Année de publication : 2019

Morabito Morgane, Larcher Magalie, Cavalli Florence MG, Foray Chloé, Forget Antoine, Mirabal-Ortega Liliana , Andrianteranagna Mamy, Druillennec Sabine, Garancher Alexandra, Masliah-Planchon Julien, Leboucher Sophie, Debalkew Abel, Raso Alessandro, Delattre Olivier , Puget Stéphanie, Doz François, Taylor Michael D, Ayrault Olivier, Bourdeaut Franck, Eychène Alain & Pouponnot Celio (2019 Jul 22)

An autocrine ActivinB mechanism drives TGFb/Activin signaling in Group3medulloblastoma

EMBO Molecular Medecine : 11 : e9830 : DOI : 10.15252/emmm.201809830

Résumé

Medulloblastoma (MB) is a pediatric tumor of the cerebellum divided into four groups. Group3 is of bad prognosis and remains poorly characterized. While the current treatment involving surgery, radiotherapy, and chemotherapy often fails, noalternative therapy is yet available. Few recurrent genomicalterations that can be therapeutically targeted have been identified. Amplifications of receptors of the TGFb/Activin pathway occur at very low frequency in Group3 MB. However, neither their functional relevance nor activation of the downstream signaling pathway has been studied. We showed that this pathway is activated in Group3 MB with some samples showing avery strong activation. Beside genetic alterations, we demonstrated that an ActivinB autocrine stimulation is responsible for pathway activation in a subset of Group3 MB characterized by high PMEPA1 levels. Importantly, Galunisertib, a kinase inhibitor of the cognate receptors currently tested in clinical trials for Glioblastoma patients, showed efficacy on orthotopically grafted MB-PDX. Our data demonstrate that the TGFb/Activin pathway is active in a subset of Group3 MB and can be therapeutically targeted.

Blanluet M, Masliah-Planchon J, Giurgea I, Bielle F, Girard E, Andrianteranagna M, Clemenceau S, Bourneix C, Burglen L, Doummar D, Rapinat A, Oumoussa BM, Ayrault O, Pouponnot C, Gentien D, Pierron G, Delattre O, Doz F, Bourdeaut F. (2019 Mar 8)

SHH medulloblastoma in a young adult with a TCF4 germline pathogenic variation.

Acta Neuropathologica : 4 : 675-678 : DOI : 10.1007/s00401-019-01983-4

Résumé

Année de publication : 2018

Michaël Cerezo, Ramdane Guemiri, Sabine Druillennec, Isabelle Girault, Hélène Malka-Mahieu, Shensi Shen, Delphine Allard, Sylvain Martineau, Caroline Welsch, Sandrine Agoussi, Charlène Estrada, Julien Adam, Cristina Libenciuc, Emilie Routier, Séverine Roy, Laurent Désaubry,

Alexander M Eggermont, Nahum Sonenberg, Jean Yves Scoazec, Alain Eychène, Stéphan Vagner, Caroline Robert (2018 Oct 29)

Translational control of tumor immune escape via the eIF4F-STAT1-PD-L1 axis in melanoma.

Nature medicine : DOI : 10.1038/s41591-018-0217-1

Résumé

Preventing the immune escape of tumor cells by blocking inhibitory checkpoints, such as the interaction between programmed death ligand-1 (PD-L1) and programmed death-1 (PD-1) receptor, is a powerful anticancer approach. However, many patients do not respond to checkpoint blockade. Tumor PD-L1 expression is a potential efficacy biomarker, but the complex mechanisms underlying its regulation are not completely understood. Here, we show that the eukaryotic translation initiation complex, eIF4F, which binds the 5′ cap of mRNAs, regulates the surface expression of interferon-γ-induced PD-L1 on cancer cells by regulating translation of the mRNA encoding the signal transducer and activator of transcription 1 (STAT1) transcription factor. eIF4F complex formation correlates with response to immunotherapy in human melanoma. Pharmacological inhibition of eIF4A, the RNA helicase component of eIF4F, elicits powerful antitumor immune-mediated effects via PD-L1 downregulation. Thus, eIF4A inhibitors, in development as anticancer drugs, may also act as cancer immunotherapies.

Forget Antoine, Martignetti Loredana, Puget Stéphanie, Calzone Laurence, Brabetz Sebastian, Picard Daniel, Montagud Arnau, Liva Stéphane, Sta Alexandre, Dingli Florent, Arras Guillaume, Rivera Jaime, Loew Damarys, Besnard Aurore, Lacombe Joëlle, Pagès Mélanie, Varlet Pascale, Dufour Christelle, Yu Hua, L. Mercier Audrey, Indersie Emilie, Chivet Anaïs, Leboucher Sophie, Sieber Laura, Beccaria Kevin, Gombert Michael, D. Meyer Frauke, Qin Nan, Bartl Jasmin, Chavez Lukas, Okonechnikov Konstantin, Sharma Tanvi, Thatikonda Venu, Bourdeaut Franck, Pouponnot Celio, Ramaswamy Vijay, Korshunov Andrey, Borkhardt Arndt, Reifenberger Guido, Poullet Patrick, D. Taylor Michael, Kool Marcel, M. Pfister Stefan, Kawauchi Daisuke, Barillot Emmanuel, Remke Marc, Ayrault Olivier (2018 Sep 10)

Aberrant ERBB4-SRC Signaling as a Hallmark of Group 4 Medulloblastoma Revealed by Integrative Phosphoproteomic Profiling

Cancer Cell : 34 : 379-395 : DOI : 10.1016/j.ccell.2018.08.002

Résumé

The current consensus recognizes four main medulloblastoma subgroups (wingless, Sonic hedgehog, group 3 and group 4). While medulloblastoma subgroups have been characterized extensively at the (epi-)genomic and transcriptomic levels, the proteome and phosphoproteome landscape remain to be comprehensively elucidated. Using quantitative (phospho)-proteomics in primary human medulloblastomas, we unravel distinct posttranscriptional regulation leading to highly divergent oncogenic signaling and kinase

activity profiles in groups 3 and 4 medulloblastomas. Specifically, proteomic and phosphoproteomic analyses identify aberrant ERBB4-SRC signaling in group 4. Hence, enforced expression of an activated SRC combined with p53 inactivation induces murine tumors that resemble group 4 medulloblastoma. Therefore, our integrative proteogenomics approach unveils an oncogenic pathway and potential therapeutic vulnerability in the most common medulloblastoma subgroup.

Alexandra Garancher, Charles Y Lin, Morgane Morabito, Wilfrid Richer, Nathalie Rocques, Magalie Larcher, Laure Bihannic, Kyle Smith, Catherine Miquel, Sophie Leboucher, Nirmitha I Herath, Fanny Dupuy, Pascale Varlet, Christine Haberler, Christine Walczak, Nadine El Tayara, Andreas Volk, Stéphanie Puget, François Doz, Olivier Delattre, Sabine Druillennec, Olivier Ayrault, Robert J Wechsler-Reya, Alain Eychène, Franck Bourdeaut, Paul A Northcott, Celio Pouponnot (2018 Mar 14)

NRL and CRX Define Photoreceptor Identity and Reveal Subgroup-Specific Dependencies in Medulloblastoma.

Cancer cell : 435-449.e6 : DOI : 10.1016/j.ccell.2018.02.006

Résumé

Cancer cells often express differentiation programs unrelated to their tissue of origin, although the contribution of these aberrant phenotypes to malignancy is poorly understood. An aggressive subgroup of medulloblastoma, a malignant pediatric brain tumor of the cerebellum, expresses a photoreceptor differentiation program normally expressed in the retina. We establish that two photoreceptor-specific transcription factors, NRL and CRX, are master regulators of this program and are required for tumor maintenance in this subgroup. Beyond photoreceptor lineage genes, we identify BCL-XL as a key transcriptional target of NRL and provide evidence substantiating anti-BCL therapy as a rational treatment opportunity for select MB patients. Our results highlight the utility of studying aberrant differentiation programs in cancer and their potential as selective therapeutic vulnerabilities.

Mélanie Mahe, Florent Dufour, Hélène Neyret-Kahn, Aura Moreno-Vega, Claire Beraud, Mingjun Shi, Imene Hamaidi, Virginia Sanchez-Quiles, Clementine Krucker, Marion Dorland-Galliot, Elodie Chapeaublanc, Remy Nicolle, Hervé Lang, Celio Pouponnot, Thierry Massfelder, François Radvanyi, Isabelle Bernard-Pierrot (2018 Feb 22)

An FGFR3/MYC positive feedback loop provides new opportunities for targeted therapies in bladder cancers.

EMBO molecular medicine : DOI : e8163

Résumé

FGFR3 alterations (mutations or translocation) are among the most frequent genetic events in bladder carcinoma. They lead to an aberrant activation of FGFR3 signaling, conferring an

oncogenic dependence, which we studied here. We discovered a positive feedback loop, in which the activation of p38 and AKT downstream from the altered FGFR3 upregulatesmRNA levels and stabilizes MYC protein, respectively, leading to the accumulation of MYC, which directly upregulatesexpression by binding to active enhancers upstream fromDisruption of this FGFR3/MYC loop in bladder cancer cell lines by treatment with FGFR3, p38, AKT, or BET bromodomain inhibitors (JQ1) preventingtranscription decreased cell viabilityand tumor growthA relevance of this loop to human bladder tumors was supported by the positive correlation betweenandlevels in tumors bearingmutations, and the decrease in FGFR3 and MYC levels following anti-FGFR treatment in a PDX model bearing anmutation. These findings open up new possibilities for the treatment of bladder tumors displaying aberrant FGFR3 activation.

Année de publication : 2017

Sabine Druillennec, Celio Pouponnot, Alain Eychène (2017 Dec 7)

NRAS-driven melanoma: A RAF can hide another.

Molecular & cellular oncology : e1344758 : DOI : 10.1080/23723556.2017.1344758

Résumé

Using mouse genetics, we recently showed that BRAF has a critical role in initiation of NRAS-driven melanoma that cannot be compensated by CRAF. In contrast, RAF proteins display compensatory functions in fully established tumors and ARAF can sustain proliferation in the absence of BRAF and CRAF, highlighting an addiction to RAF signaling in NRAS-driven melanoma.

Coralie Dorard, Charlène Estrada, Céline Barbotin, Magalie Larcher, Alexandra Garancher, Jessy Leloup, Friedrich Beermann, Manuela Baccarini, Celio Pouponnot, Lionel Larue, Alain Eychène, Sabine Druillennec (2017 May 13)

RAF proteins exert both specific and compensatory functions during tumour progression of NRAS-driven melanoma.

Nature communications : 15262 : DOI : 10.1038/ncomms15262

Résumé

NRAS and its effector BRAF are frequently mutated in melanoma. Paradoxically, CRAF but not BRAF was shown to be critical for various RAS-driven cancers, raising the question of the role of RAF proteins in NRAS-induced melanoma. Here, using conditional ablation of Raf genes in NRAS-induced mouse melanoma models, we investigate their contribution in tumour progression, from the onset of benign tumours to malignant tumour maintenance. We show that BRAF expression is required for ERK activation and nevi development, demonstrating a critical role in the early stages of NRAS-driven melanoma. After melanoma formation, single Braf or Craf ablation is not sufficient to block tumour growth, showing redundant functions for RAF kinases. Finally, proliferation of resistant cells emerging in the absence of BRAF and

CRAF remains dependent on ARAF-mediated ERK activation. These results reveal specific and compensatory functions for BRAF and CRAF and highlight an addiction to RAF signalling in NRAS-driven melanoma.

Année de publication : 2015

Marcello Niceta, Emilia Stellacci, Karen W Gripp, Giuseppe Zampino, Maria Kousi, Massimiliano Anselmi, Alice Traversa, Andrea Ciolfi, Deborah Stabley, Alessandro Bruselles, Viviana Caputo, Serena Cecchetti, Sabrina Prudente, Maria T Fiorenza, Carla Boitani, Nicole Philip, Dmitriy Niyazov, Chiara Leoni, Takaya Nakane, Kim Keppler-Noreuil, Stephen R Braddock, Gabriele Gillessen-Kaesbach, Antonio Palleschi, Philippe M Campeau, Brendan H L Lee, Celio Pouponnot, Lorenzo Stella, Gianfranco Bocchinfuso, Nicholas Katsanis, Katia Sol-Church, Marco Tartaglia (2015 Jan 22)

Mutations Impairing GSK3-Mediated MAF Phosphorylation Cause Cataract, Deafness, Intellectual Disability, Seizures, and a Down Syndrome-like Facies.

American journal of human genetics : 816-25 : DOI : 10.1016/j.ajhg.2015.03.001

Résumé

Transcription factors operate in developmental processes to mediate inductive events and cell competence, and perturbation of their function or regulation can dramatically affect morphogenesis, organogenesis, and growth. We report that a narrow spectrum of amino-acid substitutions within the transactivation domain of the v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog (MAF), a leucine zipper-containing transcription factor of the AP1 superfamily, profoundly affect development. Seven different de novo missense mutations involving conserved residues of the four GSK3 phosphorylation motifs were identified in eight unrelated individuals. The distinctive clinical phenotype, for which we propose the eponym Aymé-Gripp syndrome, is not limited to lens and eye defects as previously reported for MAF/Maf loss of function but includes sensorineural deafness, intellectual disability, seizures, brachycephaly, distinctive flat facial appearance, skeletal anomalies, mammary gland hypoplasia, and reduced growth. Disease-causing mutations were demonstrated to impair proper MAF phosphorylation, ubiquitination and proteasomal degradation, perturbed gene expression in primary skin fibroblasts, and induced neurodevelopmental defects in an in vivo model. Our findings nosologically and clinically delineate a previously poorly understood recognizable multisystem disorder, provide evidence for MAF governing a wider range of developmental programs than previously appreciated, and describe a novel instance of protein dosage effect severely perturbing development.

Caterina Pegoraro, Ana Leonor Figueiredo, Frédérique Maczkowiak, Celio Pouponnot, Alain Eychène, Anne H Monsoro-Burq (2015 Jan 20)

PFKFB4 controls embryonic patterning via Akt signalling independently of

glycolysis.
Nature communications : 5953 : DOI : 10.1038/ncomms6953

Résumé

How metabolism regulators play roles during early development remains elusive. Here we show that PFKFB4 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4), a glycolysis regulator, is critical for controlling dorsal ectoderm global patterning in gastrulating frog embryos via a non-glycolytic function. PFKFB4 is required for dorsal ectoderm progenitors to proceed towards more specified fates including neural and non-neural ectoderm, neural crest or placodes. This function is mediated by Akt signalling, a major pathway that integrates cell homeostasis and survival parameters. Restoring Akt signalling rescues the loss of PFKFB4 in vivo. In contrast, glycolysis is not essential for frog development at this stage. Our study reveals the existence of a PFKFB4-Akt checkpoint that links cell homeostasis to the ability of progenitor cells to undergo differentiation, and uncovers glycolysis-independent functions of PFKFB4.

Année de publication : 2014

Catherine Dehainault, Alexandra Garancher, Laurent Castéra, Nathalie Cassoux, Isabelle Aerts, François Doz, Laurence Desjardins, Livia Lumbroso, Rocío Montes de Oca, Geneviève Almouzni, Dominique Stoppa-Lyonnet, Celio Pouponnot, Marion Gauthier-Villars, Claude Houdayer (2014 May 23)
The survival gene MED4 explains low penetrance retinoblastoma in patients with large RB1 deletion.
Human molecular genetics : 5243-50 : DOI : 10.1093/hmg/ddu245

Résumé

Retinoblastoma is a non-hereditary as well as an inherited pediatric tumor of the developing retina resulting from the inactivation of both copies of the RB1 tumor suppressor gene. Familial retinoblastoma is a highly penetrant genetic disease that usually develops by carrying germline mutations that inactivate one allele of the RB1 gene, leading to multiple retinoblastomas. However, large and complete germline RB1 deletions are associated with low or no tumor risk for reasons that remain unknown. In this study, we define a minimal genomic region associated with this low penetrance. This region encompasses few genes including MED4 a subunit of the mediator complex. We further show that retinoblastoma RB1 -/- cells cannot survive in the absence of MED4, both in vitro and in orthotopic xenograft models in vivo, therefore identifying MED4 as a survival gene in retinoblastoma. We propose that the contiguous loss of the adjacent retinoblastoma gene, MED4, explains the low penetrance in patients with large deletions that include both RB1 and MED4. Our findings also point to another synthetic lethal target in tumors with inactivated RB1 and highlight the importance of collateral damage in carcinogenesis.

Marie-Jeannette Stahnke, Corinna Dickel, Sabine Schröder, Diana Kaiser, Roland Blume, Roland Stein, Celio Pouponnot, Elke Oetjen (2014 Apr 15)

Inhibition of human insulin gene transcription and MafA transcriptional activity by the dual leucine zipper kinase.

Cellular signalling : 1792-9 : DOI : 10.1016/j.cellsig.2014.04.006

Résumé

Insulin biosynthesis is an essential β-cell function and inappropriate insulin secretion and biosynthesis contribute to the pathogenesis of diabetes mellitus type 2. Previous studies showed that the dual leucine zipper kinase (DLK) induces β-cell apoptosis. Since β-cell dysfunction precedes β-cell loss, in the present study the effect of DLK on insulin gene transcription was investigated in the HIT-T15 β-cell line. Downregulation of endogenous DLK increased whereas overexpression of DLK decreased human insulin gene transcription. 5′- and 3′-deletion human insulin promoter analyses resulted in the identification of a DLK responsive element that mapped to the DNA binding-site for the β-cell specific transcription factor MafA. Overexpression of DLK wild-type but not its kinase-dead mutant inhibited MafA transcriptional activity conferred by its transactivation domain. Furthermore, in the non-β-cell line JEG DLK inhibited MafA overexpression-induced human insulin promoter activity. Overexpression of MafA and DLK or its kinase-dead mutant into JEG cells revealed that DLK but not its mutant reduced MafA protein content. Inhibition of the down-stream DLK kinase c-Jun N-terminal kinase (JNK) by SP600125 attenuated DLK-induced MafA loss. Furthermore, mutation of the serine 65 to alanine, shown to confer MafA protein stability, increased MafA-dependent insulin gene transcription and prevented DLK-induced MafA loss in JEG cells. These data suggest that DLK by activating JNK triggers the phosphorylation and degradation of MafA thereby attenuating insulin gene transcription. Given the importance of MafA for β-cell function, the inhibition of DLK might preserve β-cell function and ultimately retard the development of diabetes mellitus type 2.

N I Herath, N Rocques, A Garancher, A Eychène, C Pouponnot (2014 Jan 21)

GSK3-mediated MAF phosphorylation in multiple myeloma as a potential therapeutic target.

Blood cancer journal : e175 : DOI : 10.1038/bcj.2013.67

Résumé

Multiple myeloma (MM) is an incurable haematological malignancy characterised by the proliferation of mature antibody-secreting plasma B cells in the bone marrow. MM can arise from initiating translocations, of which the musculoaponeurotic fibrosarcoma (MAF) family is implicated in ~5%. MMs bearing Maf translocations are of poor prognosis. These translocations are associated with elevated Maf expression, including c-MAF, MAFB and MAFA, and with t(14;16) and t(14;20) translocations, involving c-MAF and MAFB, respectively. c-MAF is also overexpressed in MM through MEK/ERK activation, bringing the number of MMs driven by the deregulation of a Maf gene close to 50%. Here we demonstrate that MAFB and c-MAF are phosphorylated by the Ser/Thr kinase GSK3 in human MM cell lines. We show that

LiCl-induced GSK3 inhibition targets these phosphorylations and specifically decreases proliferation and colony formation of Maf-expressing MM cell lines. Interestingly, bortezomib induced stabilisation of Maf phosphorylation, an observation that could explain, at least partially, the low efficacy of bortezomib for patients carrying Maf translocations. Thus, GSK3 inhibition could represent a new therapeutic approach for these patients.

Année de publication : 2013

Z Hamze, C Vercherat, A Bernigaud-Lacheretz, W Bazzi, R Bonnavion, J Lu, A Calender, C Pouponnot, P Bertolino, C Roche, R Stein, J Y Scoazec, C X Zhang, M Cordier-Bussat (2013 Oct 26)

Altered MENIN expression disrupts the MAFA differentiation pathway in insulinoma.

Endocrine-related cancer : 833-48 : DOI : 10.1530/ERC-13-0164

Résumé

The protein MENIN is the product of the multiple endocrine neoplasia type I (MEN1) gene. Altered MENIN expression is one of the few events that are clearly associated with foregut neuroendocrine tumours (NETs), classical oncogenes or tumour suppressors being not involved. One of the current challenges is to understand how alteration of MENIN expression contributes to the development of these tumours. We hypothesised that MENIN might regulate factors maintaining endocrine-differentiated functions. We chose the insulinoma model, a paradigmatic example of well-differentiated pancreatic NETs, to study whether MENIN interferes with the expression of v-MAF musculoaponeurotic fibrosarcoma oncogene homologue A (MAFA), a master glucose-dependent transcription factor in differentiated β-cells. Immunohistochemical analysis of a series of human insulinomas revealed a correlated decrease in both MENIN and MAFA. Decreased MAFA expression resulting from targeted Men1 ablation was also consistently observed in mouse insulinomas. In vitro analyses using insulinoma cell lines showed that MENIN regulated MAFA protein and mRNA levels, and bound to Mafa promoter sequences. MENIN knockdown concomitantly decreased mRNA expression of both Mafa and β-cell differentiation markers (Ins1/2, Gck, Slc2a2 and Pdx1) and, in parallel, increased the proliferation rate of tumours as measured by bromodeoxyuridine incorporation. Interestingly, MAFA knockdown alone also increased proliferation rate but did not affect the expression of candidate proliferation genes regulated by MENIN. Finally, MENIN variants with missense mutations detected in patients with MEN1 lost the WT MENIN properties to regulate MAFA. Together, our findings unveil a previously unsuspected MENIN/MAFA connection regarding control of the β-cell differentiation/proliferation balance, which could contribute to tumorigenesis.

Année de publication : 2012

Agathe Valluet, Sabine Druillennec, Céline Barbotin, Coralie Dorard, Anne H Monsoro-Burq, Magalie Larcher, Celio Pouponnot, Manuela Baccarini, Lionel Larue, Alain Eychène (2012 Oct 2)

B-Raf and C-Raf are required for melanocyte stem cell self-maintenance.
Cell reports : 774-80 : DOI : 10.1016/j.celrep.2012.08.020

Résumé

B-Raf and C-Raf kinases have emerged as critical players in melanoma. However, little is known about their role during development and homeostasis of the melanocyte lineage. Here, we report that knockout of B-raf and C-raf genes in this lineage results in normal pigmentation at birth with no defect in migration, proliferation, or differentiation of melanoblasts in mouse hair follicles. In contrast, the double raf knockout mice displayed hair graying resulting from a defect in cell-cycle entry of melanocyte stem cells (MSCs) and their subsequent depletion in the hair follicle bulge. Therefore, Raf signaling is dispensable for early melanocyte lineage development, but necessary for MSC maintenance.