Année de publication : 2019

Ruffin N1, Gea-Mallorquí E1, Brouiller F1, Jouve M2, Silvin A1,3, See P3, Dutertre CA3,4, Ginhoux F5, Benaroch P6. (2020 Mar 22)

Constitutive Siglec-1 expression confers susceptibility to HIV-1 infection of human dendritic cell precursors.

Proceedings of the National Academy of Sciences : 116 : Proc Natl Acad Sci U S A. 2019 Oct 22;116(43):21685-21693. doi: 10.1073/pnas.1911007116. Epub 2019 Oct 7. : 21685,21693 : DOI : 10.1073/pnas.1911007116

Résumé

The human dendritic cell (DC) lineage has recently been unraveled by high-dimensional mapping, revealing the existence of a discrete new population of blood circulating DC precursors (pre-DCs). Whether this new DC population possesses specific functional features as compared to the other blood DC subset upon pathogen encounter remained to be evaluated. A unique feature of pre-DCs among blood DCs is their constitutive expression of the viral adhesion receptor Siglec-1. Here, we show that pre-DCs, but not other blood DC subsets, are susceptible to infection by HIV-1 in a Siglec-1-dependent manner. Siglec-1 mediates pre-DC infection of CCR5- and CXCR4-tropic strains. Infection of pre-DCs is further enhanced in the presence of HIV-2/SIVmac Vpx, indicating that Siglec-1 does not counteract restriction factors such as SAMHD1. Instead, Siglec-1 promotes attachment and fusion of viral particles. HIV-1-infected pre-DCs produce new infectious viral particles that accumulate in intracellular compartments reminiscent of the virus-containing compartment of macrophages. Pre-DC activation by toll-like receptor (TLR) ligands induces an antiviral state that inhibits HIV-1 fusion and infection, but Siglec-1 remains functional and mediates replication-independent transfer of HIV-1 to activated primary T lymphocytes. Altogether, Siglec-1-mediated susceptibility to HIV-1 infection of pre-DCs constitutes a unique functional feature that might represent a preferential relationship of this emerging cell type with viruses.

Année de publication : 2020

Abhijit Saha, Patricia Duchambon, Vanessa Masson, Damarys Loew, Sophie Bombard, Marie-Paule Teulade-Fichou (2020 Mar 20)

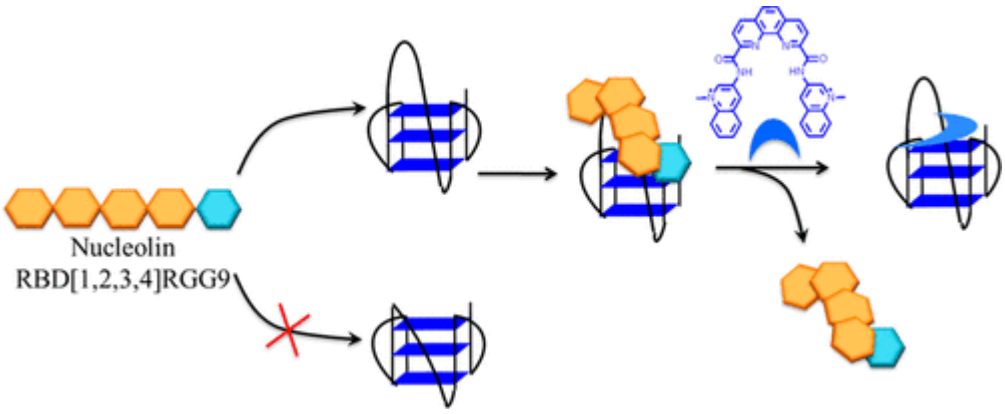
Nucleolin Discriminates Drastically between Long-Loop and Short-Loop Quadruplexes.

Biochemistry : 59 : 1261-1272 : DOI : 10.1021/acs.biochem.9b01094

Résumé

We investigate herein the interaction between nucleolin (NCL) and a set of G4 sequences derived from the CEB25 human minisatellite that adopt a parallel topology while differing in the length of the central loop (from nine nucleotides to one nucleotide). It is revealed that NCL strongly binds to long-loop (five to nine nucleotides) G4 while interacting weakly with

the shorter variants (loop with fewer than three nucleotides). Photo-cross-linking experiments using 5-bromo-2′-deoxyuridine (BrU)-modified sequences further confirmed the loop-length dependency, thereby indicating that the WT-CEB25-L191 (nine-nucleotide loop) is the best G4 substrate. Quantitative proteomic analysis (LC-MS/MS) of the product(s) obtained by photo-cross-linking NCL to this sequence enabled the identification of one contact site corresponding to a 15-amino acid fragment located in helix α2 of RNA binding domain 2 (RBD2), which sheds light on the role of this structural element in G4-loop recognition. Then, the ability of a panel of benchmark G4 ligands to prevent the NCL-G4 interaction was explored. It was found that only the most potent ligand PhenDC3 can inhibit NCL binding, thereby suggesting that the terminal guanine quartet is also a strong determinant of G4 recognition, putatively through interaction with the RGG domain. This study describes the molecular mechanism by which NCL recognizes G4-containing long loops and leads to the proposal of a model implying a concerted action of RBD2 and RGG domains to achieve specific G4 recognition via a dual loop-quartet interaction.



Samah Matmati, Sarah Lambert, Vincent Géli, Stéphane Coulon (2020 Mar 12)
Telomerase Repairs Collapsed Replication Forks at Telomeres.
Cell reports : 3312-3322.e3 : DOI : S2211-1247(20)30233-3

Résumé

Telomeres are difficult-to-replicate sites whereby replication itself may threaten telomere integrity. We investigate, in fission yeast, telomere replication dynamics in telomerase-negative cells to unmask problems associated with telomere replication. Two-dimensional gel analysis reveals that replication of telomeres is severely impaired and correlates with an accumulation of replication intermediates that arises from stalled and collapsed forks. In the absence of telomerase, Rad51, Mre11-Rad50-Nbs1 (MRN) complex, and its co-factor CtIP become critical to maintain telomeres, indicating that homologous recombination processes these intermediates to facilitate fork restart. We further show that a catalytically dead mutant of telomerase prevents Ku recruitment to telomeres, suggesting that telomerase and Ku both compete for the binding of telomeric-free DNA ends that are likely to originate from a reversed fork. We infer that Ku removal at collapsed telomeric forks allows telomerase to repair broken telomeres, thereby shielding telomeres from homologous recombination.

Paudel B.P., Moye A.L., Assi H.A., El-Khoury R., Cohen S.B., Birrento M.L., Samosorn S., Intharapichai K., Tomlinson C.G., Teulade-Fichou M.P., Gonz'alez C., Beck J.L., Damha M.J., van Oijen A.M., Bryan T.M. (2020 Feb 27)

A mechanism for the extension and unfolding of parallel telomeric G-quadruplexes by human telomerase at single-molecule resolution

bioRxiv : DOI : 10.1101/2020.02.26.965269

Résumé

Telomeric G-quadruplexes (G4) were long believed to form a protective structure at telomeres, preventing their extension by the ribonucleoprotein telomerase. Contrary to this belief, we have previously demonstrated that parallel-stranded conformations of telomeric G4 can be extended by human and ciliate telomerase. However, a mechanistic understanding of the interaction of telomerase with structured DNA remained elusive. Here, we use single-molecule fluorescence resonance energy transfer (smFRET) microscopy and bulk-phase enzymology to propose a mechanism for the resolution and extension of parallel G4 by telomerase. Binding is initiated by the RNA template of telomerase interacting with the G-quadruplex; nucleotide addition then proceeds to the end of the RNA template. It is only through the large conformational change of translocation following synthesis that the G-quadruplex structure is completely unfolded to a linear product. Surprisingly, parallel G4 stabilization with either small molecule ligands or by chemical modification does not always inhibit G4 unfolding and extension by telomerase. These data reveal that telomerase is a parallel G-quadruplex resolvase.

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.

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.

Année de publication : 2019

Manel N1, Di Santo JP2. (2020 Feb 2)
Editorial overview: Pillars of innate immunity: constantly learning and trying to remember. Manel N1,
Current opinion in immunology : 56 : DOI : 10.1016/j.coi.2019.03.002

Résumé

Année de publication : 2020

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

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.