Année de publication : 2019

Matteo Gentili, Xavier Lahaye, Francesca Nadalin, Guilherme P F Nader, Emilia Puig Lombardi, Solène Herve, Nilushi S De Silva, Derek C Rookhuizen, Elina Zueva, Christel Goudot, Mathieu Maurin, Aurore Bochnakian, Sebastian Amigorena, Matthieu Piel, Daniele Fachinetti, Arturo Londoño-Vallejo, Nicolas Manel (2019 Mar 28)

The N-Terminal Domain of cGAS Determines Preferential Association with Centromeric DNA and Innate Immune Activation in the Nucleus.

Cell reports : 3798 : DOI : S2211-1247(19)30365-1

Résumé

Daisuke Inoue, Dorian Obino, Judith Pineau, Francesca Farina, Jérémie Gaillard, Christophe Guerin, Laurent Blanchoin, Ana-Maria Lennon-Duménil, Manuel Théry (2019 Mar 24)

Actin filaments regulate microtubule growth at the centrosome.

The EMBO journal : DOI : e99630

Résumé

The centrosome is the main microtubule-organizing centre. It also organizes a local network of actin filaments. However, the precise function of the actin network at the centrosome is not well understood. Here, we show that increasing densities of actin filaments at the centrosome of lymphocytes are correlated with reduced amounts of microtubules. Furthermore, lymphocyte activation resulted in disassembly of centrosomal actin and an increase in microtubule number. To further investigate the direct crosstalk between actin and microtubules at the centrosome, we performed reconstitution assays based on (i) purified centrosomes and (ii) on the co-micropatterning of microtubule seeds and actin filaments. These two assays demonstrated that actin filaments constitute a physical barrier blocking elongation of nascent microtubules. Finally, we showed that cell adhesion and cell spreading lead to lower densities of centrosomal actin, thus resulting in higher microtubule growth. We therefore propose a novel mechanism, by which the number of centrosomal microtubules is regulated by cell adhesion and actin-network architecture.

Vasco Rodrigues, Philippe Benaroch (2019 Mar 23)

Macrophages hide HIV in the urethra.

Nature microbiology : 556-557 : DOI : 10.1038/s41564-019-0418-5

Résumé

Roselli E1, Araya P1, Núñez NG2, Gatti G3, Graziano F4, Sedlik C4, Benaroch P4, Piaggio E4, Maccioni M1. (2019 Mar 20)

TLR3 Activation of Intratumoral CD103+ Dendritic Cells Modifies the Tumor Infiltrate Conferring Anti-tumor Immunity.
Frontiers in immunology : 10 : 503 : DOI : 10.3389/fimmu.2019.00503

Résumé

Simon C*, Kusters R*, Caorsi V*, Allard A, Abou-Ghali M, Manzi J, Di Cicco A, Lévy D, Lenz M, Joanny J-F, Campillo C, Plastino J, Sens P*, Sykes C* (2019 Mar 18)
Actin dynamics drive cell-like membrane deformation
Nature Physics : DOI : 10.1038/s41567-019-0464-1

Résumé

Cell membrane deformations are crucial for proper cell function. Specialized protein assemblies initiate inward or outward membrane deformations that the cell uses respectively to uptake external substances or probe the environment. The assembly and dynamics of the actin cytoskeleton are involved in this process, although their detailed role remains controversial. We show here that a dynamic, branched actin network is sufficient to initiate both inward and outward membrane deformation. The polymerization of a dense actin network at the membrane of liposomes produces inward membrane bending at low tension, while outward deformations are robustly generated regardless of tension. Our results shed light on the mechanism cells use to internalize material, both in mammalian cells, where actin polymerization forces are required when membrane tension is increased, and in yeast, where those forces are necessary to overcome the opposing turgor pressure. By combining experimental observations with physical modelling, we propose a mechanism that explains how membrane tension and the architecture of the actin network regulate cell-like membrane deformations.

Daniel E Murphy, Olivier G de Jong, Maarten Brouwer, Matthew J Wood, Grégory Lavieu, Raymond M Schiffelers, Pieter Vader (2019 Mar 16)
Extracellular vesicle-based therapeutics: natural versus engineered targeting and trafficking.
Experimental & molecular medicine : 32 : DOI : 10.1038/s12276-019-0223-5

Résumé

Extracellular vesicles (EVs) are increasingly being recognized as mediators of intercellular signaling via the delivery of effector molecules. Interestingly, certain types of EVs are also capable of inducing therapeutic responses. For these reasons, the therapeutic potential of EVs is a topic of intense research, both in the context of drug delivery and regenerative medicine. However, to fully utilize EVs for therapeutic purposes, an improved understanding of the mechanisms by which they function would be highly advantageous. Here, the current state of knowledge regarding the cellular uptake and trafficking of EVs is reviewed, along with a consideration of how these pathways potentially influence the functions of therapeutic

EVs. Furthermore, the natural cell-targeting abilities, biodistribution profiles, and pharmacokinetics of exogenously administered EVs, along with the components responsible for these features are discussed. An overview of the potential clinical applications and preclinical examples of their successful use is also provided. Finally, examples of EV modifications that have successfully been employed to improve their therapeutic characteristics receive a particular focus. We suggest that, in addition to investigation of EV cell targeting and routes of uptake, future research into the routes of intracellular trafficking in recipient cells is required to optimally utilize EVs for therapeutic purposes.

Hélène Salmon, Romain Remark, Sacha Gnjatic, Miriam Merad (2019 Mar 15)
Host tissue determinants of tumour immunity.
Nature Reviews Cancer : 215-227 : DOI : 10.1038/s41568-019-0125-9

Résumé

Although common evolutionary principles drive the growth of cancer cells regardless of the tissue of origin, the microenvironment in which tumours arise substantially differs across various organ sites. Recent studies have established that, in addition to cell-intrinsic effects, tumour growth regulation also depends on local cues driven by tissue environmental factors. In this Review, we discuss how tissue-specific determinants might influence tumour development and argue that unravelling the tissue-specific contribution to tumour immunity should help the development of precise immunotherapeutic strategies for patients with cancer.

Michel Wassef, Armelle Luscan, Setareh Aflaki, Dina Zielinski, Pascal W T C Jansen, H Irem Baymaz, Aude Battistella, Carole Kersouani, Nicolas Servant, Margaret R Wallace, Pierre Romero, Olivier Kosmider, Pierre-Alexandre Just, Mikaël Hivelin, Sébastien Jacques, Anne Vincent-Salomon, Michiel Vermeulen, Michel Vidaud, Eric Pasmant, Raphaël Margueron (2019 Mar 15)
EZH1/2 function mostly within canonical PRC2 and exhibit proliferation-dependent redundancy that shapes mutational signatures in cancer.
Proceedings of the National Academy of Sciences of the United States of America : 6075-6080 : DOI : 10.1073/pnas.1814634116

Résumé

Genetic mutations affecting chromatin modifiers are widespread in cancers. In malignant peripheral nerve sheath tumors (MPNSTs), Polycomb repressive complex 2 (PRC2), which plays a crucial role in gene silencing, is inactivated through recurrent mutations in core subunits embryonic ectoderm development (EED) and suppressor of zeste 12 homolog (SUZ12), but mutations in PRC2's main catalytic subunit enhancer of zeste homolog 2 (EZH2) have never been found. This is in contrast to myeloid and lymphoid malignancies, which harbor frequent loss-of-function mutations in EZH2. Here, we investigated whether the absence of EZH2 mutations in MPNST is due to a PRC2-independent (i.e., noncanonical) function of the enzyme or to redundancy with EZH1. We show that, in the absence of SUZ12,

EZH2 remains bound to EED but loses its interaction with all other core and accessory PRC2 subunits. Through genetic and pharmacological analyses, we unambiguously establish that EZH2 is functionally inert in this context, thereby excluding a PRC2-independent function. Instead, we show that EZH1 and EZH2 are functionally redundant in the slowly proliferating MPNST precursors. We provide evidence that the compensatory function of EZH1 is alleviated upon higher proliferation. This work reveals how context-dependent redundancies can shape tumor-type specific mutation patterns in chromatin regulators.

Virginie Carmignac, Julie Barberet, Julian Iranzo, Ronan Quéré, Magali Guilleman, Déborah Bourc'his, Patricia Fauque (2019 Mar 14)
Effects of assisted reproductive technologies on transposon regulation in the mouse pre-implanted embryo.
Human reproduction (Oxford, England) : 612-622 : DOI : 10.1093/humrep/dez020

Résumé

Do assisted reproductive technologies (ARTs) impact on the expression of transposable elements (TEs) in preimplantation embryos?

Pierre Guermonprez, Julie Helft (2019 Mar 13)
Inflammasome activation: a monocyte lineage privilege.
Nature immunology : 383-385 : DOI : 10.1038/s41590-019-0348-7

Résumé

Isabelle Loiodice, Marcel E Janson, Penny Tavormina, Sebastien Schaub, Divya Bhatt, Ryan Cochran, Julie Czupryna, Chuanhai Fu, Phong T Tran (2019 Mar 7)
Quantifying Tubulin Concentration and Microtubule Number Throughout the Fission Yeast Cell Cycle.
Biomolecules : DOI : E86

Résumé

The fission yeast serves as a good genetic model organism for the molecular dissection of the microtubule (MT) cytoskeleton. However, analysis of the number and distribution of individual MTs throughout the cell cycle, particularly during mitosis, in living cells is still lacking, making quantitative modelling imprecise. We use quantitative fluorescent imaging and analysis to measure the changes in tubulin concentration and MT number and distribution throughout the cell cycle at a single MT resolution in living cells. In the wild-type cell, both mother and daughter spindle pole body (SPB) nucleate a maximum of 23 ± 6 MTs at the onset of mitosis, which decreases to a minimum of 4 ± 1 MTs at spindle break down. Interphase MT bundles, astral MT bundles, and the post anaphase array (PAA) microtubules

are composed primarily of 1 ± 1 individual MT along their lengths. We measure the cellular concentration of αβ-tubulin subunits to be ~5 μM throughout the cell cycle, of which one-third is in polymer form during interphase and one-quarter is in polymer form during mitosis. This analysis provides a definitive characterization of αβ-tubulin concentration and MT number and distribution in fission yeast and establishes a foundation for future quantitative comparison of mutants defective in MTs.

Paul D., Marchand A., Verga D., Bombard S., Teulade-Fichou M.P., Rosu F., Gabelica V. (2019 Feb 28)

Probing Ligand and Cation Binding Sites in G-Quadruplex Nucleic Acids by Mass Spectrometry and Electron Photodetachment Dissociation Sequencing

Analyst : 144 : 3518-3524 : DOI : 10.1039/C9AN00398C

Résumé

Mass spectrometry provides exquisite detail on ligand and cation binding stoichiometries with a DNA target. The next important step is to develop reliable methods to determine the cation and ligand binding sites in each complex separated by the mass spectrometer. To circumvent the caveat of ligand derivatization for cross-linking, which may alter the ligand binding mode, we explored a tandem mass spectrometry (MS/MS) method that does not require ligand derivatization, and is therefore also applicable to localize metal cations. By obtaining more negative charge states for the complexes using supercharging agents, and by creating radical ions by electron photodetachment, oligonucleotide bonds become weaker than the DNA-cation or DNA-ligand noncovalent bonds upon collision-induced dissociation of the radicals. This electron photodetachment (EPD) method allows to locate the binding regions of cations and ligands by top-down sequencing of the oligonucleotide target. The very potent G-quadruplex ligands 360A and PhenDC3 were found to replace a potassium cation and bind close to the central loop of 4-repeat human telomeric sequences.

Lara Katharina Krüger, Jérémie-Luc Sanchez, Anne Paoletti, Phong Thanh Tran (2019 Feb 27)

Kinesin-6 regulates cell-size-dependent spindle elongation velocity to keep mitosis duration constant in fission yeast.

eLife : DOI : 10.7554/eLife.42182

Résumé

The length of the mitotic spindle scales with cell size in a wide range of organisms during embryonic development. Interestingly, in embryos, this goes along with temporal regulation: larger cells speed up spindle assembly and elongation. We demonstrate that, similarly in fission yeast, spindle length and spindle dynamics adjust to cell size, which allows to keep mitosis duration constant. Since prolongation of mitosis was shown to affect cell viability, this may resemble a mechanism to regulate mitosis duration. We further reveal how the velocity of spindle elongation is regulated: coupled to cell size, the amount of kinesin-6 Klp9 molecules increases, resulting in an acceleration of spindle elongation in anaphase B. In

addition, the number of Klp9 binding sites to microtubules increases overproportionally to Klp9 molecules, suggesting that molecular crowding inversely correlates to cell size and might have an impact on spindle elongation velocity control.

Marco Lucchino, Anne Billet, Antoine Versini, Harikrishna Bavireddi, Bhanu-Das Dasari, Sylvain Debieu, Ludovic Colombeau, Tatiana Cañeque, Alain Wagner, Géraldine Masson, Frédéric Taran, Philippe Karoyan, Muriel Delepierre, Christine Gaillet, Anne Houdusse, Sébastien Britton, Frédéric Schmidt, Jean-Claude Florent, Philippe Belmont, David Monchaud, Janine Cossy, Christophe Thomas, Arnaud Gautier, Ludger Johannes, Raphaël Rodriguez (2019 Feb 26)

2nd PSL Chemical Biology Symposium (2019): At the Crossroads of Chemistry and Biology.

Chembiochem : a European journal of chemical biology : 968-973 : DOI : 10.1002/cbic.201900092

Résumé

Chemical Biology is the science of designing chemical tools to dissect and manipulate biology at different scales. It provides the fertile ground from which to address important problems of our society, such as human health and environment.

Derya Deveci, Francisco A Martin, Pierre Leopold*, Nuria M Romero*, (*Corr. author) (2019 Feb 26)

AstA Signaling Functions as an Evolutionary Conserved Mechanism Timing Juvenile to Adult Transition.

Current biology : CB : 813-822.e4 : DOI : 10.1016/j.cub.2019.01.053

Résumé

The onset of sexual maturation is the result of a hormonal cascade peaking with the production of steroid hormones. In animals undergoing a program of determinate growth, sexual maturation also coincides with the attainment of adult size. The exact signals that time the onset of maturation and the mechanisms coupling growth and maturation remain elusive. Here, we show that the Drosophila neuropeptide AstA and its receptor AstAR1 act as a brain trigger for maturation and juvenile growth. We first identified AstAR1 in an RNAi-based genetic screen as a key regulator of sexual maturation. Its specific knockdown in prothoracicotropic hormone (PTTH)-producing neurons delays the onset of maturation by impairing PTTH secretion. In addition to its role in PTTH neurons, AstAR1 is required in the brain insulin-producing cells (IPCs) to promote insulin secretion and systemic growth. AstAR1 function is mediated by the AstA neuropeptide that is expressed in two bilateral neurons contacting the PTTH neurons and the IPCs. Silencing brain AstA expression delays the onset of maturation, therefore extending the growth period. However, no pupal overgrowth is observed, indicating that, in these conditions, the growth-promoting function of AstAR1 is also impaired. These data suggest that AstA/AstAR1 acts to coordinate juvenile growth with

maturation. Interesting, AstA/AstAR1 is homologous to KISS/GPR54, a ligand-receptor signal required for human puberty, suggesting that an evolutionary conserved neural circuitry controls the onset of maturation.