Année de publication : 2020

Forrester A, Rathjen SJ, Garcia Castillo MD, Bachert C, Couhert A, Tepshi L, Pichard S, Martinez J, Renard H-F, Valades Cruz CA, Dingli F, Loew D, Lamaze C, Cintrat JC, Linstedt AD, Gillet D, Barbier J, Johannes L (2020 May 29)
Functional dissection of the retrograde Shiga toxin trafficking inhibitor Retro-2
Nature Chemical BiologyNature

Résumé

The retrograde transport inhibitor Retro-2 has a protective effect on cells and in mice against Shiga-like toxins and ricin. Retro-2 causes toxin accumulation in early endosomes and relocalization of the Golgi SNARE protein syntaxin-5 to the endoplasmic reticulum. The molecular mechanisms by which this is achieved remain unknown. Here, we show that Retro-2 targets the endoplasmic reticulum exit site component Sec16A, affecting anterograde transport of syntaxin-5 from the endoplasmic reticulum to the Golgi. The formation of canonical SNARE complexes involving syntaxin-5 is not affected in Retro-2-treated cells. By contrast, the interaction of syntaxin-5 with a newly discovered binding partner, the retrograde trafficking chaperone GPP130, is abolished, and we show that GPP130 must indeed bind to syntaxin-5 to drive Shiga toxin transport from the endosomes to the Golgi. We therefore identify Sec16A as a druggable target and provide evidence for a non-SNARE function for syntaxin-5 in interaction with GPP130.

Bellesoeur A1, Torossian N2, Amigorena S3, Romano E4. (2020 May 24)
Advances in theranostic biomarkers for tumor immunotherapy.
Cuurent opinion in chemical biology : 24;56 : DOI: 10.1016/j.cbpa.2020.02.005 : 79-90 : DOI : 10.1016/j.cbpa.2020.02.005

Résumé

Erra Díaz F1, Ochoa V1, Merlotti A2, Dantas E1, Mazzitelli I1, Gonzalez Polo V1, Sabatté J1, Amigorena S2, Segura E2, Geffner J3. (2020 May 16)
Extracellular Acidosis and mTOR Inhibition Drive the Differentiation of Human Monocyte-Derived Dendritic Cells.
Cell reports : 31(5) : DOI : 10.1016/j.celrep.2020.107613

Résumé

Simon Gemble, Géraldine Buhagiar-Labarchède, Rosine Onclercq-Delic, Gaëlle Fontaine, Sarah Lambert, Mounira Amor-Guéret (2020 May 14)

Topoisomerase IIα prevents ultrafine anaphase bridges by two mechanisms.
Open biology : 190259 : DOI : 10.1098/rsob.190259

Résumé

Topoisomerase IIα (Topo IIα), a well-conserved double-stranded DNA (dsDNA)-specific decatenase, processes dsDNA catenanes resulting from DNA replication during mitosis. Topo IIα defects lead to an accumulation of ultrafine anaphase bridges (UFBs), a type of chromosome non-disjunction. Topo IIα has been reported to resolve DNA anaphase threads, possibly accounting for the increase in UFB frequency upon Topo IIα inhibition. We hypothesized that the excess UFBs might also result, at least in part, from an impairment of the prevention of UFB formation by Topo IIα. We found that Topo IIα inhibition promotes UFB formation without affecting the global disappearance of UFBs during mitosis, but leads to an aberrant UFB resolution generating DNA damage within the next G1. Moreover, we demonstrated that Topo IIα inhibition promotes the formation of two types of UFBs depending on cell cycle phase. Topo IIα inhibition during S-phase compromises complete DNA replication, leading to the formation of UFB-containing unreplicated DNA, whereas Topo IIα inhibition during mitosis impedes DNA decatenation at metaphase-anaphase transition, leading to the formation of UFB-containing DNA catenanes. Thus, Topo IIα activity is essential to prevent UFB formation in a cell-cycle-dependent manner and to promote DNA damage-free resolution of UFBs.

P Lansonneur, H Mammar, C Nauraye, A Patriarca, E Hierso, R Dendale, Y Prezado, L De Marzi (2020 Apr 29)
First proton minibeam radiation therapy treatment plan evaluation.
Scientific reports : 7025 : DOI : 10.1038/s41598-020-63975-9

Résumé

Proton minibeam radiation therapy (pMBRT) is a novel dose delivery method based on spatial dose fractionation. pMBRT has been shown to be promising in terms of reduced side effects and superior tumour control in high-grade glioma-bearing rats compared to standard irradiation. These findings, together with the recent optimized implementation of pMBRT in a clinical pencil beam scanning system, have triggered reflection on the possible application to patient treatments. In this context, the present study was designed to conduct a first theoretical investigation of the clinical potential of this technique. For this purpose, a dedicated dose engine was developed and used to evaluate two clinically relevant patient treatment plans (high-grade glioma and meningioma). Treatment plans were compared with standard proton therapy plans assessed by means of a commercial treatment planning system (ECLIPSE-Varian Medical systems) and Monte Carlo simulations. A multislit brass collimator consisting of 0.4 mm wide slits separated by a centre-to-centre distance of 4 or 6 mm was placed between the nozzle and the patient to shape the planar minibeams. For each plan, spread-out Bragg peaks and homogeneous dose distributions (±7% dose variations) can be obtained in target volumes. The Peak-to-Valley Dose Ratios (PVDR) were evaluated between 9.2 and 12.8 at a depth of 20 mm for meningioma and glioma, respectively. Dose volume histograms (DVHs) for target volumes and organs at risk were

quantitatively compared, resulting in a slightly better target homogeneity with standard PT than with pMBRT plans, but similar DVHs for deep-seated organs-at-risk and lower average dose for shallow organs. The proposed delivery method evaluated in this work opens the way to an effective treatment for radioresistant tumours and will support the design of future clinical research.

Johanna Theruvath, Elena Sotillo, Christopher W Mount, Claus Moritz Graef, Alberto Delaidelli, Sabine Heitzeneder, Louai Labanieh, Shaurya Dhingra, Amaury Leruste, Robbie G Majzner, Peng Xu, Sabine Mueller, Derek W Yecies, Martina A Finetti, Daniel Williamson, Pascal D Johann, Marcel Kool, Stefan Pfister, Martin Hasselblatt, Michael C Frühwald, Olivier Delattre, Didier Surdez, Franck Bourdeaut, Stephanie Puget, Sakina Zaidi, Siddhartha S Mitra, Samuel Cheshier, Poul H Sorensen, Michelle Monje, Crystal L Mackall (2020 Apr 29)

Locoregionally administered B7-H3-targeted CAR T cells for treatment of atypical teratoid/rhabdoid tumors.

Nature medicine : DOI : 10.1038/s41591-020-0821-8

Résumé

Atypical teratoid/rhabdoid tumors (ATRTs) typically arise in the central nervous system (CNS) of children under 3 years of age. Despite intensive multimodal therapy (surgery, chemotherapy and, if age permits, radiotherapy), median survival is 17 months. We show that ATRTs robustly express B7-H3/CD276 that does not result from the inactivating mutations in SMARCB1 (refs.), which drive oncogenesis in ATRT, but requires residual SWItch/Sucrose Non-Fermentable (SWI/SNF) activity mediated by BRG1/SMARCA4. Consistent with the embryonic origin of ATRT, B7-H3 is highly expressed on the prenatal, but not postnatal, brain. B7-H3.BB.z-chimeric antigen receptor (CAR) T cells administered intracerebroventricularly or intratumorally mediate potent antitumor effects against cerebral ATRT xenografts in mice, with faster kinetics, greater potency and reduced systemic levels of inflammatory cytokines compared to CAR T cells administered intravenously. CAR T cells administered ICV also traffic from the CNS into the periphery; following clearance of ATRT xenografts, B7-H3.BB.z-CAR T cells administered intracerebroventricularly or intravenously mediate antigen-specific protection from tumor rechallenge, both in the brain and periphery. These results identify B7-H3 as a compelling therapeutic target for this largely incurable pediatric tumor and demonstrate important advantages of locoregional compared to systemic delivery of CAR T cells for the treatment of CNS malignancies.

Yuvia A Pérez-Rico, Emmanuel Barillot, Alena Shkumatava (2020 Apr 26)

Demarcation of Topologically Associating Domains Is Uncoupled from Enriched CTCF Binding in Developing Zebrafish.

iScience : 101046 : DOI : S2589-0042(20)30231-5

Résumé

CCCTC-binding factor (CTCF) is a conserved architectural protein that plays crucial roles in gene regulation and three-dimensional (3D) chromatin organization. To better understand mechanisms and evolution of vertebrate genome organization, we analyzed genome occupancy of CTCF in zebrafish utilizing an endogenously epitope-tagged CTCF knock-in allele. Zebrafish CTCF shares similar facets with its mammalian counterparts, including binding to enhancers, active promoters and repeat elements, and bipartite sequence motifs of its binding sites. However, we found that in vivo CTCF binding is not enriched at boundaries of topologically associating domains (TADs) in developing zebrafish, whereas TAD demarcation by chromatin marks did not differ from mammals. Our data suggest that general mechanisms underlying 3D chromatin organization, and in particular the involvement of CTCF in this process, differ between distant vertebrate species.

Villar J1, Segura E2. (2020 Apr 24)
Recent advances towards deciphering human dendritic cell development.
Moecular immunology : 122 : 109 - 115 : DOI : DOI: 10.1016/j.molimm.2020.04.004

Résumé

Rahima Chennoufi, Ngoc-Duong Trinh, Françoise Simon, Guillaume Bordeau, Delphine Naud-Martin, Albert Moussaron, Bertrand Cinquin, Houcine Bougherara, Béatrice Rambaud, Patrick Tauc, Céline Frochot, Marie-Paule Teulade-Fichou, Florence Mahuteau-Betzer & Eric Deprez (2020 Apr 23)
Interplay between cellular uptake, intracellular localization and the cell death mechanism in triphenylamine-mediated photoinduced cell death
Scientific Reports : 10 : 6881 : DOI : 10.1038/s41598-020-63991-9

Résumé

Triphenylamines (TPAs) were previously shown to trigger cell death under prolonged one- or two-photon illumination. Their initial subcellular localization, before prolonged illumination, is exclusively cytoplasmic and they translocate to the nucleus upon photoactivation. However, depending on their structure, they display significant differences in terms of precise initial localization and subsequent photoinduced cell death mechanism. Here, we investigated the structural features of TPAs that influence cell death by studying a series of molecules differing by the number and chemical nature of vinyl branches. All compounds triggered cell death upon one-photon excitation, however to different extents, the nature of the electron acceptor group being determinant for the overall cell death efficiency. Photobleaching susceptibility was also an important parameter for discriminating efficient/inefficient compounds in two-photon experiments. Furthermore, the number of branches, but not their chemical nature, was crucial for determining the cellular uptake mechanism of TPAs and their intracellular fate. The uptake of all TPAs is an active endocytic process but two- and three-branch compounds are taken up via distinct endocytosis pathways, clathrin-dependent or -independent (predominantly caveolae-dependent), respectively. Two-branch TPAs preferentially target mitochondria and photoinduce both apoptosis and a proper necrotic

process, whereas three-branch TPAs preferentially target late endosomes and photoinduce apoptosis only.

Zuffo M., Gandolfini A., Heddi B., Granzhan A. (2020 Apr 20)
Harnessing intrinsic fluorescence for typing of secondary structures of DNA
Nucleic Acids Research : Epub ahead of print : DOI : 10.1093/nar/gkaa257

Résumé

High-throughput investigation of structural diversity of nucleic acids is hampered by the lack of suitable label-free methods, combining fast and cheap experimental workflow with high information content. Here, we explore the use of intrinsic fluorescence emitted by nucleic acids for this scope. After a preliminary assessment of suitability of this phenomenon for tracking conformational changes of DNA, we examined steady-state emission spectra of an 89-membered set of oligonucleotides with reported conformation (G-quadruplexes (G4s), i-motifs, single- and double-strands) by means of multivariate analysis. Principal component analysis of emission spectra resulted in successful clustering of oligonucleotides into three corresponding conformational groups, without discrimination between single- and double-stranded structures. Linear discriminant analysis was exploited for the assessment of novel sequences, allowing the evaluation of their G4-forming propensity. Our method does not require any labeling agent or dye, avoiding the related bias, and can be utilized to screen novel sequences of interest in a high-throughput and cost-effective manner. In addition, we observed that left-handed (Z-) G4 structures were systematically more fluorescent than most other G4 structures, almost reaching the quantum yield of 5′-d[$(G_3T)_3G_3$]-3′ (G_3T, the most fluorescent G4 structure reported to date).

Ehlen A., Martin C., Miron S., Julien M., Theillet F.X., Boucherit V., Ropars V., Duchambon P., El Marjou A., Zinn Justin S., Carreira A. (2020 Apr 14)
Proper chromosome alignment depends on BRCA2 phosphorylation by PLK1
Nature Communications : 11 : 1819 : DOI : 10.1038/s41467-020-15689-9

Résumé

The BRCA2 tumor suppressor protein is involved in the maintenance of genome integrity through its role in homologous recombination. In mitosis, BRCA2 is phosphorylated by Polo-like kinase 1 (PLK1). Here we describe how this phosphorylation contributes to the control of mitosis. We identify a conserved phosphorylation site at T207 of BRCA2 that constitutes a bona fide docking site for PLK1 and is phosphorylated in mitotic cells. We show that BRCA2 bound to PLK1 forms a complex with the phosphatase PP2A and phosphorylated-BUBR1. Reducing BRCA2 binding to PLK1, as observed in *BRCA2* breast cancer variants S206C and T207A, alters the tetrameric complex resulting in unstable kinetochore-microtubule interactions, misaligned chromosomes, faulty chromosome segregation and aneuploidy. We thus reveal a role of BRCA2 in the alignment of chromosomes, distinct from its DNA repair function, with important consequences on chromosome stability. These findings may explain

in part the aneuploidy observed in *BRCA2*-mutated tumors.

Åsa Ehlén, Charlotte Martin, Simona Miron, Manon Julien, François-Xavier Theillet, Virginie Ropars, Gaetana Sessa, Romane Beaurepere, Virginie Boucherit, Patricia Duchambon, Ahmed El Marjou, Sophie Zinn-Justin, Aura Carreira (2020 Apr 14)
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Nature communications : 1819 : DOI : 10.1038/s41467-020-15689-9

Résumé

The BRCA2 tumor suppressor protein is involved in the maintenance of genome integrity through its role in homologous recombination. In mitosis, BRCA2 is phosphorylated by Polo-like kinase 1 (PLK1). Here we describe how this phosphorylation contributes to the control of mitosis. We identify a conserved phosphorylation site at T207 of BRCA2 that constitutes a bona fide docking site for PLK1 and is phosphorylated in mitotic cells. We show that BRCA2 bound to PLK1 forms a complex with the phosphatase PP2A and phosphorylated-BUBR1. Reducing BRCA2 binding to PLK1, as observed in BRCA2 breast cancer variants S206C and T207A, alters the tetrameric complex resulting in unstable kinetochore-microtubule interactions, misaligned chromosomes, faulty chromosome segregation and aneuploidy. We thus reveal a role of BRCA2 in the alignment of chromosomes, distinct from its DNA repair function, with important consequences on chromosome stability. These findings may explain in part the aneuploidy observed in BRCA2-mutated tumors.

Ye M1, Goudot C1, Hoyler T1, Lemoine B2, Amigorena S3, Zueva E3. (2020 Apr 7)
Specific subfamilies of transposable elements contribute to different domains of T lymphocyte enhancers.
Proceedings of the National Academy of Sciences : 117 (14) : doi: 10.1073/pnas.1912008117 : 7905-7916 : DOI : 10.1073/pnas.1912008117

Résumé

Zablocki-Thomas L, Menzies SA, Lehner PJ, Manel N, Benaroch P. (2020 Apr 4)
A genome-wide CRISPR screen identifies regulation factors of the TLR3 signalling pathway.
Innate immunology : DOI : 10.1177/1753425920915507

Résumé

Zablocki-Thomas L1, Menzies SA2, Lehner PJ2, Manel N1, Benaroch P1. (2020 Apr 4)
A genome-wide CRISPR screen identifies regulation factors of the TLR3

signalling pathway.
Innate immunology : DOI : 10.1177/1753425920915507

Résumé