2%), at a germline level in 12 (22%) cases, whereas for the remaining cases, only tumor material could be analyzed. The most frequently altered genes were ATRX (5%), SMARCA4 (2.5%), MLL3 (2.5%) and ARID1B (2.5%). Double events (SNVs/small InDels/CNAs associated with LOH) were observed in SMARCA4 (n=3), ATRX (n=1) and PBRM1 (n=1). Among the 60 variations, 24 (8.4%) targeted domains of functional importance for chromatin remodeling or highly conserved domains but of unknown function. Variations in SMARCA4 and ATRX occurred more frequently in the NB as compared to the gnomAD control cohort (OR=4.49, 95%CI:1.63-9.97, P=0.038; OR 3.44, 95%CI:1.46-6.91, P=0.043, respectively). Cases with CRG/EMG variations showed a poorer overall survival compared to cases without variations. Genetic variations of CRGs/EMGs with likely functional impact were observed in 8.4% (24/283) of NB. Our case-control approach suggests a role of SMARCA4 as a player of NB oncogenesis.

Année de publication : 2018

Mitchell J Machiela, Thomas G P Grünewald, Didier Surdez, Stephanie Reynaud, Olivier Mirabeau, Eric Karlins, Rebeca Alba Rubio, Sakina Zaidi, Sandrine Grossetete-Lalami, Stelly Ballet, Eve Lapouble, Valérie Laurence, Jean Michon, Gaelle Pierron, Heinrich Kovar, Nathalie Gaspar, Udo Kontny, Anna González-Neira, Piero Picci, Javier Alonso, Ana Patino-Garcia, Nadège Corradini, Perrine Marec Bérard, Neal D Freedman, Nathaniel Rothman, Casey L Dagnall, Laurie Burdett, Kristine Jones, Michelle Manning, Kathleen Wyatt, Weiyin Zhou, Meredith Yeager, David G Cox, Robert N Hoover, Javed Khan, Gregory T Armstrong, Wendy M Leisenring, Smita Bhatia, Leslie L Robison, Andreas E Kulozik, Jennifer Kriebel, Thomas Meitinger, Markus Metzler, Wolfgang Hartmann, Konstantin Strauch, Thomas Kirchner, Uta Dirksen, Lindsay M Morton, Lisa Mirabello, Margaret A Tucker, Franck Tirode, Stephen J Chanock, Olivier Delattre (2018 Aug 11)
Genome-wide association study identifies multiple new loci associated with Ewing sarcoma susceptibility.
Nature communications : 3184 : DOI : 10.1038/s41467-018-05537-2

Résumé

Ewing sarcoma (EWS) is a pediatric cancer characterized by the EWSR1-FLI1 fusion. We performed a genome-wide association study of 733 EWS cases and 1346 unaffected individuals of European ancestry. Our study replicates previously reported susceptibility loci at 1p36.22, 10q21.3 and 15q15.1, and identifies new loci at 6p25.1, 20p11.22 and 20p11.23. Effect estimates exhibit odds ratios in excess of 1.7, which is high for cancer GWAS, and striking in light of the rarity of EWS cases in familial cancer syndromes. Expression quantitative trait locus (eQTL) analyses identify candidate genes at 6p25.1 (RREB1) and 20p11.23 (KIZ). The 20p11.22 locus is near NKX2-2, a highly overexpressed gene in EWS. Interestingly, most loci reside near GGAA repeat sequences and may disrupt binding of the EWSR1-FLI1 fusion protein. The high locus to case discovery ratio from 733 EWS cases suggests a genetic architecture in which moderate risk SNPs constitute a significant fraction

of risk.

Kathleen I Pishas, Christina D Drenberg, Cenny Taslim, Emily R Theisen, Kirsten M Johnson, Ranajeet S Saund, Ioana L Pop, Brian D Crompton, Elizabeth R Lawlor, Franck Tirode, Jaume Mora, Olivier Delattre, Mary C Beckerle, David F Callen, Sunil Sharma, Stephen L Lessnick (2018 Jul 13)

Therapeutic Targeting of KDM1A/LSD1 in Ewing Sarcoma with SP-2509 Engages the Endoplasmic Reticulum Stress Response.

Molecular cancer therapeutics : 1902-1916 : DOI : 10.1158/1535-7163.MCT-18-0373

Résumé

Multi-agent chemotherapeutic regimes remain the cornerstone treatment for Ewing sarcoma, the second most common bone malignancy diagnosed in pediatric and young adolescent populations. We have reached a therapeutic ceiling with conventional cytotoxic agents, highlighting the need to adopt novel approaches that specifically target the drivers of Ewing sarcoma oncogenesis. As KDM1A/ysine-pecific emethylase 1 (LSD1) is highly expressed in Ewing sarcoma cell lines and tumors, with elevated expression levels associated with worse overall survival (= 0.033), this study has examined biomarkers of sensitivity and mechanisms of cytotoxicity to targeted inhibition using SP-2509 (reversible inhibitor). We report, that innate resistance to SP-2509 was not observed in our Ewing sarcoma cell line cohort (= 17; IC range, 81 -1,593 nmol/L), in contrast resistance to the next-generation irreversible inhibitor GSK-LSD1 was observed across multiple cell lines (IC > 300 μmol/L). Although status and basal KDM1A mRNA and protein levels did not correlate with SP-2509 response, induction of KDM1B following SP-2509 treatment was strongly associated with SP-2509 hypersensitivity. We show that the transcriptional profile driven by SP-2509 strongly mirrors genetic depletion. Mechanistically, RNA-seq analysis revealed that SP-2509 imparts robust apoptosis through engagement of the endoplasmic reticulum stress pathway. In addition, were specifically induced/repressed, respectively following SP-2509 treatment only in our hypersensitive cell lines. Together, our findings provide key insights into the mechanisms of SP-2509 cytotoxicity as well as biomarkers that can be used to predict inhibitor sensitivity in Ewing sarcoma. .

Thomas G P Grünewald, Florencia Cidre-Aranaz, Didier Surdez, Eleni M Tomazou, Enrique de Álava, Heinrich Kovar, Poul H Sorensen, Olivier Delattre, Uta Dirksen (2018 Jul 7)

Ewing sarcoma.

Nature reviews. Disease primers : 5 : DOI : 10.1038/s41572-018-0003-x

Résumé

Ewing sarcoma is the second most frequent bone tumour of childhood and adolescence that can also arise in soft tissue. Ewing sarcoma is a highly aggressive cancer, with a survival of 70-80% for patients with standard-risk and localized disease and ~30% for those with metastatic disease. Treatment comprises local surgery, radiotherapy and polychemotherapy,

which are associated with acute and chronic adverse effects that may compromise quality of life in survivors. Histologically, Ewing sarcomas are composed of small round cells expressing high levels of CD99. Genetically, they are characterized by balanced chromosomal translocations in which a member of the FET gene family is fused with an ETS transcription factor, with the most common fusion being EWSR1-FLI1 (85% of cases). Ewing sarcoma breakpoint region 1 protein (EWSR1)-Friend leukaemia integration 1 transcription factor (FLI1) is a tumour-specific chimeric transcription factor (EWSR1-FLI1) with neomorphic effects that massively rewires the transcriptome. Additionally, EWSR1-FLI1 reprogrammes the epigenome by inducing de novo enhancers at GGAA microsatellites and by altering the state of gene regulatory elements, creating a unique epigenetic signature. Additional mutations at diagnosis are rare and mainly involve STAG2, TP53 and CDKN2A deletions. Emerging studies on the molecular mechanisms of Ewing sarcoma hold promise for improvements in early detection, disease monitoring, lower treatment-related toxicity, overall survival and quality of life.

Irene Jiménez, Mathieu Chicard, Léo Colmet-Daage, Nathalie Clément, Adrien Danzon, Eve Lapouble, Gaelle Pierron, Mylène Bohec, Sylvain Baulande, Dominique Berrebi, Paul Fréneaux, Aurore Coulomb, Louise Galmiche-Rolland, Sabine Sarnacki, Georges Audry, Pascale Philippe-Chomette, Hervé J Brisse, François Doz, Jean Michon, Olivier Delattre, Gudrun Schleiermacher (2018 Jun 21)

Circulating tumor DNA analysis enables molecular characterization of pediatric renal tumors at diagnosis.

International journal of cancer : DOI : 10.1002/ijc.31620

Résumé

Circulating tumor DNA (ctDNA) is a powerful tool for the molecular characterization of cancer. The most frequent pediatric kidney tumors (KT) are Wilms' tumors (WT), but other diagnoses may occur. According to the SIOP strategy, in most countries pediatric KT have a presumptive diagnosis of WT if they are clinically and radiologically compatible. The histologic confirmation is established after post-chemotherapy nephrectomy. Thus, there is a risk for a small fraction of patients to receive neoadjuvant chemotherapy that is not adapted to the disease. The aim of this work is to perform molecular diagnosis of pediatric KT by tumor genetic characterization based on the analysis of ctDNA. We analyzed ctDNA extracted from plasma samples of 18 pediatric patients with KT by whole-exome sequencing and compared the results to their matched tumor and germline DNA. Copy number alterations (CNAs) and single nucleotide variations (SNVs) were analyzed. We were able to detect tumor cell specific genetic alterations-CNAs, SNVs or both-in ctDNA in all patients except in one (for whom the plasma sample was obtained long after nephrectomy). These results open the door to new applications for the study of ctDNA with regards to the molecular diagnosis of KT, with a possibility of its usefulness for adapting the treatment early after diagnosis, but also for disease monitoring and follow up.