Year of publication 2020

Andrea Dimitracopoulos, Pragya Srivastava, Agathe Chaigne, Zaw Win, Roie Shlomovitz, Oscar M Lancaster, Maël Le Berre, Matthieu Piel, Kristian Franze, Guillaume Salbreux, Buzz Baum (2020 Aug 1)

Mechanochemical Crosstalk Produces Cell-Intrinsic Patterning of the Cortex to Orient the Mitotic Spindle.

Current biology : CB : DOI : S0960-9822(20)30984-2

Summary

Proliferating animal cells are able to orient their mitotic spindles along their interphase cell axis, setting up the axis of cell division, despite rounding up as they enter mitosis. This has previously been attributed to molecular memory and, more specifically, to the maintenance of adhesions and retraction fibers in mitosis [1-6], which are thought to act as local cues that pattern cortical Gαi, LGN, and nuclear mitotic apparatus protein (NuMA) [3, 7-18]. This cortical machinery then recruits and activates Dynein motors, which pull on astral microtubules to position the mitotic spindle. Here, we reveal a dynamic two-way crosstalk between the spindle and cortical motor complexes that depends on a Ran-guanosine triphosphate (GTP) signal [12], which is sufficient to drive continuous monopolar spindle motion independently of adhesive cues in flattened human cells in culture. Building on previous work [1, 12, 19-23], we implemented a physical model of the system that recapitulates the observed spindle-cortex interactions. Strikingly, when this model was used to study spindle dynamics in cells entering mitosis, the chromatin-based signal was found to preferentially clear force generators from the short cell axis, so that cortical motors pulling on astral microtubules align bipolar spindles with the interphase long cell axis, without requiring a fixed cue or a physical memory of interphase shape. Thus, our analysis shows that the ability of chromatin to pattern the cortex during the process of mitotic rounding is sufficient to translate interphase shape into a cortical pattern that can be read by the spindle, which then guides the axis of cell division.

Jamie Zagozewski, Ghazaleh M Shahriary, Ludivine Coudière Morrison, Olivier Saulnier, Margaret Stromecki, Agnes Fresnoza, Gareth Palidwor, Christopher J Porter, Antoine Forget, Olivier Ayrault, Cynthia Hawkins, Jennifer A Chan, Maria C Vladoiu, Lakshmikirupa Sundaresan, Janilyn Arsenio, Michael D Taylor, Vijay Ramaswamy, Tamra E Werbowetski-Ogilvie (2020 Jul 21)

An OTX2-PAX3 signaling axis regulates Group 3 medulloblastoma cell fate.

Nature communications : 3627 : DOI : 10.1038/s41467-020-17357-4

Summary

OTX2 is a potent oncogene that promotes tumor growth in Group 3 medulloblastoma. However, the mechanisms by which OTX2 represses neural differentiation are not well characterized. Here, we perform extensive multiomic analyses to identify an OTX2 regulatory network that controls Group 3 medulloblastoma cell fate. OTX2 silencing modulates the

repressive chromatin landscape, decreases levels of PRC2 complex genes and increases the expression of neurodevelopmental transcription factors including PAX3 and PAX6. Expression of PAX3 and PAX6 is significantly lower in Group 3 medulloblastoma patients and is correlated with reduced survival, yet only PAX3 inhibits self-renewal in vitro and increases survival in vivo. Single cell RNA sequencing of Group 3 medulloblastoma tumorspheres demonstrates expression of an undifferentiated progenitor program observed in primary tumors and characterized by translation/elongation factor genes. Identification of mTORC1 signaling as a downstream effector of OTX2-PAX3 reveals roles for protein synthesis pathways in regulating Group 3 medulloblastoma pathogenesis.

Hadi T Nia, Meenal Datta, Giorgio Seano, Sue Zhang, William W Ho, Sylvie Roberge, Peigen Huang, Lance L Munn, Rakesh K Jain (2020 Jul 19)

In vivo compression and imaging in mouse brain to measure the effects of solid stress.

Nature protocols : DOI : 10.1038/s41596-020-0328-2

Summary

We recently developed an in vivo compression device that simulates the solid mechanical forces exerted by a growing tumor on the surrounding brain tissue and delineates the physical versus biological effects of a tumor. This device, to our knowledge the first of its kind, can recapitulate the compressive forces on the cerebellar cortex from primary (e.g., glioblastoma) and metastatic (e.g., breast cancer) tumors, as well as on the cerebellum from tumors such as medulloblastoma and ependymoma. We adapted standard transparent cranial windows normally used for intravital imaging studies in mice to include a turnable screw for controlled compression (acute or chronic) and decompression of the cerebral cortex. The device enables longitudinal imaging of the compressed brain tissue over several weeks or months as the screw is progressively extended against the brain tissue to recapitulate tumor growth-induced solid stress. The cranial window can be simply installed on the mouse skull according to previously established methods, and the screw mechanism can be readily manufactured in-house. The total time for construction and implantation of the in vivo compressive cranial window is <1 h (per mouse). This technique can also be used to study a variety of other diseases or disorders that present with abnormal solid masses in the brain, including cysts and benign growths.

Bourdely P, Anselmi G, Vaivode K, Ramos RN, MISSOLO-KOUSSOU Y, Hidalgo S, Tosselo J, Nuñez N, Richer W, Vincent-Salomon A, Saxena A, Wood K, Lladser A, Piaggio E, Helft J*, Guermonprez P* (2020 Jun 30)

Transcriptional and Functional Analysis of CD1c+ Human Dendritic Cells Identifies a CD163+ Subset Priming CD8+CD103+ T Cells

ImmunityImmunity : DOI : 10.1016/j.immuni.2020.06.002

Summary

Núñez NG, Tosello Boari J, Ramos RN, Richer W, Cagnard N, Anderfuhren CD, Niborski LL, Bigot J, Meseure D, De La Rochere P, Milder M, Viel S, Loirat D, Pérol L, Vincent-Salomon A, Sastre-Garau X, Burkhard B, Sedlik C, Lantz O, Amigorena S, Piaggio E (2020 Jun 29)
Tumor invasion in draining lymph nodes is associated with Treg accumulation in breast cancer patients
Nat CommunNat Commun : DOI : 10.1038/s41467-020-17046-2

Summary

Myriam Ruault, Vittore F. Scolari, Luciana Lazar-Stefanita, Antoine Hocher, Isabelle Loïodice, Camille Noûs, Romain Koszul, Angela Taddei (2020 Jun 29)
The silencing factor Sir3 is a molecular bridge that sticks together distant loci
preprint- : DOI : 10.1101/2020.06.29.178368

Summary

Martina Bonucci, Nicolas Kuperwasser, Serena Barbe, Vonda Koka, Delphine de Villeneuve, Chi Zhang, Nishit Srivastava, Xiaoying Jia, Matthew P Stokes, Frank Bienaimé, Virginie Verkarre, Jean Baptiste Lopez, Fanny Jaulin, Marco Pontoglio, Fabiola Terzi, Benedicte Delaval, Matthieu Piel, Mario Pende (2020 Jun 26)
mTOR and S6K1 drive polycystic kidney by the control of Afadin-dependent oriented cell division.
Nature communications : 3200 : DOI : 10.1038/s41467-020-16978-z

Summary

mTOR activation is essential and sufficient to cause polycystic kidneys in Tuberous Sclerosis Complex (TSC) and other genetic disorders. In disease models, a sharp increase of proliferation and cyst formation correlates with a dramatic loss of oriented cell division (OCD). We find that OCD distortion is intrinsically due to S6 kinase 1 (S6K1) activation. The concomitant loss of S6K1 in Tsc1-mutant mice restores OCD but does not decrease hyperproliferation, leading to non-cystic harmonious hyper growth of kidneys. Mass spectrometry-based phosphoproteomics for S6K1 substrates revealed Afadin, a known component of cell-cell junctions required to couple intercellular adhesions and cortical cues to spindle orientation. Afadin is directly phosphorylated by S6K1 and abnormally decorates the apical surface of Tsc1-mutant cells with E-cadherin and α-catenin. Our data reveal that S6K1 hyperactivity alters centrosome positioning in mitotic cells, affecting oriented cell division and promoting kidney cysts in conditions of mTOR hyperactivity.

Cao Luyan, Yonis Amina, Vaghela Malti, Barriga Elias, Chugh Priyamvada, Smith Matthew, Maufront Julien, Lavoie Geneviève, Méant Antoine, Ferber Emma, Bovellan Miia, Alberts Art,

Bertin Aurélie, Mayor Roberto, Paluch Eva, Roux Philippe, Jégou Antoine, Romet-Lemonne Guillaume, Charras Guillaume (2020 Jun 22)

SPIN90 associates with mDia1 and the Arp2/3 complex to regulate cortical actin organization

Nature Cell BiologyNature Cell Biology : DOI : 10.1038/s41556-020-0531-y

Summary

Cell shape is controlled by the submembranous cortex, an actomyosin network mainly generated by two actin nucleators: the Arp2/3 complex and the formin mDia1. Changes in relative nucleator activity may alter cortical organization, mechanics and cell shape. Here we investigate how nucleation-promoting factors mediate interactions between nucleators. In vitro, the nucleation-promoting factor SPIN90 promotes formation of unbranched filaments by Arp2/3, a process thought to provide the initial filament for generation of dendritic networks. Paradoxically, in cells, SPIN90 appears to favour a formin-dominated cortex. Our in vitro experiments reveal that this feature stems mainly from two mechanisms: efficient recruitment of mDia1 to SPIN90–Arp2/3 nucleated filaments and formation of a ternary SPIN90–Arp2/3–mDia1 complex that greatly enhances filament nucleation. Both mechanisms yield rapidly elongating filaments with mDia1 at their barbed ends and SPIN90–Arp2/3 at their pointed ends. Thus, in networks, SPIN90 lowers branching densities and increases the proportion of long filaments elongated by mDia1.

Judith Miné-Hattab*, Mathias Heltberg, Marie Villemeur, Chloé Guedj, Thierry Mora, Aleksandra M. Walczak, Maxime Dahan, Angela Taddei*, co-corresponding authors (2020 Jun 19)

Single molecule microscopy reveals key physical features of repair foci in living cells

preprint- : DOI : 10.1101/2020.06.18.160085

Summary

Nicolò Capobianco, Michel A Meignan, Anne-Segolene Cottereau, Laetitia Vercellino, Ludovic Sibille, Bruce Spottiswoode, Sven Zuehlsdorff, Olivier Casasnovas, Catherine Thieblemont, Irene Buvat (2020 Jun 14)

Deep learning FDG uptake classification enables total metabolic tumor volume estimation in diffuse large B-cell lymphoma.

Journal of nuclear medicine : official publication, Society of Nuclear Medicine : DOI : jnumed.120.242412

Summary

Total metabolic tumor volume (TMTV), calculated from F-labeled fluoro-2-deoxyglucose (F-FDG) positron-emission tomography-computed tomography (PET/CT) baseline studies, is a prognostic factor in diffuse large B-cell lymphoma (DLBCL) whose measurement requires the

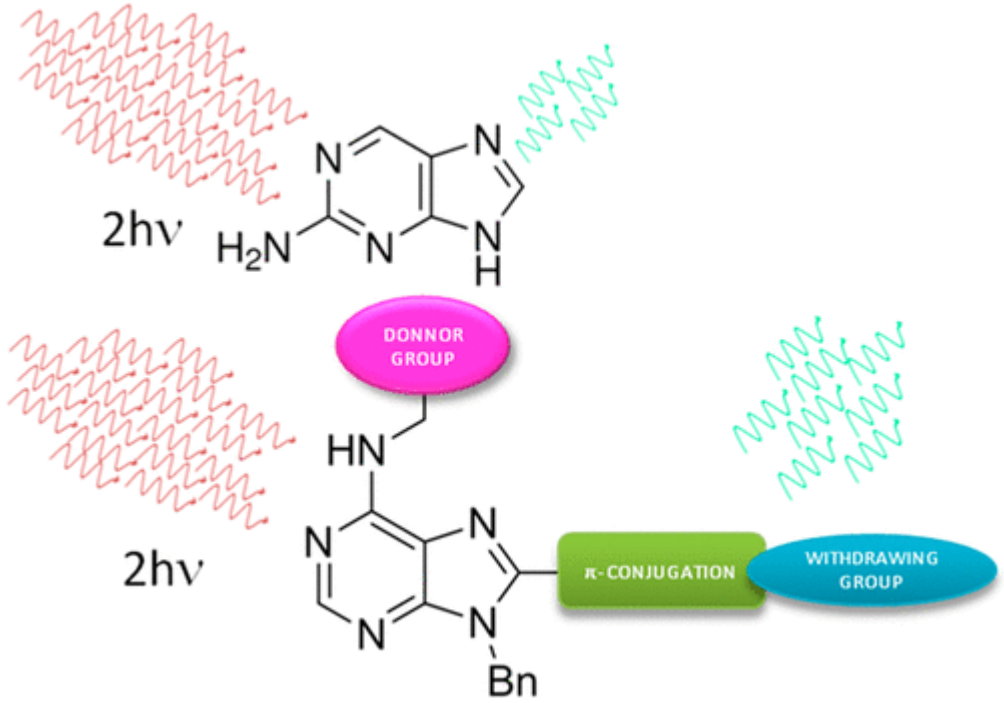
segmentation of all malignant foci throughout the body. No consensus currently exists regarding the most accurate approach for such segmentation. Further, all methods still require extensive manual input from an experienced reader. We examined whether an artificial intelligence (AI)-based method could estimate TMTV with a comparable prognostic value to TMTV measured by experts. Baseline F-FDG PET/CT scans of 301 DLBCL patients from the REMARC trial (NCT01122472) were retrospectively analyzed. An automated whole-body high-uptake segmentation algorithm identified all three-dimensional regions of interest (ROI) with increased tracer uptake. The resulting ROIs were processed using a convolutional neural network trained on an independent cohort and classified as nonsuspicious or suspicious uptake. The AI-based TMTV was estimated as the sum of the volumes of ROIs classified as suspicious uptake. The reference TMTV was measured by two experienced readers using independent semiautomatic software. The AI-based TMTV was compared to the reference TMTV in terms of prognostic value for progression-free survival (PFS) and overall survival (OS). The AI-based TMTV was significantly correlated with the reference TMTV ($\rho=0.76$; $p<0.001$). Using the AI-based approach, an average of 24 regions per subject with increased tracer uptake were identified, and an average of 20 regions per subject were correctly identified as nonsuspicious or suspicious, yielding 85% classification accuracy, 80% sensitivity, 88% specificity, compared to the reference TMTV region. Both TMTV results were predictive of PFS (hazard ratio: 2.4 and 2.6 for AI-based and reference TMTVs, respectively; $p<0.001$) and OS (hazard ratio: 2.8 and 3.7 for AI-based and reference TMTVs, respectively; $p<0.001$). TMTV estimated fully automatically using an AI-based approach was consistent with that obtained by experts and displayed a significant prognostic value for PFS and OS in DLBCL patients. Classification of high uptake regions using deep learning for rapidly discarding physiological uptake may considerably simplify TMTV estimation, reduce observer variability and facilitate the use of TMTV as a predictive factor in DLBCL patients.

Leandro H. Zucolotto Cocca, Luis M. G. Abegão, Lucas F. Sciuti, Roxane Vabre, Jonathas de Paula Siqueira, Kenji Kamada, Cleber R. Mendonca, Sandrine Piguel, and Leonardo De Boni (2020 Jun 11)

Two-Photon Emissive Dyes Based on Push–Pull Purines Derivatives: Toward the Development of New Photoluminescence Bioprobes

The Journal of Physical Chemistry C : 124 : 12185-12864 : DOI : 10.1021/acs.jpcc.0c01859

Summary



Fluorescent organic molecules have received great attention due to their largest applications, for example, in DNA and RNA spectroscopies studies, development of new photoluminescence bioprobes, and applications in fluorescence spectroscopy. In specific, purine base analog molecules present high fluorescence quantum yields and significant Stokes shift. Furthermore, the addition of push–pull structures at the purine core could increase the photoluminescence properties, making candidates for photoluminescence bioprobes. To consider this, a complete spectroscopic study was performed on nine push–pull purines, distinguished by different push–pull structures. In specific, for this research, the two-photon absorption (2PA) study showed that the compounds present induced two-photon fluorescence at the therapeutic window, desired for fluorescence microscopy. The brightness property was evaluated, indicating that all chromospheres are fluorescent by a 2PA process. Additionally, ultrafast transient absorption was performed to elucidate contribution of the excited states on the 2PA spectra, and quantum chemistry calculations were performed to corroborate the experimental results.

Pierluigi Scerbo, Anne H Monsoro-Burq (2020 Jun 5)

The vertebrate-specific VENTX/NANOG gene empowers neural crest with ectomesenchyme potential.

Science advances : eaaz1469 : DOI : 10.1126/sciadv.aaz1469

Summary

During Cambrian, unipotent progenitors located at the neural (plate) border (NB) of an chordate embryo acquired the competence to form ectomesenchyme, pigment cells and neurons, initiating the rise of the multipotent neural crest cells (NC) specific to vertebrates. Surprisingly, the known vertebrate NB/NC transcriptional circuitry is a constrained feature

also found in invertebrates. Therefore, evidence for vertebrate-specific innovations endowing vertebrate NC with multipotency is still missing. Here, we identified VENTX/NANOG and POU5/OCT4 as vertebrate-specific innovations. When VENTX was depleted in vivo and in directly-induced NC, the NC lost its early multipotent state and its skeletogenic potential, but kept sensory neuron and pigment identity, thus reminiscent of invertebrate NB precursors. In vivo, VENTX gain-of-function enabled NB specifiers to reprogram embryonic non-neural ectoderm towards early NC identity. We propose that skeletogenic NC evolved by acquiring VENTX/NANOG activity, promoting a novel multipotent progenitor regulatory state into the pre-existing sensory neuron/pigment NB program.

L Boeckemeier, R Kraehenbuehl, A Keszthelyi, M U Gasasira, E G Vernon, R Beardmore, C B Vågbø, D Chaplin, S Gollins, H E Krokan, S A E Lambert, B Paizs, E Hartsuiker (2020 May 29)
Mre11 exonuclease activity removes the chain-terminating nucleoside analog gemcitabine from the nascent strand during DNA replication.
Science advances : eaaz4126 : DOI : 10.1126/sciadv.aaz4126

Summary

The Mre11 nuclease is involved in early responses to DNA damage, often mediated by its role in DNA end processing. mutations and aberrant expression are associated with carcinogenesis and cancer treatment outcomes. While, in recent years, progress has been made in understanding the role of Mre11 nuclease activities in DNA double-strand break repair, their role during replication has remained elusive. The nucleoside analog gemcitabine, widely used in cancer therapy, acts as a replication chain terminator; for a cell to survive treatment, gemcitabine needs to be removed from replicating DNA. Activities responsible for this removal have, so far, not been identified. We show that Mre11 3′ to 5′ exonuclease activity removes gemcitabine from nascent DNA during replication. This contributes to replication progression and gemcitabine resistance. We thus uncovered a replication-supporting role for Mre11 exonuclease activity, which is distinct from its previously reported detrimental role in uncontrolled resection in recombination-deficient cells.

Aurélie Bertin , Nicola de Franceschi , Eugenio de la Mora , Sourav Maiti, Maryam Alqabandi, Nolwen Miguet, Aurélie di Cicco, Wouter H. Roos, Stéphanie Mangenot , Winfried Weissenhorn, Patricia Bassereau (2020 May 29)
Human ESCRT-III polymers assemble on positively curved membranes and induce helical membrane tube formation
Nature Communications : 11 : 2663 : DOI : 10.1038/s41467-020-16368-5

Summary

Endosomal sorting complexes for transport-III (ESCRT-III) assemble in vivo onto membranes with negative Gaussian curvature. How membrane shape influences ESCRT-III polymerization and how ESCRT-III shapes membranes is yet unclear. Human core ESCRT-III proteins,

CHMP4B, CHMP2A, CHMP2B and CHMP3 are used to address this issue in vitro by combining membrane nanotube pulling experiments, cryo-electron tomography and AFM. We show that CHMP4B filaments preferentially bind to flat membranes or to tubes with positive mean curvature. Both CHMP2B and CHMP2A/CHMP3 assemble on positively curved membrane tubes. Combinations of CHMP4B/CHMP2B and CHMP4B/CHMP2A/CHMP3 are recruited to the neck of pulled membrane tubes and reshape vesicles into helical “corkscrewlike” membrane tubes. Sub-tomogram averaging reveals that the ESCRT-III filaments assemble parallel and locally perpendicular to the tube axis, highlighting the mechanical stresses imposed by ESCRT-III. Our results underline the versatile membrane remodeling activity of ESCRT-III that may be a general feature required for cellular membrane remodeling processes.

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

Summary

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.