Année de publication : 2020

Hélène D Moreau, Ana-Maria Lennon-Duménil, Paolo Pierobon (2020 Mar 4)

« If you please… draw me a cell ». Insights from immune cells.

Journal of cell science : DOI : jcs244806

Résumé

Studies in recent years have shed light on the particular features of cytoskeleton dynamics in immune cells, challenging the classical picture drawn from typical adherent cell lines. New mechanisms linking the dynamics of the membrane-cytoskeleton interface to the mechanical properties of immune cells have been uncovered and shown to be essential for immune surveillance functions. In this Essay, we discuss these features, and propose immune cells as a new playground for cell biologists who try to understand how cells adapt to different microenvironments to fulfil their functions efficiently.

Helian Feng, Alexander Gusev, Bogdan Pasaniuc, Lang Wu, Jirong Long, Zomoroda Abu-Full, Kristiina Aittomäki, Irene L Andrulis, Hoda Anton-Culver, Antonis C Antoniou, Adalgeir Arason, Volker Arndt, Kristan J Aronson, Banu K Arun, Ella Asseryanis, Paul L Auer, Jacopo Azzollini, Judith Balmaña, Rosa B Barkardottir, Daniel R Barnes, Daniel Barrowdale, Matthias W Beckmann, Sabine Behrens, Javier Benitez, Marina Bermisheva, Katarzyna Białkowska, Ana Blanco, Carl Blomqvist, Bram Boeckx, Natalia V Bogdanova, Stig E Bojesen, Manjeet K Bolla, Bernardo Bonanni, Ake Borg, Hiltrud Brauch, Hermann Brenner, Ignacio Briceno, Annegien Broeks, Thomas Brüning, Barbara Burwinkel, Qiuyin Cai, Trinidad Caldés, Maria A Caligo, Ian Campbell, Sander Canisius, Daniele Campa, Brian D Carter, Jonathan Carter, Jose E Castelao, Jenny Chang-Claude, Stephen J Chanock, Hans Christiansen, Wendy K Chung, Kathleen B M Claes, Christine L Clarke, , , , Fergus J Couch, Angela Cox, Simon S Cross, Cezary Cybulski, Kamila Czene, Mary B Daly, Miguel de la Hoya, Kim De Leeneer, Joe Dennis, Peter Devilee, Orland Diez, Susan M Domchek, Thilo Dörk, Isabel Dos-Santos-Silva, Alison M Dunning, Miriam Dwek, Diana M Eccles, Bent Ejlertsen, Carolina Ellberg, Christoph Engel, Mikael Eriksson, Peter A Fasching, Olivia Fletcher, Henrik Flyger, Florentia Fostira, Eitan Friedman, Lin Fritschi, Debra Frost, Marike Gabrielson, Patricia A Ganz, Susan M Gapstur, Judy Garber, Montserrat García-Closas, José A García-Sáenz, Mia M Gaudet, Graham G Giles, Gord Glendon, Andrew K Godwin, Mark S Goldberg, David E Goldgar, Anna González-Neira, Mark H Greene, Jacek Gronwald, Pascal Guénel, Christopher A Haiman, Per Hall, Ute Hamann, Christopher Hake, Wei He, Jane Heyworth, Frans B L Hogervorst, Antoinette Hollestelle, Maartje J Hooning, Robert N Hoover, John L Hopper, Guanmengqian Huang, Peter J Hulick, Keith Humphreys, Evgeny N Imyanitov, , , , , Claudine Isaacs, Milena Jakimovska, Anna Jakubowska, Paul James, Ramunas Janavicius, Rachel C Jankowitz, Esther M John, Nichola Johnson, Vijai Joseph, Audrey Jung, Beth Y Karlan, Elza Khusnutdinova, Johanna I Kiiski, Irene Konstantopoulou, Vessela N Kristensen, Yael Laitman, Diether Lambrechts, Conxi

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Transcriptome-wide association study of breast cancer risk by estrogen-receptor status.

Genetic epidemiology : 442-468 : DOI : 10.1002/gepi.22288

Résumé

Previous transcriptome-wide association studies (TWAS) have identified breast cancer risk genes by integrating data from expression quantitative loci and genome-wide association studies (GWAS), but analyses of breast cancer subtype-specific associations have been limited. In this study, we conducted a TWAS using gene expression data from GTEx and summary statistics from the hitherto largest GWAS meta-analysis conducted for breast cancer overall, and by estrogen receptor subtypes (ER+ and ER-). We further compared associations with ER+ and ER- subtypes, using a case-only TWAS approach. We also conducted multigene conditional analyses in regions with multiple TWAS associations. Two genes, STXBP4 and HIST2H2BA, were specifically associated with ER+ but not with ER- breast cancer. We further identified 30 TWAS-significant genes associated with overall breast cancer risk, including four that were not identified in previous studies. Conditional analyses identified single independent breast-cancer gene in three of six regions harboring multiple TWAS-significant genes. Our study provides new information on breast cancer genetics and

biology, particularly about genomic differences between ER+ and ER- breast cancer.

Carsten Janke, Maria M Magiera (2020 Feb 27)
The tubulin code and its role in controlling microtubule properties and functions.
Nature reviews. Molecular cell biology : DOI : 10.1038/s41580-020-0214-3

Résumé

Microtubules are core components of the eukaryotic cytoskeleton with essential roles in cell division, shaping, motility and intracellular transport. Despite their functional heterogeneity, microtubules have a highly conserved structure made from almost identical molecular building blocks: the tubulin proteins. Alternative tubulin isotypes and a variety of post-translational modifications control the properties and functions of the microtubule cytoskeleton, a concept known as the 'tubulin code'. Here we review the current understanding of the molecular components of the tubulin code and how they impact microtubule properties and functions. We discuss how tubulin isotypes and post-translational modifications control microtubule behaviour at the molecular level and how this translates into physiological functions at the cellular and organism levels. We then go on to show how fine-tuning of microtubule function by some tubulin modifications can affect homeostasis and how perturbation of this fine-tuning can lead to a range of dysfunctions, many of which are linked to human disease.

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.

Rodrigo Nalio Ramos, Céline Rodriguez, Margaux Hubert, Maude Ardin, Isabelle Treilleux, Carola H Ries, Emilie Lavergne, Sylvie Chabaud, Amélie Colombe, Olivier Trédan, Henrique Gomes Guedes, Fábio Laginha, Wilfrid Richer, Eliane Piaggio, José Alexandre M Barbuto, Christophe Caux, Christine Ménétrier-Caux, Nathalie Bendriss-Vermare (2020 Feb 22)
CD163 tumor-associated macrophage accumulation in breast cancer patients reflects both local differentiation signals and systemic skewing of monocytes.
Clinical & translational immunology : e1108 : DOI : 10.1002/cti2.1108

Résumé

The accumulation of tumor-associated macrophages (TAMs) is correlated with poor clinical outcome, but the mechanisms governing their differentiation from circulating monocytes remain unclear in humans.

Antoine Molaro, Harmit S Malik, Deborah Bourc'his (2020 Feb 21)
Dynamic evolution of de novo DNA methyltransferases in rodent and primate genomes.
Molecular biology and evolution : DOI : msaa044

Résumé

Transcriptional silencing of retrotransposons via DNA methylation is paramount for mammalian fertility and reproductive fitness. During germ cell development, most mammalian species utilize the de novo DNA methyltransferases DNMT3A and DNMT3B to establish DNA methylation patterns. However, many rodent species deploy a third enzyme, DNMT3C, to selectively methylate the promoters of young retrotransposon insertions in their germline. The evolutionary forces that shaped DNMT3C's unique function are unknown. Using a phylogenomic approach, we confirm here that Dnmt3C arose through a single duplication of Dnmt3B that occurred around 60Mya in the last common ancestor of muroid rodents. Importantly, we reveal that DNMT3C is composed of two independently evolving segments: the latter two-thirds has undergone recurrent gene conversion with Dnmt3B, whereas the N-terminus has instead evolved under strong diversifying selection. We hypothesize that positive selection of Dnmt3C is the result of an ongoing evolutionary arms race with young retrotransposon lineages in muroid genomes. Interestingly, although primates lack DNMT3C, we find that the N-terminus of DNMT3A has also evolved under diversifying selection. Thus, the N-termini of two independent de novo methylation enzymes have evolved under diversifying selection in rodents and primates. We hypothesize that repression of young retrotransposons might be driving the recurrent innovation of a functional domain in the N-termini on germline DNMT3s in mammals.

Mara De Martino, Mercedes Tkach, Sofía Bruni, Darío Rocha, María F Mercogliano, Mauro E Cenciarini, María F Chervo, Cecilia J Proietti, Florent Dingli, Damarys Loew, Elmer A Fernández, Patricia V Elizalde, Eliane Piaggio, Roxana Schillaci (2020 Feb 18)

Blockade of Stat3 oncogene addiction induces cellular senescence and reveals a cell-nonautonomous activity suitable for cancer immunotherapy.

Oncoimmunology : 1715767 : DOI : 10.1080/2162402X.2020.1715767

Résumé

Stat3 is constitutively activated in several tumor types and plays an essential role in maintaining their malignant phenotype and immunosupression. To take advantage of the promising antitumor activity of Stat3 targeting, it is vital to understand the mechanism by which Stat3 regulates both cell autonomous and non-autonomous processes. Here, we demonstrated that turning off Stat3 constitutive activation in different cancer cell types induces senescence, thus revealing their Stat3 addiction. Taking advantage of the senescence-associated secretory phenotype (SASP) induced by Stat3 silencing (SASP-siStat3), we designed an immunotherapy. The administration of SASP-siStat3 immunotherapy induced a strong inhibition of triple-negative breast cancer and melanoma growth associated with activation of CD4 + T and NK cells. Combining this immunotherapy with anti-PD-1 antibody resulted in survival improvement in mice bearing melanoma. The characterization of the SASP components revealed that type I IFN-related mediators, triggered by the activation of the cyclic GMP-AMP synthase DNA sensing pathway, are important for its immunosurveillance activity. Overall, our findings provided evidence that administration of SASP-siStat3 or low dose of Stat3-blocking agents would benefit patients with Stat3-addicted tumors to unleash an antitumor immune response and to improve the effectiveness of immune checkpoint inhibitors.

Luigia Pace, Sebastian Amigorena (2020 Feb 18)

Epigenetics of T cell fate decision.

Current opinion in immunology : 43-50 : DOI : S0952-7915(20)30002-9

Résumé

The changes of transcription factor activity and chromatin dynamics guide functional differentiation of T cell subsets, including commitment to short-lived effectors and long-term survival of memory T cells. Understanding the lineage relationships among the different stages of effector and memory differentiation has profound therapeutic implications for the development of new vaccine and immunotherapy protocols. Here we review the contribution of chromatin architecture to T cell specification, focusing on the interplay between epigenetic changes and transcriptional programs linked to T cell plasticity, commitment and memory. We will also discuss the translational implications of epigenetic control in the context of infections and cancer.

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 : 30 : 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.

Satish Bodakuntla, Anne Schnitzler, Cristopher Villablanca, Christian Gonzalez-Billault, Ivan Bieche, Carsten Janke, Maria M Magiera (2020 Feb 13)

Tubulin polyglutamylation is a general traffic-control mechanism in hippocampal neurons.

Journal of cell science : DOI : jcs241802

Résumé

Neurons are highly complex cells that heavily rely on intracellular transport to distribute a range of functionally essential cargoes within the cell. Post-translational modifications of tubulin are emerging as mechanisms for regulating microtubule functions, but their impact on neuronal transport is only marginally understood. Here, we have systematically studied the impact of post-translational polyglutamylation on axonal transport. In cultured hippocampal neurons, deletion of a single deglutamylase, CCP1 (also known as AGTPBP1), is sufficient to induce abnormal accumulation of polyglutamylation, i.e. hyperglutamylation. We next investigated how hyperglutamylation affects axonal transport of a range of functionally different neuronal cargoes: mitochondria, lysosomes, LAMP1 endosomes and BDNF vesicles. Strikingly, we found a reduced motility for all these cargoes, suggesting that polyglutamylation could act as a regulator of cargo transport in neurons. This, together with the recent discovery that hyperglutamylation induces neurodegeneration, makes it likely that perturbed neuronal trafficking could be one of the central molecular causes underlying this novel type of degeneration.This article has an associated First Person interview with the

first author of the paper.

Emmanuelle Jeannot, Lauren Darrigues, Marc Michel, Marc-Henri Stern, Jean-Yves Pierga, Aurore Rampanou, Samia Melaabi, Camille Benoist, Ivan Bièche, Anne Vincent-Salomon, Radouane El Ayachy, Aurélien Noret, Nicolas Epaillard, Luc Cabel, François-Clément Bidard, Charlotte Proudhon (2020 Feb 12)

A single droplet digital PCR for ESR1 activating mutations detection in plasma.

Oncogene : 2987-2995 : DOI : 10.1038/s41388-020-1174-y

Résumé

Activating mutations in the estrogen receptor 1 (ESR1) gene confer resistance to aromatase inhibitors (AI), and may be targeted by selective estrogen receptor downregulators. We designed a multiplex droplet digital PCR (ddPCR), which combines a drop-off assay, targeting the clustered hotspot mutations found in exon 8, with an unconventional assay interrogating the E380Q mutation in exon 5. We assessed its sensitivity in vitro using synthetic oligonucleotides, harboring E380Q, L536R, Y537C, Y537N, Y537S, or D538G mutations. Further validation was performed on plasma samples from a prospective study and compared with next generation sequencing (NGS) data. The multiplex ESR1-ddPCR showed a high sensitivity with a limit of detection ranging from 0.07 to 0.19% in mutant allele frequency. The screening of plasma samples from patients with AI-resistant metastatic breast cancer identified ESR1 mutations in 29% of them, all mutations being confirmed by NGS. In addition, this test identifies patients harboring polyclonal alterations. Furthermore, the monitoring of circulating tumor DNA using this technique during treatment follow-up predicts the clinical benefit of palbociclib-fulvestrant. The multiplex ESR1-ddPCR detects, in a single reaction, the most frequent ESR1 activating mutations with good sensitivity. This method allows real-time liquid biopsy for ESR1 mutation monitoring in large cohorts of patients.

Anna Barg-Wojas, Jakub Muraszko, Karol Kramarz, Kamila Schirmeisen, Gabriela Baranowska, Antony M Carr, Dorota Dziadkowiec (2020 Feb 10)

DNA translocases Rrp1 and Rrp2 have distinct roles at centromeres and telomeres that ensure genome stability.

Journal of cell science : DOI : jcs230193

Résumé

The regulation of telomere and centromere structure and function is essential for maintaining genome integrity. Rrp1 and Rrp2 are orthologues of Uls1, a SWI2/SNF2 DNA translocase and SUMO-targeted ubiquitin ligase. Here, we show that Rrp1 or Rrp2 overproduction leads to chromosome instability and growth defects, a reduction in global histone levels and mislocalisation of centromere-specific histone Cnp1. These phenotypes depend on putative DNA translocase activities of Rrp1 and Rrp2, suggesting that Rrp1 and Rrp2 may be involved in modulating nucleosome dynamics. Furthermore, we confirm that

Rrp2, but not Rrp1, acts at telomeres, reflecting a previously described interaction between Rrp2 and Top2. In conclusion, we identify roles for Rrp1 and Rrp2 in maintaining centromere function by modulating histone dynamics, contributing to the preservation of genome stability during vegetative cell growth.

Diana Bello Roufai, François-Clément Bidard (2020 Feb 5)

Impact of circulating tumor DNA early detection and serial monitoring in the management of stage I to III colorectal cancer.

Annals of translational medicine : S315 : DOI : 10.21037/atm.2019.10.30

Résumé

Alejandro Mazal, Yolanda Prezado, Carme Ares, Ludovic de Marzi, Annalisa Patriarca, Raymond Miralbell, Vincent Favaudon (2020 Feb 1)

FLASH and minibeams in radiation therapy: the effect of microstructures on time and space and their potential application to protontherapy.

The British journal of radiology : 20190807 : DOI : 10.1259/bjr.20190807

Résumé

After years of lethargy, studies on two non-conventional microstructures in time and space of the beams used in radiation therapy are enjoying a huge revival. The first effect called « FLASH » is based on very high dose-rate irradiation (pulse amplitude ≥10 Gy/s), short beam-on times (≤100 ms) and large single doses (≥10 Gy) as experimental parameters established so far to give biological and potential clinical effects. The second effect relies on the use of arrays of minibeams (0.5-1 mm, spaced 1-3.5 mm). Both approaches have been shown to protect healthy tissues as an endpoint that must be clearly specified and could be combined with each other (minibeams under FLASH conditions). FLASH depends on the presence of oxygen and could proceed from the chemistry of peroxyradicals and a reduced incidence on DNA and membrane damage. Minibeams action could be based on abscopal effects, cell signalling and/or migration of cells between « valleys and hills » present in the non-uniform irradiation field as well as faster repair of vascular damage. Both effects are expected to maintain intact the tumour control probability and might even preserve antitumoural immunological reactions. FLASH experiments involving Zebrafish, mice, pig and cats have been done with electron beams, while minibeams are an intermediate approach between X-GRID and synchrotron X-ray microbeams radiation. Both have an excellent rationale to converge and be applied with proton beams, combining focusing properties and high dose rates in the beam path of pencil beams, and the inherent advantage of a controlled limited range. A first treatment with electron FLASH (cutaneous lymphoma) has recently been achieved, but clinical trials have neither been presented for FLASH with protons, nor under the minibeam conditions. Better understanding of physical, chemical and biological mechanisms of both effects is essential to optimize the technical developments and devise clinical trials.

Lambert, S. Borde, V. Charbonnier, J. B. Dantzer, F. Espeli, O. Guirouilh-Barbat, J. Llorente, B. Legube, G. Prioleau, M. N. Radicella, P. (2020 Feb 1)

Des mécanismes moléculaires aux applications cliniques. L'essentiel du Colloque Réplication-Réparation-Recombinaison 2019

Bull Cancer : 283-287 : DOI : 10.1016/j.bulcan.2020.01.003

Résumé

https://www.sciencedirect.com/science/article/abs/pii/S0007455120300060?via%3Dihub