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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.

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.

Pace L1, Amigorena S2. (2020 Feb 14)
Epigenetics of T cell fate decision.
Current opinion in immunology : 63 : Curr Opin Immunol. 2020 Feb 14;63:43-50. doi: 10.1016/j.coi.2020.01.002. [Epub ahead of print] : 43,50 : DOI : 10.1016/j.coi.2020.01.002

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.

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.

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.

Ramos RN1,2, Rodriguez C1, Hubert M1, Ardin M1, Treilleux I3, Ries CH4, Lavergne E3, Chabaud S3, Colombe A3, Trédan O3, Guedes HG5, Laginha F5, Richer W6,7, Piaggio E6,7, Barbuto JAM2, Caux C1, Ménétrier-Caux C1, Bendriss-Vermare N1. (2020 Feb 13)

CD163+ tumor-associated macrophage accumulation in breast cancer patients reflects both local differentiation signals and systemic skewing of monocytes.

Clinical ans translationnal immunology : 9(2) : DOI : 10.1002/cti2.1108

Résumé

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

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.

Tim Schneider, Ludovic De Marzi, Annalisa Patriarca, Yolanda Prezado (2020 Jan 30)
Advancing proton minibeam radiation therapy: magnetically focussed proton minibeams at a clinical centre.
Scientific reports : 1384 : DOI : 10.1038/s41598-020-58052-0

Résumé

Proton minibeam radiation therapy (pMBRT) is a novel therapeutic strategy that has proven

to significantly increase dose tolerances and sparing of normal tissue. It uses very narrow proton beams (diameter ≤1 mm), roughly one order of magnitude smaller than state-of-the-art pencil beams. The current implementation of pMBRT with mechanical collimators is suboptimal as it is inflexible, decreases efficiency and produces additional secondary neutrons. As a potential solution, we explore in this article minibeam generation through magnetic focussing and investigate possibilities for the integration of such a technique at existing clinical centres. For this, a model of the pencil beam scanning (PBS) nozzle and beam at the Orsay Proton Therapy Centre was established and Monte Carlo simulations were performed to determine its focussing capabilities. Moreover, various modifications of the nozzle geometry were considered. It was found that the PBS nozzle in its current state is not suitable for magnetic minibeam generation. Instead, a new, optimised nozzle design has been proposed and conditions necessary for minibeam generation were benchmarked. In addition, dose simulations in a water phantom were performed which showed improved dose distributions compared to those obtained with mechanical collimators.

De Martino M1, Tkach M2, Bruni S1, Rocha D3, Mercogliano MF1, Cenciarini ME1, Chervo MF1, Proietti CJ1, Dingli F4, Loew D4, Fernández EA3,5, Elizalde PV1, Piaggio E2, Schillaci R1. (2020 Jan 29)

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

Oncoimmunology. : 9(1) : DOI : 10.1080/2162402X.2020.1715767

Résumé

Johnson Courtney R. , Steingesser Marc G., Khan Anum, Gladfelter Amy, Bertin Aurélie, McMurray Michael A. (2020 Jan 28)

Guanidine hydrochloride reactivates an ancient septin hetero-oligomer assembly pathway in budding yeast

eLife : eLife 2020;9:e54355 : DOI : DOI: 10.7554/eLife.54355

Résumé

Septin proteins evolved from ancestral GTPases and co-assemble into hetero-oligomers and cytoskeletal filaments. In *Saccharomyces cerevisiae*, five septins comprise two species of hetero-octamers, Cdc11/Shs1–Cdc12–Cdc3–Cdc10–Cdc10–Cdc3–Cdc12–Cdc11/Shs1. Slow GTPase activity by Cdc12 directs the choice of incorporation of Cdc11 vs Shs1, but many septins, including Cdc3, lack GTPase activity. We serendipitously discovered that guanidine hydrochloride rescues septin function in *cdc10* mutants by promoting assembly of non-native Cdc11/Shs1–Cdc12–Cdc3–Cdc3–Cdc12–Cdc11/Shs1 hexamers. We provide evidence that in *S. cerevisiae* Cdc3 guanidinium occupies the site of a 'missing' Arg side chain found in other fungal species where (i) the Cdc3 subunit is an active GTPase and (ii) Cdc10-less hexamers natively co-exist with octamers. We propose that guanidinium reactivates a latent septin assembly pathway that was suppressed during fungal evolution in order to restrict assembly to octamers. Since homodimerization by a GTPase-active human septin also creates

hexamers that exclude Cdc10-like central subunits, our new mechanistic insights likely apply throughout phylogeny.

Nishit Srivastava, David Traynor, Matthieu Piel, Alexandre J Kabla, Robert R Kay (2020 Jan 23)
Pressure sensing through Piezo channels controls whether cells migrate with blebs or pseudopods.
Proceedings of the National Academy of Sciences of the United States of America : DOI : 201905730

Résumé

Blebs and pseudopods can both power cell migration, with blebs often favored in tissues, where cells encounter increased mechanical resistance. To investigate how migrating cells detect and respond to mechanical forces, we used a « cell squasher » to apply uniaxial pressure to cells chemotaxing under soft agarose. As little as 100 Pa causes a rapid (<10 s), sustained shift to movement with blebs rather than pseudopods. Cells are flattened under load and lose volume; the actin cytoskeleton is reorganized, with myosin II recruited to the cortex, which may pressurize the cytoplasm for blebbing. The transition to bleb-driven motility requires extracellular calcium and is accompanied by increased cytosolic calcium. It is largely abrogated in cells lacking the Piezo stretch-operated channel; under load, these cells persist in using pseudopods and chemotax poorly. We propose that migrating cells sense pressure through Piezo, which mediates calcium influx, directing movement with blebs instead of pseudopods.

Floriane Pelon, Brigitte Bourachot, Yann Kieffer, Ilaria Magagna, Fanny Mermet-Meillon, Ana Costa, Anne-Marie Givel, Youmna Attieh, Jorge Barbazan, Laetitia Fuhrmann, Stéphanie Descroix, Danijela Vignjevic, Pascal Silberzan, Isabelle Bonnet, Claire Bonneau, Maria Carla Parrini, Anne Vincent-Salomon & Fatima Mechta-Grigoriou (2020 Jan 21)
Cancer-associated fibroblast heterogeneity in axillary lymph nodes drives metastases in breast cancer through complementary mechanisms
Nature Communication : 11 : 1-20 : DOI : 10.1038/s41467-019-14134-w

Résumé

Although fibroblast heterogeneity is recognized in primary tumors, both its characterization in and its impact on metastases remain unknown. Here, combining flow cytometry, immunohistochemistry and RNA-sequencing on breast cancer samples, we identify four Cancer-Associated Fibroblast (CAF) subpopulations in metastatic lymph nodes (LN). Two myofibroblastic subsets, CAF-S1 and CAF-S4, accumulate in LN and correlate with cancer cell invasion. By developing functional assays on primary cultures, we demonstrate that these subsets promote metastasis through distinct functions. While CAF-S1 stimulate cancer cell migration and initiate an epithelial-to-mesenchymal transition through CXCL12 and TGFβ pathways, highly contractile CAF-S4 induce cancer cell invasion in 3-dimensions via NOTCH

signaling. Patients with high levels of CAFs, particularly CAF-S4, in LN at diagnosis are prone to develop late distant metastases. Our findings suggest that CAF subset accumulation in LN is a prognostic marker, suggesting that CAF subsets could be examined in axillary LN at diagnosis.

Johnson JS1, De Veaux N2, Rives AW2, Lahaye X3, Lucas SY4, Perot BP5, Luka M5, Garcia-Paredes V5, Amon LM4, Watters A2, Abdessalem G5, Aderem A6, Manel N3, Littman DR7, Bonneau R8, Ménager MM9. (2020 Jan 21)

A Comprehensive Map of the Monocyte-Derived Dendritic Cell Transcriptional Network Engaged upon Innate Sensing of HIV.

Cell reports : 30 : Cell Rep. 2020 Jan 21;30(3):914-931.e9. doi: 10.1016/j.celrep.2019.12.054. : 914,931 : DOI : 10.1016/j.celrep.2019.12.054

Résumé

Transcriptional programming of the innate immune response is pivotal for host protection. However, the transcriptional mechanisms that link pathogen sensing with innate activation remain poorly understood. During HIV-1 infection, human dendritic cells (DCs) can detect the virus through an innate sensing pathway, leading to antiviral interferon and DC maturation. Here, we develop an iterative experimental and computational approach to map the HIV-1 innate response circuitry in monocyte-derived DCs (MDDCs). By integrating genome-wide chromatin accessibility with expression kinetics, we infer a gene regulatory network that links 542 transcription factors with 21,862 target genes. We observe that an interferon response is required, yet insufficient, to drive MDDC maturation and identify PRDM1 and RARA as essential regulators of the interferon response and MDDC maturation, respectively. Our work provides a resource for interrogation of regulators of HIV replication and innate immunity, highlighting complexity and cooperativity in the regulatory circuit controlling the response to infection.

Xavier Sabaté-Cadenas, Alena Shkumatava (2020 Jan 18)

In-Cell Discovery of RNA-Protein Interactions.

Trends in biochemical sciences : DOI : S0968-0004(19)30264-6

Résumé