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Sebastian Müller, Fabien Sindikubwabo , Tatiana Cañeque, Anne Lafon, Antoine Versini, Bérangère Lombard, Damarys Loew, Ting-Di Wu, Christophe Ginestier, Emmanuelle Charafe-Jauffret, Adeline Durand, Céline Vallot, Sylvain Baulande, Nicolas Servant, Raphaël Rodriguez (2020 Oct 1)
CD44 regulates epigenetic plasticity by mediating iron endocytosis
Nature Chemistry : 12 : 929-938 : DOI : 10.1038/s41557-020-0513-5

Résumé

Charlotte Lamirault, Elise Brisebard, Annalisa Patriarca, Marjorie Juchaux, Delphine Crepin, Dalila Labiod, Frederic Pouzoulet, Catherine Sebrie, Laurene Jourdain, Marine Le Dudal, David Hardy, Ludovic de Marzi, Remi Dendale, Gregory Jouvion, Yolanda Prezado (2020 Sep 29)
Spatially Modulated Proton Minibeams Results in the Same Increase of Lifespan as a Uniform Target Dose Coverage in F98-Glioma-Bearing Rats.
Radiation research : DOI : 10.1667/RADE-19-00013.1

Résumé

Proton minibeam radiation therapy (pMBRT) is a new approach in proton radiotherapy, by which a significant increase in the therapeutic index has already been demonstrated in RG2 glioma-bearing rats. In the current study we investigated the response of other types of glioma (F98) and performed a comparative evaluation of tumor control effectiveness by pMBRT (with different levels of dose heterogeneity) versus conventional protons. The results of our study showed an equivalent increase in the lifespan for all evaluated groups (conventional proton irradiation and pMBRT) and no significant differences in the histopathological analysis of the tumors or remaining brain tissue. The reduced long-term toxicity observed with pMBRT in previous evaluations at the same dose suggests a possible use of pMBRT to treat glioma with less side effects while ensuring the same tumor control achieved with standard proton therapy.

Daniele Fachinetti, Hiroshi Masumoto, Natalay Kouprina (2020 Sep 27)
Artificial chromosomes.
Experimental cell research : 112302 : DOI : S0014-4827(20)30551-6

Résumé

Gururaj Rao Kidiyoor, Qingsen Li, Giulia Bastianello, Christopher Bruhn, Irene Giovannetti, Adhil Mohamood, Galina V Beznoussenko, Alexandre Mironov, Matthew Raab, Matthieu Piel, Umberto Restuccia, Vittoria Matafora, Angela Bachi, Sara Barozzi, Dario Parazzoli, Emanuela Frittoli,

Andrea Palamidessi, Tito Panciera, Stefano Piccolo, Giorgio Scita, Paolo Maiuri, Kristina M Havas, Zhong-Wei Zhou, Amit Kumar, Jiri Bartek, Zhao-Qi Wang, Marco Foiani (2020 Sep 25)

ATR is essential for preservation of cell mechanics and nuclear integrity during interstitial migration.

Nature communications : 4828 : DOI : 10.1038/s41467-020-18580-9

Résumé

ATR responds to mechanical stress at the nuclear envelope and mediates envelope-associated repair of aberrant topological DNA states. By combining microscopy, electron microscopic analysis, biophysical and in vivo models, we report that ATR-defective cells exhibit altered nuclear plasticity and YAP delocalization. When subjected to mechanical stress or undergoing interstitial migration, ATR-defective nuclei collapse accumulating nuclear envelope ruptures and perinuclear cGAS, which indicate loss of nuclear envelope integrity, and aberrant perinuclear chromatin status. ATR-defective cells also are defective in neuronal migration during development and in metastatic dissemination from circulating tumor cells. Our findings indicate that ATR ensures mechanical coupling of the cytoskeleton to the nuclear envelope and accompanying regulation of envelope-chromosome association. Thus the repertoire of ATR-regulated biological processes extends well beyond its canonical role in triggering biochemical implementation of the DNA damage response.

Václav Brázda, Yu Luo, Martin Bartas, Patrik Kaura, Otilia Porubiaková, Jiří Šťastný, Petr Pečinka, Daniela Verga, Violette Da Cunha, Tomio S Takahashi, Patrick Forterre, Hannu Myllykallio, Miroslav Fojta, Jean-Louis Mergny (2020 Sep 24)

G-Quadruplexes in the Archaea Domain.

Biomolecules : 10 : 1349 : DOI : 10.3390/biom10091349

Résumé

The importance of unusual DNA structures in the regulation of basic cellular processes is an emerging field of research. Amongst local non-B DNA structures, G-quadruplexes (G4s) have gained in popularity during the last decade, and their presence and functional relevance at the DNA and RNA level has been demonstrated in a number of viral, bacterial, and eukaryotic genomes, including humans. Here, we performed the first systematic search of G4-forming sequences in all archaeal genomes available in the NCBI database. In this article, we investigate the presence and locations of G-quadruplex forming sequences using the G4Hunter algorithm. G-quadruplex-prone sequences were identified in all archaeal species, with highly significant differences in frequency, from 0.037 to 15.31 potential quadruplex sequences per kb. While G4 forming sequences were extremely abundant in (strikingly, more than 50% of the isolate WYZ-LMO6 genome is a potential part of a G4-motif), they were very rare in the phylum. The presence of G-quadruplex forming sequences does not follow a random distribution with an over-representation in non-coding RNA, suggesting possible roles for ncRNA regulation. These data illustrate the unique and non-random localization of G-quadruplexes in Archaea.

Aleksandra S Chikina, Francesca Nadalin, Mathieu Maurin, Mabel San-Roman, Thibault Thomas-Bonafos, Xin V Li, Sonia Lameiras, Sylvain Baulande, Sandrine Henri, Bernard Malissen, Livia Lacerda Mariano, Jorge Barbazan, J Magarian Blander, Iliyan D Iliev, Danijela Matic Vignjevic, Ana-Maria Lennon-Duménil (2020 Sep 24)

Macrophages Maintain Epithelium Integrity by Limiting Fungal Product Absorption.

Cell : 411-428.e16 : DOI : S0092-8674(20)31090-4

Résumé

The colon is primarily responsible for absorbing fluids. It contains a large number of microorganisms including fungi, which are enriched in its distal segment. The colonic mucosa must therefore tightly regulate fluid influx to control absorption of fungal metabolites, which can be toxic to epithelial cells and lead to barrier dysfunction. How this is achieved remains unknown. Here, we describe a mechanism by which the innate immune system allows rapid quality check of absorbed fluids to avoid intoxication of colonocytes. This mechanism relies on a population of distal colon macrophages that are equipped with « balloon-like » protrusions (BLPs) inserted in the epithelium, which sample absorbed fluids. In the absence of macrophages or BLPs, epithelial cells keep absorbing fluids containing fungal products, leading to their death and subsequent loss of epithelial barrier integrity. These results reveal an unexpected and essential role of macrophages in the maintenance of colon-microbiota interactions in homeostasis. VIDEO ABSTRACT.

Arijita Chakraborty, Piroon Jenjaroenpun, Jing Li, Sami El Hilali, Andrew McCulley, Brian Haarer, Elizabeth A Hoffman, Aimee Belak, Audrey Thorland, Heidi Hehnly, Carl Schildkraut, Chun-Long Chen, Vladimir A Kuznetsov, Wenyi Feng (2020 Sep 23)

Replication Stress Induces Global Chromosome Breakage in the Fragile X Genome.

Cell reports : 108179 : DOI : S2211-1247(20)31168-2

Résumé

Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by mutations in the FMR1 gene and deficiency of a functional FMRP protein. FMRP is known as a translation repressor whose nuclear function is not understood. We investigated the global impact on genome stability due to FMRP loss. Using Break-seq, we map spontaneous and replication stress-induced DNA double-strand breaks (DSBs) in an FXS patient-derived cell line. We report that the genomes of FXS cells are inherently unstable and accumulate twice as many DSBs as those from an unaffected control. We demonstrate that replication stress-induced DSBs in FXS cells colocalize with R-loop forming sequences. Exogenously expressed FMRP in FXS fibroblasts ameliorates DSB formation. FMRP, not the I304N mutant, abates R-loop-induced DSBs during programmed replication-transcription conflict. These results suggest that FMRP is a genome maintenance protein that prevents R-loop accumulation. Our study provides insights into the etiological basis for FXS.

Sebastiaan Jw van den Berg, Lars Et Jansen (2020 Sep 22)
Centromeres: genetic input to calibrate an epigenetic feedback loop.
The EMBO journal : e106638 : DOI : 10.15252/embj.2020106638

Résumé

Centromeres are chromatin domains maintained by a self-templating feedback loop based on nucleosomes bearing the histone H3 variant CENP-A. The underlying centromeric DNA sequence is largely dispensable, yet paradoxically, it has highly conserved features. Hoffmann et al (2020) now uncover that when the epigenetic chromatin cycle falters, a genetically hardwired mechanism offers robustness to a dynamic epigenetic feedback loop ensuring long-term centromere inheritance.

Laura Mouton, Monica Ribeiro, Marc-André Mouthon, Fawzi Boumezbeur, Denis Le Bihan, Damien Ricard, François D. Boussin, Pierre Verrelle (2020 Sep 18)
Experimental and Preclinical Tools to Explore the Main Neurological Impacts of Brain Irradiation: Current Insights and Perspectives
Brain Tumors : 158 : 239-261 : DOI : 10.1007/978-1-0716-0856-2_11

Résumé

Radiation therapy is a powerful tool in the treatment of primary and metastatic cancers of the brain. However, brain tissue tolerance is limited, and radiation doses must be tailored to minimize deleterious effects on the nervous system. Due to improved treatments, including radiotherapy techniques, many patients with brain tumors survive longer, but they experience late effects of radiotherapy, especially cognitive decline, for which no efficient treatment is currently available. Improving the prevention and treatment of radiation-induced neurological defects first needs to better characterize radiation injuries in brain cells and tissues. Rodent models have been widely used for this.

Here, observations from patients will be reviewed briefly as an introduction, mainly regarding clinical cognitive defects and anatomical alterations using magnetic resonance imaging (MRI). This limited descriptive clinical knowledge addresses many questions that arise in preclinical models regarding understanding the mechanism of radiation-induced brain dysfunction. From this perspective, we next present methods to characterize radiation-induced neurogenesis alterations in adult mice and then detail how MRI could be used as a powerful tool to explore these alterations.

Sebastian Hoffmann, Helena M Izquierdo, Riccardo Gamba, Florian Chardon, Marie Dumont, Veer Keizer, Solène Hervé, Shannon M McNulty, Beth A Sullivan, Nicolas Manel, Daniele Fachinetti (2020 Sep 18)
A genetic memory initiates the epigenetic loop necessary to preserve

centromere position.
The EMBO journal : e105505 : DOI : 10.15252/embj.2020105505

Résumé

Centromeres are built on repetitive DNA sequences (CenDNA) and a specific chromatin enriched with the histone H3 variant CENP-A, the epigenetic mark that identifies centromere position. Here, we interrogate the importance of CenDNA in centromere specification by developing a system to rapidly remove and reactivate CENP-A (CENP-A). Using this system, we define the temporal cascade of events necessary to maintain centromere position. We unveil that CENP-B bound to CenDNA provides memory for maintenance on human centromeres by promoting de novo CENP-A deposition. Indeed, lack of CENP-B favors neocentromere formation under selective pressure. Occasionally, CENP-B triggers centromere re-activation initiated by CENP-C, but not CENP-A, recruitment at both ectopic and native centromeres. This is then sufficient to initiate the CENP-A-based epigenetic loop. Finally, we identify a population of CENP-A-negative, CENP-B/C-positive resting CD4 T cells capable to re-express and reassembles CENP-A upon cell cycle entry, demonstrating the physiological importance of the genetic memory.

Raquel Pérez-Palacios, Patricia Fauque, Aurélie Teissandier, Déborah Bourc'his (2020 Sep 18)
Deciphering the Early Mouse Embryo Transcriptome by Low-Input RNA-Seq.
Methods in molecular biology (Clifton, N.J.) : 189-205 : DOI : 10.1007/978-1-0716-0958-3_13

Résumé

Early preimplantation embryos are precious and scarce samples that contain limited numbers of cells, which can be problematic for quantitative gene expression analyses. Nonetheless, low-input genome-wide techniques coupled with cDNA amplification steps have become a gold standard for RNA profiling of as minimal as a single blastomere. Here, we describe a single-cell/single-embryo RNA sequencing (RNA-seq) method, from embryo collection to sample validation steps prior to DNA library preparation and sequencing. Key quality controls and external Spike-In normalization approaches are also detailed.

Marie Dumont, Daniele Fachinetti (2020 Sep 18)
Centromere strength: just a sense of proportion.
Molecular & cellular oncology : 1742063 : DOI : 10.1080/23723556.2020.1742063

Résumé

The overall structure and composition of human centromeres have been well reported, but how these elements vary between individual chromosomes and influence the chromosome-specific behavior during mitosis remains untested. In our study, we discover the existence of heterogeneity of centromeric DNA features that dictates the chromosome segregation fidelity during mitosis.

Gabriele Manzella, Leonie D Schreck, Willemijn B Breunis, Jan Molenaar, Hans Merks, Frederic G Barr, Wenyue Sun, Michaela Römmele, Luduo Zhang, Joelle Tchinda, Quy A Ngo, Peter Bode, Olivier Delattre, Didier Surdez, Bharat Rekhi, Felix K Niggli, Beat W Schäfer, Marco Wachtel (2020 Sep 16)

Phenotypic profiling with a living biobank of primary rhabdomyosarcoma unravels disease heterogeneity and AKT sensitivity.

Nature communications : 4629 : DOI : 10.1038/s41467-020-18388-7

Résumé

Cancer therapy is currently shifting from broadly used cytotoxic drugs to patient-specific precision therapies. Druggable driver oncogenes, identified by molecular analyses, are present in only a subset of patients. Functional profiling of primary tumor cells could circumvent these limitations, but suitable platforms are unavailable for most cancer entities. Here, we describe an in vitro drug profiling platform for rhabdomyosarcoma (RMS), using a living biobank composed of twenty RMS patient-derived xenografts (PDX) for high-throughput drug testing. Optimized in vitro conditions preserve phenotypic and molecular characteristics of primary PDX cells and are compatible with propagation of cells directly isolated from patient tumors. Besides a heterogeneous spectrum of responses of largely patient-specific vulnerabilities, profiling with a large drug library reveals a strong sensitivity towards AKT inhibitors in a subgroup of RMS. Overall, our study highlights the feasibility of in vitro drug profiling of primary RMS for patient-specific treatment selection in a co-clinical setting.

Luc Cabel, Dan Rosenblum, Florence Lerebours, Etienne Brain, Delphine Loirat, Mattias Bergqvist, Paul Cottu, Anne Donnadieu, Anne Bethune, Nicolas Kiavue, Manuel Rodrigues, Jean-Yves Pierga, Marie-Laure Tanguy, François-Clément Bidard (2020 Sep 15)

Plasma thymidine kinase 1 activity and outcome of ER+ HER2- metastatic breast cancer patients treated with palbociclib and endocrine therapy.

Breast cancer research : BCR : 98 : DOI : 10.1186/s13058-020-01334-2

Résumé

Previous cohort studies have reported plasma TK1 activity (pTKa) as a potential prognostic biomarker in estrogen receptor-positive (ER+) HER2-negative (HER2-) metastatic breast cancer (MBC). In this prospective study, we report here the prognostic impact of pTKa in ER+/HER2- MBC patients treated with endocrine therapy and CDK4/6 inhibitor.

Zhiming Li, Xu Hua, Albert Serra-Cardona, Xiaowei Xu, Songlin Gan, Hui Zhou, Wen-Si Yang, Chun-Long Chen, Rui-Ming Xu, Zhiguo Zhang (2020 Sep 14)

DNA polymerase α interacts with H3-H4 and facilitates the transfer of parental

histones to lagging strands.
Science advances : eabb5820 : DOI : 10.1126/sciadv.abb5820

Résumé

How parental histones, the carriers of epigenetic modifications, are deposited onto replicating DNA remains poorly understood. Here, we describe the eSPAN method (enrichment and sequencing of protein-associated nascent DNA) in mouse embryonic stem (ES) cells and use it to detect histone deposition onto replicating DNA strands with a relatively small number of cells. We show that DNA polymerase α (Pol α), which synthesizes short primers for DNA synthesis, binds histone H3-H4 preferentially. A Pol α mutant defective in histone binding in vitro impairs the transfer of parental H3-H4 to lagging strands in both yeast and mouse ES cells. Last, dysregulation of both coding genes and noncoding endogenous retroviruses is detected in mutant ES cells defective in parental histone transfer. Together, we report an efficient eSPAN method for analysis of DNA replication-linked processes in mouse ES cells and reveal the mechanism of Pol α in parental histone transfer.