Année de publication : 2020

Moutel S1, Beugnet A1, Schneider A1, Lombard B2, Loew D2, Amigorena S3, Perez F1, Segura E4. (2020 Mar 16)

Surface LSP-1 Is a Phenotypic Marker Distinguishing Human Classical versus Monocyte-Derived Dendritic Cells.

iScience. : 23(4) : DOI : 10.1016/j.isci.2020.100987

Résumé

Martin F Orth, Tilman L B Hölting, Marlene Dallmayer, Fabienne S Wehweck, Tanja Paul, Julian Musa, Michaela C Baldauf, Didier Surdez, Olivier Delattre, Maximilian M L Knott, Laura Romero-Pérez, Merve Kasan, Florencia Cidre-Aranaz, Julia S Gerke, Shunya Ohmura, Jing Li, Aruna Marchetto, Anton G Henssen, Özlem Özen, Shintaro Sugita, Tadashi Hasegawa, Takayuki Kanaseki, Stefanie Bertram, Uta Dirksen, Wolfgang Hartmann, Thomas Kirchner, Thomas G P Grünewald (2020 Mar 14)

High Specificity of BCL11B and GLG1 for EWSR1-FLI1 and EWSR1-ERG Positive Ewing Sarcoma.

Cancers : DOI : E644

Résumé

Ewing sarcoma (EwS) is an aggressive cancer displaying an undifferentiated small-round-cell histomorphology that can be easily confused with a broad spectrum of differential diagnoses. Using comparative transcriptomics and immunohistochemistry (IHC), we previously identified BCL11B and GLG1 as potential specific auxiliary IHC markers for -positive EwS. Herein, we aimed at validating the specificity of both markers in a far larger and independent cohort of EwS (including -positive cases) and differential diagnoses. Furthermore, we evaluated their intra-tumoral expression heterogeneity. Thus, we stained tissue microarrays from 133 molecularly confirmed EwS cases and 320 samples from morphological mimics, as well as a series of patient-derived xenograft (PDX) models for BCL11B, GLG1, and CD99, and systematically assessed the immunoreactivity and optimal cut-offs for each marker. These analyses demonstrated that high BCL11B and/or GLG1 immunoreactivity in CD99-positive cases had a specificity of 97.5% and an accuracy of 87.4% for diagnosing EwS solely by IHC, and that the markers were expressed by -positive EwS. Only little intra-tumoral heterogeneity in immunoreactivity was observed for differential diagnoses. These results indicate that BCL11B and GLG1 may help as specific auxiliary IHC markers in diagnosing EwS in conjunction with CD99, especially if confirmatory molecular diagnostics are not available.

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.

Alex Zwanenburg, Martin Vallières, Mahmoud A Abdalah, Hugo J W L Aerts, Vincent Andrearczyk, Aditya Apte, Saeed Ashrafinia, Spyridon Bakas, Roelof J Beukinga, Ronald Boellaard, Marta Bogowicz, Luca Boldrini, Irène Buvat, Gary J R Cook, Christos Davatzikos, Adrien Depeursinge, Marie-Charlotte Desseroit, Nicola Dinapoli, Cuong Viet Dinh, Sebastian Echegaray, Issam El Naqa, Andriy Y Fedorov, Roberto Gatta, Robert J Gillies, Vicky Goh, Michael Götz, Matthias Guckenberger, Sung Min Ha, Mathieu Hatt, Fabian Isensee, Philippe Lambin, Stefan Leger, Ralph T H Leijenaar, Jacopo Lenkowicz, Fiona Lippert, Are Losnegård, Klaus H Maier-Hein, Olivier Morin, Henning Müller, Sandy Napel, Christophe Nioche, Fanny Orlhac, Sarthak Pati, Elisabeth A G Pfaehler, Arman Rahmim, Arvind U K Rao, Jonas Scherer, Muhammad Musib Siddique, Nanna M Sijtsema, Jairo Socarras Fernandez, Emiliano Spezi, Roel J H M Steenbakkers, Stephanie Tanadini-Lang, Daniela Thorwarth, Esther G C Troost, Taman Upadhaya, Vincenzo Valentini, Lisanne V van Dijk, Joost van Griethuysen, Floris H P van Velden, Philip Whybra, Christian Richter, Steffen Löck (2020 Mar 11)

The Image Biomarker Standardization Initiative: Standardized Quantitative Radiomics for High-Throughput Image-based Phenotyping.

Radiology : 328-338 : DOI : 10.1148/radiol.2020191145

Résumé

Background Radiomic features may quantify characteristics present in medical imaging. However, the lack of standardized definitions and validated reference values have hampered clinical use. Purpose To standardize a set of 174 radiomic features. Materials and Methods Radiomic features were assessed in three phases. In phase I, 487 features were derived from the basic set of 174 features. Twenty-five research teams with unique radiomics software implementations computed feature values directly from a digital phantom, without any additional image processing. In phase II, 15 teams computed values for 1347 derived features using a CT image of a patient with lung cancer and predefined image processing configurations. In both phases, consensus among the teams on the validity of tentative

reference values was measured through the frequency of the modal value and classified as follows: less than three matches, weak; three to five matches, moderate; six to nine matches, strong; 10 or more matches, very strong. In the final phase (phase III), a public data set of multimodality images (CT, fluorine 18 fluorodeoxyglucose PET, and T1-weighted MRI) from 51 patients with soft-tissue sarcoma was used to prospectively assess reproducibility of standardized features. Results Consensus on reference values was initially weak for 232 of 302 features (76.8%) at phase I and 703 of 1075 features (65.4%) at phase II. At the final iteration, weak consensus remained for only two of 487 features (0.4%) at phase I and 19 of 1347 features (1.4%) at phase II. Strong or better consensus was achieved for 463 of 487 features (95.1%) at phase I and 1220 of 1347 features (90.6%) at phase II. Overall, 169 of 174 features were standardized in the first two phases. In the final validation phase (phase III), most of the 169 standardized features could be excellently reproduced (166 with CT; 164 with PET; and 164 with MRI). Conclusion A set of 169 radiomics features was standardized, which enabled verification and calibration of different radiomics software. © RSNA, 2020 See also the editorial by Kuhl and Truhn in this issue.

Lynn GM1,2, Sedlik C3,4, Baharom F5, Zhu Y6, Ramirez-Valdez RA5, Coble VL6, Tobin K5, Nichols SR6, Itzkowitz Y6, Zaidi N5, Gammon JM7, Blobel NJ5, Denizeau J3,4, de la Rochere P3,4, Francica BJ8,9, Decker B6, Maciejewski M6, Cheung J5, Yamane H5, Smelkinson MG10, Francica JR5, Laga R11, Bernstock JD6,12, Seymour LW13, Drake CG8,14, Jewell CM7, Lantz O3,4, Piaggio E3,4, Ishizuka AS5,6, Seder RA15. (2020 Mar 2)

Peptide-TLR-7/8a conjugate vaccines chemically programmed for nanoparticle self-assembly enhance CD8 T-cell immunity to tumor antigens.

Nature biotechnology : 38(3) : 320-332 : DOI : 10.1038/s41587-019-0390-x

Résumé

Edwards-Jorquera SS, Bosveld F, Bellaïche YA, Lennon-Duménil AM, Glavic Á. (2020 Mar 2)

Trpml controls actomyosin contractility and couples migration to phagocytosis in fly macrophages.

Journal of cell biology : 2 : J Cell Biol. 2020 Mar 2;219(3). pii: e201905228. doi: 10.1083/jcb.201905228. : DOI : 10.1083/jcb.201905228

Résumé

Phagocytes use their actomyosin cytoskeleton to migrate as well as to probe their environment by phagocytosis or macropinocytosis. Although migration and extracellular material uptake have been shown to be coupled in some immune cells, the mechanisms involved in such coupling are largely unknown. By combining time-lapse imaging with genetics, we here identify the lysosomal Ca2+ channel Trpml as an essential player in the coupling of cell locomotion and phagocytosis in hemocytes, the Drosophila macrophage-like immune cells. Trpml is needed for both hemocyte migration and phagocytic processing at distinct subcellular localizations: Trpml regulates hemocyte migration by controlling

actomyosin contractility at the cell rear, whereas its role in phagocytic processing lies near the phagocytic cup in a myosin-independent fashion. We further highlight that Vamp7 also regulates phagocytic processing and locomotion but uses pathways distinct from those of Trpml. Our results suggest that multiple mechanisms may have emerged during evolution to couple phagocytic processing to cell migration and facilitate space exploration by immune cells.

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.

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.

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

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.

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.