Année de publication : 2019

CAMPAGNE Antoine, LEE Ming-Kang, ZIELINSKI Dina, MICHAUD Audrey, LE CORRE Stéphanie, DINGLI Florent, CHEN Hong, SHAHIDIAN Lara Z, SERVANT Nicolas, LOEW Damarys, PASMANT Eric, PISTEL-VINAY Sophie, WASSEF Michel, MARGUERON Raphaël (2019 Jan 21)

BAP1 complex promotes transcription by opposing PRC1-mediated H2A ubiquitylation

Nature Communications : DOI : 10.1038/s41467-018-08255-x

Résumé

In Drosophila, a complex consisting of Calypso and ASX catalyzes H2A deubiquitination and has been reported to act as part of the Polycomb machinery in transcriptional silencing. The mammalian homologs of these proteins (BAP1 and ASXL1/2/3, respectively), are frequently mutated in various cancer types, yet their precise functions remain unclear. Using an integrative approach based on isogenic cell lines generated with CRISPR/Cas9, we uncover an unanticipated role for BAP1 in gene activation. This function requires the assembly of an enzymatically active BAP1-associated core complex (BAP1.com) containing one of the redundant ASXL proteins. We investigate the mechanism underlying BAP1.com-mediated transcriptional regulation and show that it does not participate in Polycomb-mediated silencing. Instead, our results establish that the function of BAP1.com is to safeguard transcriptionally active genes against silencing by the Polycomb Repressive Complex 1.

Année de publication : 2018

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.

Année de publication : 2017

Loda A., Brandsma J.H., Vassilev I., Servant N., Loos F., Amirnasr A., Splinter E., Barillot E., Poot R.A., Heard E., Gribnau J. (2017 Jan 1)

Genetic and epigenetic features direct differential efficiency of Xist-mediated silencing at X-chromosomal and autosomal locations.

Nature communications : 8 : 690 : DOI : 10.1038/s41467-017-00528-1

Résumé

Xist is indispensable for X chromosome inactivation. However, how Xist RNA directs chromosome-wide silencing and why some regions are more efficiently silenced than others remains unknown. Here, we explore the function of Xist by inducing ectopic Xist expression from multiple different X-linked and autosomal loci in mouse aneuploid and female diploid embryonic stem cells in which Xist-mediated silencing does not lead to lethal functional monosomy. We show that ectopic Xist expression faithfully recapitulates endogenous X chromosome inactivation from any location on the X chromosome, whereas long-range silencing of autosomal genes is less efficient. Long interspersed elements facilitate inactivation of genes located far away from the Xist transcription locus, and genes escaping X chromosome inactivation show enrichment of CTCF on X chromosomal but not autosomal loci. Our findings highlight important genomic and epigenetic features acquired during sex chromosome evolution to facilitate an efficient X chromosome inactivation process.Xist RNA is required for X chromosome inactivation but it is not well understood how Xist silences some regions more efficiently than others. Here, the authors induce ectopic Xist expression from multiple different X-linked and autosomal loci in cells to explore Xist function.

Portoso M., Ragazzini R., Brenčič ?., Moiani A., Michaud A., Vassilev I., Wassef M., Servant N., Sargueil B., Margueron R. (2017 Jan 1)

PRC2 is dispensable for HOTAIR-mediated transcriptional repression.

The EMBO journal : 36 : 981-994 : DOI : 10.15252/embj.201695335

Résumé

Long non-coding RNAs (lncRNAs) play diverse roles in physiological and pathological

processes. Several lncRNAs have been suggested to modulate gene expression by guiding chromatin-modifying complexes to specific sites in the genome. However, besides the example of Xist, clear-cut evidence demonstrating this novel mode of regulation remains sparse. Here, we focus on HOTAIR, a lncRNA that is overexpressed in several tumor types and previously proposed to play a key role in gene silencing through direct recruitment of Polycomb Repressive Complex 2 (PRC2) to defined genomic loci. Using genetic tools and a novel RNA-tethering system, we investigated the interplay between HOTAIR and PRC2 in gene silencing. Surprisingly, we observed that forced overexpression of HOTAIR in breast cancer cells leads to subtle transcriptomic changes that appear to be independent of PRC2. Mechanistically, we found that artificial tethering of HOTAIR to chromatin causes transcriptional repression, but that this effect does not require PRC2. Instead, PRC2 recruitment appears to be a consequence of gene silencing. We propose that PRC2 binding to RNA might serve functions other than chromatin targeting.

Année de publication : 2016

Marick Laé, Philippe La Rosa, Jonas Mandel, Fabien Reyal, Philippe Hupé, Philippe Terrier, Jérôme Couturier (2016 May 22)

Whole-genome profiling helps to classify phyllodes tumours of the breast.

Journal of clinical pathology : DOI : jclinpath-2016-203684

Résumé

The aim of this study was to analyse a series of borderline and malignant phyllodes tumours (PTs) of the breast by whole-genome profiling to identify genomic markers that could help to recognise potentially malignant tumours within borderline tumours.

Chow J.C., Ciaudo C., Fazzari M.J., Mise N., Servant N., Glass J.L., Attreed M., Avner P., Wutz A., Barillot E., Greally J.M., Voinnet O., Heard E. (2016 Jan 1)

LINE-1 Activity in Facultative Heterochromatin Formation during X Chromosome Inactivation.

Cell : 166 : 782 : DOI : 10.1016/j.cell.2016.07.013

Résumé

Année de publication : 2015

Nicolas Servant, Nelle Varoquaux, Bryan R Lajoie, Eric Viara, Chong-Jian Chen, Jean-Philippe Vert, Edith Heard, Job Dekker, Emmanuel Barillot (2015 Aug 10)

HiC-Pro: an optimized and flexible pipeline for Hi-C data processing.

Genome biology : 259 : DOI : 10.1186/s13059-015-0831-x

Résumé

HiC-Pro is an optimized and flexible pipeline for processing Hi-C data from raw reads to normalized contact maps. HiC-Pro maps reads, detects valid ligation products, performs quality controls and generates intra- and inter-chromosomal contact maps. It includes a fast implementation of the iterative correction method and is based on a memory-efficient data format for Hi-C contact maps. In addition, HiC-Pro can use phased genotype data to build allele-specific contact maps. We applied HiC-Pro to different Hi-C datasets, demonstrating its ability to easily process large data in a reasonable time. Source code and documentation are available at http://github.com/nservant/HiC-Pro .

I Kuperstein, E Bonnet, H-A Nguyen, D Cohen, E Viara, L Grieco, S Fourquet, L Calzone, C Russo, M Kondratova, M Dutreix, E Barillot, A Zinovyev (2015 Jul 21)

Atlas of Cancer Signalling Network: a systems biology resource for integrative analysis of cancer data with Google Maps.

Oncogenesis : e160 : DOI : 10.1038/oncsis.2015.19

Résumé

Cancerogenesis is driven by mutations leading to aberrant functioning of a complex network of molecular interactions and simultaneously affecting multiple cellular functions. Therefore, the successful application of bioinformatics and systems biology methods for analysis of high-throughput data in cancer research heavily depends on availability of global and detailed reconstructions of signalling networks amenable for computational analysis. We present here the Atlas of Cancer Signalling Network (ACSN), an interactive and comprehensive map of molecular mechanisms implicated in cancer. The resource includes tools for map navigation, visualization and analysis of molecular data in the context of signalling network maps. Constructing and updating ACSN involves careful manual curation of molecular biology literature and participation of experts in the corresponding fields. The cancer-oriented content of ACSN is completely original and covers major mechanisms involved in cancer progression, including DNA repair, cell survival, apoptosis, cell cycle, EMT and cell motility. Cell signalling mechanisms are depicted in detail, together creating a seamless ‘geographic-like’ map of molecular interactions frequently deregulated in cancer. The map is browsable using NaviCell web interface using the Google Maps engine and semantic zooming principle. The associated web-blog provides a forum for commenting and curating the ACSN content. ACSN allows uploading heterogeneous omics data from users on top of the maps for visualization and performing functional analyses. We suggest several scenarios for ACSN application in cancer research, particularly for visualizing high-throughput data, starting from small interfering RNA-based screening results or mutation frequencies to innovative ways of exploring transcriptomes and phosphoproteomes. Integration and analysis of these data in the context of ACSN may help interpret their biological significance and formulate mechanistic hypotheses. ACSN may also support patient stratification, prediction of treatment response and resistance to cancer drugs, as well as design of novel treatment strategies.

Natasha Zamudio, Joan Barau, Aurélie Teissandier, Marius Walter, Maté Borsos, Nicolas Servant, Déborah Bourc'his (2015 Jun 26)

DNA methylation restrains transposons from adopting a chromatin signature permissive for meiotic recombination.

Genes & development : 1256-70 : DOI : 10.1101/gad.257840.114

Résumé

DNA methylation is essential for protecting the mammalian germline against transposons. When DNA methylation-based transposon control is defective, meiotic chromosome pairing is consistently impaired during spermatogenesis: How and why meiosis is vulnerable to transposon activity is unknown. Using two DNA methylation-deficient backgrounds, the Dnmt3L and Miwi2 mutant mice, we reveal that DNA methylation is largely dispensable for silencing transposons before meiosis onset. After this, it becomes crucial to back up to a developmentally programmed H3K9me2 loss. Massive retrotransposition does not occur following transposon derepression, but the meiotic chromatin landscape is profoundly affected. Indeed, H3K4me3 marks gained over transcriptionally active transposons correlate with formation of SPO11-dependent double-strand breaks and recruitment of the DMC1 repair enzyme in Dnmt3L(-/-) meiotic cells, whereas these features are normally exclusive to meiotic recombination hot spots. Here, we demonstrate that DNA methylation restrains transposons from adopting chromatin characteristics amenable to meiotic recombination, which we propose prevents the occurrence of erratic chromosomal events.

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sebastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, (2015 Jun 22)

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial.

The Lancet. Oncology : 1324-34 : DOI : 10.1016/S1470-2045(15)00188-6

Résumé

Molecularly targeted agents have been reported to have anti-tumour activity for patients whose tumours harbour the matching molecular alteration. These results have led to increased off-label use of molecularly targeted agents on the basis of identified molecular alterations. We assessed the efficacy of several molecularly targeted agents marketed in France, which were chosen on the basis of tumour molecular profiling but used outside their indications, in patients with advanced cancer for whom standard-of-care therapy had failed.

Loredana Martignetti, Bruno Tesson, Anna Almeida, Andrei Zinovyev, Gordon C Tucker, Thierry

Dubois, Emmanuel Barillot (2015 Jun 1)
Detection of miRNA regulatory effect on triple negative breast cancer transcriptome.
BMC genomics : S4 : DOI : 10.1186/1471-2164-16-S6-S4

Résumé

Identifying key microRNAs (miRNAs) contributing to the genesis and development of a particular disease is a focus of many recent studies. We introduce here a rank-based algorithm to detect miRNA regulatory activity in cancer-derived tissue samples which combines measurements of gene and miRNA expression levels and sequence-based target predictions. The method is designed to detect modest but coordinated changes in the expression of sequence-based predicted target genes. We applied our algorithm to a cohort of 129 tumour and healthy breast tissues and showed its effectiveness in identifying functional miRNAs possibly involved in the disease. These observations have been validated using an independent publicly available breast cancer dataset from The Cancer Genome Atlas. We focused on the triple negative breast cancer subtype to highlight potentially relevant miRNAs in this tumour subtype. For those miRNAs identified as potential regulators, we characterize the function of affected target genes by enrichment analysis. In the two independent datasets, the affected targets are not necessarily the same, but display similar enriched categories, including breast cancer related processes like cell substrate adherens junction, regulation of cell migration, nuclear pore complex and integrin pathway. The R script implementing our method together with the datasets used in the study can be downloaded here (http://bioinfo-out.curie.fr/projects/targetrunningsum).

Antonio Cappuccio, Raphaël Zollinger, Mirjam Schenk, Aleksandra Walczak, Nicolas Servant, Emmanuel Barillot, Philippe Hupé, Robert L Modlin, Vassili Soumelis (2015 Apr 21)
Combinatorial code governing cellular responses to complex stimuli.
Nature communications : 6847 : DOI : 10.1038/ncomms7847

Résumé

Cells adapt to their environment through the integration of complex signals. Multiple signals can induce synergistic or antagonistic interactions, currently considered as homogenous behaviours. Here, we use a systematic theoretical approach to enumerate the possible interaction profiles for outputs measured in the conditions 0 (control), signals X, Y, X+Y. Combinatorial analysis reveals 82 possible interaction profiles, which we biologically and mathematically grouped into five positive and five negative interaction modes. To experimentally validate their use in living cells, we apply an original computational workflow to transcriptomics data of innate immune cells integrating physiopathological signal combinations. Up to 9 of the 10 defined modes coexisted in context-dependent proportions. Each interaction mode was preferentially used in specific biological pathways, suggesting a functional role in the adaptation to multiple signals. Our work defines an exhaustive map of interaction modes for cells integrating pairs of physiopathological and pharmacological stimuli.

Maxime Touzot, Alix Dahirel, Antonio Cappuccio, Elodie Segura, Philippe Hupé, Vassili Soumelis (2015 Feb 24)

Using Transcriptional Signatures to Assess Immune Cell Function: From Basic Mechanisms to Immune-Related Disease.

Journal of molecular biology : 3356-67 : DOI : 10.1016/j.jmb.2015.05.006

Résumé

Assessing human immune response remains a challenge as it involves multiple cell types in specific tissues. The use of microarray-based expression profiling as a tool for assessing the immune response has grown increasingly over the past decade. Transcriptome analyses provide investigators with a global perspective of the complex molecular and cellular events that unfold during the development of an immune response. In this review, we will detail the broad use of gene expression profiling to decipher the complexity of immune responses from disease biomarkers identification to cell activation, polarisation or functional specialisation. We will also describe how such data-driven strategies revealed the flexibility of immune function with common and specific transcriptional programme under multiple stimuli.

Oumou Goundiam, Pierre Gestraud, Tatiana Popova, Thibault De la Motte Rouge, Virginie Fourchotte, David Gentien, Philippe Hupé, Véronique Becette, Claude Houdayer, Sergio Roman-Roman, Marc-Henri Stern, Xavier Sastre-Garau (2015 Jan 9)

Histo-genomic stratification reveals the frequent amplification/overexpression of CCNE1 and BRD4 genes in non-BRCAness high grade ovarian carcinoma.

International journal of cancer : 1890-900 : DOI : 10.1002/ijc.29568

Résumé

The treatment of epithelial ovarian cancer (EOC) is narrowly focused despite the heterogeneity of this disease in which outcomes remain poor. To stratify EOC patients for targeted therapy, we developed an approach integrating expression and genomic analyses including the BRCAness status. Gene expression and genomic profiling were used to identify genes recurrently (>5%) amplified and overexpressed in 105 EOC. The LST (Large-scale State Transition) genomic signature of BRCAness was applied to define molecular subgroups of EOC. Amplified/overexpressed genes clustered mainly in 3q, 8q, 19p and 19q. These changes were generally found mutually exclusive. In the 85 patients for which the genomic signature could be determined, genomic BRCAness was found in 52 cases (61.1%) and non-BRCAness in 33 (38.8%). A striking mutual exclusivity was observed between BRCAness and amplification/overexpression data. Whereas 3q and 8q alterations were preferentially observed in BRCAness EOC, most alterations on chromosome 19 were in non-BRCAness cases. CCNE1 (19q12) and BRD4 (19p13.1) amplification/overexpression was found in 19/33 (57.5%) of non-BRCAness cases. Such disequilibrium was also found in the TCGA EOC data set used for validation. Potential target genes are frequently amplified/overexpressed in non-BRCAness EOC. We report that BRD4, already identified as a target in several tumor models, is a new potential target in high grade non-BRCAness ovarian carcinoma.

Torres-Roca J.F., Fulp W.J., Caudell J.J., Servant N., Bollet M.A., van de Vijver M., Naghavi A.O., Harris E.E., Eschrich S.A. (2015 Jan 1)

Integration of a Radiosensitivity Molecular Signature Into the Assessment of Local Recurrence Risk in Breast Cancer.

International journal of radiation oncology, biology, physics : 93 : 631-638 : DOI : 10.1016/j.ijrobp.2015.06.021

Résumé

Recently, we developed radiosensitivity (RSI), a clinically validated molecular signature that estimates tumor radiosensitivity. In the present study, we tested whether integrating RSI with the molecular subtype refines the classification of local recurrence (LR) risk in breast cancer. RSI and molecular subtype were evaluated in 343 patients treated with breast-conserving therapy that included whole-breast radiation therapy with or without a tumor bed boost (dose range 45-72 Gy). The follow-up period for patients without recurrence was 10 years. The clinical endpoint was LR-free survival. Although RSI did not uniformly predict for LR across the entire cohort, combining RSI and the molecular subtype identified a subpopulation with an increased risk of LR: triple negative (TN) and radioresistant (reference TN-radioresistant, hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.15-0.92, P=.02). TN patients who were RSI-sensitive/intermediate had LR rates similar to those of luminal (LUM) patients (HR 0.86, 95% CI 0.47-1.57, P=.63). On multivariate analysis, combined RSI and molecular subtype (P=.004) and age (P=.001) were the most significant predictors of LR. In contrast, integrating RSI into the LUM subtype did not identify additional risk groups. We hypothesized that radiation dose escalation was affecting radioresistance in the LUM subtype and serving as a confounder. An increased radiation dose decreased LR only in the luminal-resistant (LUM-R) subset (HR 0.23, 95% CI 0.05-0.98, P=.03). On multivariate analysis, the radiation dose was an independent variable only in the LUMA/B-RR subset (HR 0.025, 95% CI 0.001-0.946, P=.046), along with age (P=.008), T stage (P=.004), and chemotherapy (P=.008). The combined molecular subtype-RSI identified a novel molecular subpopulation (TN and radioresistant) with an increased risk of LR after breast-conserving therapy. We propose that the combination of RSI and molecular subtype could be useful in guiding radiation therapy-based decisions in breast cancer.