Year of publication 2019

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

Summary

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

Summary

Jamecna D, Polidori DJ, Mesmin B, Dezi M, Lévy D, Bigay J, Antonny B (2019 Mar 22)
An intrinsically disordered region in OSBP acts as an entropic barrier to control protein dynamics and orientation at membrane contact sites
Developmental cell * : * highlighted Trend in Cell Biology 2019 : DOI : 10.1016/j.devcel.2019.02.021

Summary

Lipid transfer proteins (LTPs) acting at membrane contact sites (MCS) between the ER and other organelles contain domains involved in heterotypic (e.g. ER to Golgi) membrane tethering as well as domains involved in lipid transfer. Here, we show that a long ≈ 90 aa intrinsically unfolded sequence at the N-terminus of oxysterol binding protein (OSBP) controls OSBP orientation and dynamics at MCS. This Gly-Pro-Ala-rich sequence, whose hydrodynamic radius is twice as that of folded domains, prevents the two PH domains of the OSBP dimer from homotypically tethering two Golgi-like membranes and considerably

facilitates OSBP in-plane diffusion and recycling at MCS. Although quite distant in sequence, the N-terminus of OSBP-related protein-4 (ORP4) has similar effects. We propose that N-terminal sequences of low complexity in ORPs form an entropic barrier that restrains protein orientation, limits protein density and facilitates protein mobility in the narrow and crowded MCS environment.

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

Summary

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

Summary

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.

Aria Ronsmans, Maxime Wery, Ugo Szachnowski, Camille Gautier, Marc Descrimes, Evelyne Dubois, Antonin Morillon, Isabelle Georis (2019 Mar 1)
Transcription-dependent spreading of the Dal80 yeast GATA factor across the body of highly expressed genes.
PLoS genetics : e1007999 : DOI : 10.1371/journal.pgen.1007999

Summary

GATA transcription factors are highly conserved among eukaryotes and play roles in transcription of genes implicated in cancer progression and hematopoiesis. However, although their consensus binding sites have been well defined in vitro, the in vivo selectivity for recognition by GATA factors remains poorly characterized. Using ChIP-Seq, we identified the Dal80 GATA factor targets in yeast. Our data reveal Dal80 binding to a large set of promoters, sometimes independently of GATA sites, correlating with nitrogen- and/or Dal80-

sensitive gene expression. Strikingly, Dal80 was also detected across the body of promoter-bound genes, correlating with high expression. Mechanistic single-gene experiments showed that Dal80 spreading across gene bodies requires active transcription. Consistently, Dal80 co-immunoprecipitated with the initiating and post-initiation forms of RNA Polymerase II. Our work suggests that GATA factors could play dual, synergistic roles during transcription initiation and post-initiation steps, promoting efficient remodeling of the gene expression program in response to environmental changes.

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 : Accepted Manuscript : DOI : 10.1039/C9AN00398C

Summary

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.

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

Summary

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.

Paola Bonaventura, Tala Shekarian, Vincent Alcazer, Jenny Valladeau-Guilemond, Sandrine Valsesia-Wittmann, Sebastian Amigorena, Christophe Caux, Stéphane Depil (2019 Feb 26)
Cold Tumors: A Therapeutic Challenge for Immunotherapy.
Frontiers in immunology : 168 : DOI : 10.3389/fimmu.2019.00168

Summary

Therapeutic monoclonal antibodies targeting immune checkpoints (ICPs) have changed the treatment landscape of many tumors. However, response rate remains relatively low in most cases. A major factor involved in initial resistance to ICP inhibitors is the lack or paucity of tumor T cell infiltration, characterizing the so-called “cold tumors.” In this review, we describe the main mechanisms involved in the absence of T cell infiltration, including lack of tumor antigens, defect in antigen presentation, absence of T cell activation and deficit of homing into the tumor bed. We discuss then the different therapeutic approaches that could turn cold into hot tumors. In this way, specific therapies are proposed according to their mechanism of action. In addition, ”supra-physiological” therapies, such as T cell recruiting bispecific antibodies and Chimeric Antigen Receptor (CAR) T cells, may be active regardless of the mechanism involved, especially in MHC class I negative tumors. The determination of the main factors implicated in the lack of preexisting tumor T cell infiltration is crucial for the development of adapted algorithms of treatments for cold tumors.

Daghildjian K., Kasselouri A., N’Diaye M., Michel J.P., Vergnaud J., Poyer F., Maillard P., Rosilio V. (2019 Feb 23)
Mannose distribution in glycoconjugated tetraphenylporphyrins governs their uptake mechanism and phototoxicity
Journal of Porphyrins and Phthalocyanines : 23 : 175-184 : DOI : 10.1142/S1088424619500184

Summary

Tetraphenylporphyrins (TPPs) have been proposed for the treatment of retinoblastoma by photodynamic therapy. Glycoconjugated compounds were synthesized for improving TPP

solubility and amphipathy, and to specifically target mannose receptors overexpressed at the surface of cells. The efficiency of four TPP derivatives with different chemical structures was compared by phototoxicity tests and flow cytometry experiments. Interestingly, the absence/presence and distribution of saccharide moieties in the various compounds affected differently their mechanism of interaction with cancer cells and their phototoxic efficiency. For glycodendrimeric **TPP-1** and **TPP-2** incubated with retinoblastoma cells, a fast two-step uptake-equilibrium process was observed, whereas for a dendrimeric TPP without saccharide moieties (**TPP-1c**) and a glycoconjugated compound with no dendrimeric structure (**TPP(DegMan)**3) uptake was very slow. The difference in uptake profiles and kinetics between **TPP-1c** on the one hand and **TPP-1** and **TPP-2** on the other hand would account for the interaction of the two glycodendrimeric compounds with a mannose receptor. These TPPs encapsulated in endosomes would induce less damage to cells upon illumination. **TPP(DegMan)**3 showed the highest phototoxicity, but its efficiency was unaffected by pretreatment of cells by mannan. The penetration of this glycoconjugated compound in cells and its phototoxic effect appeared independent of its interaction with a mannose receptor. Thus, if glycoconjugation influenced TPPs behavior in solution and interaction with serum proteins, phototoxicity was not necessarily related to upfront molecular recognition.

Bingning Xie, Emmanuelle Becker, Igor Stuparevic, Maxime Wery, Ugo Szachnowski, Antonin Morillon, Michael Primig (2019 Feb 15)

The anti-cancer drug 5-fluorouracil affects cell cycle regulators and potential regulatory long non-coding RNAs in yeast.

RNA biology : 1-15 : DOI : 10.1080/15476286.2019.1581596

Summary

5-fluorouracil (5-FU) was isolated as an inhibitor of thymidylate synthase, which is important for DNA synthesis. The drug was later found to also affect the conserved 3′-5′ exoribonuclease EXOSC10/Rrp6, a catalytic subunit of the RNA exosome that degrades and processes protein-coding and non-coding transcripts. Work on 5-FU's cytotoxicity has been focused on mRNAs and non-coding transcripts such as rRNAs, tRNAs and snoRNAs. However, the effect of 5-FU on long non-coding RNAs (lncRNAs), which include regulatory transcripts important for cell growth and differentiation, is poorly understood. RNA profiling of synchronized 5-FU treated yeast cells and protein assays reveal that the drug specifically inhibits a set of cell cycle regulated genes involved in mitotic division, by decreasing levels of the paralogous Swi5 and Ace2 transcriptional activators. We also observe widespread accumulation of different lncRNA types in treated cells, which are typically present at high levels in a strain lacking EXOSC10/Rrp6. 5-FU responsive lncRNAs include potential regulatory antisense transcripts that form double-stranded RNAs (dsRNAs) with overlapping sense mRNAs. Some of these transcripts encode proteins important for cell growth and division, such as the transcription factor Ace2, and the RNA exosome subunit EXOSC6/Mtr3. In addition to revealing a transcriptional effect of 5-FU action via DNA binding regulators involved in cell cycle progression, our results have implications for the function of putative regulatory lncRNAs in 5-FU mediated cytotoxicity. The data raise the intriguing possibility that the drug deregulates lncRNAs/dsRNAs involved in controlling eukaryotic cell division, thereby highlighting a new class of promising therapeutical targets.

Catherine Strassel, Maria M Magiera, Arnaud Dupuis, Morgane Batzenschlager, Agnès Hovasse, Irina Pleines, Paul Guéguen, Anita Eckly, Sylvie Moog, Léa Mallo, Quentin Kimmerlin, Stéphane Chappaz, Jean-Marc Strub, Natarajan Kathiresan, Henri de la Salle, Alain Van Dorsselaer, Claude Ferec, Jean-Yves Py, Christian Gachet, Christine Schaeffer-Reiss, Benjamin T Kile, Carsten Janke, François Lanza (2019 Feb 15)

An essential role for α4A-tubulin in platelet biogenesis.

Life science alliance : DOI : e201900309

Summary

During platelet biogenesis, microtubules (MTs) are arranged into submembranous structures (the marginal band) that encircle the cell in a single plane. This unique MT array has no equivalent in any other mammalian cell, and the mechanisms responsible for this particular mode of assembly are not fully understood. One possibility is that platelet MTs are composed of a particular set of tubulin isotypes that carry specific posttranslational modifications. Although β1-tubulin is known to be essential, no equivalent roles of α-tubulin isotypes in platelet formation or function have so far been reported. Here, we identify α4A-tubulin as a predominant α-tubulin isotype in platelets. Similar to β1-tubulin, α4A-tubulin expression is up-regulated during the late stages of megakaryocyte differentiation. Missense mutations in the α4A-tubulin gene cause macrothrombocytopenia in mice and humans. Defects in α4A-tubulin lead to changes in tubulin tyrosination status of the platelet tubulin pool. Ultrastructural defects include reduced numbers and misarranged MT coils in the platelet marginal band. We further observed defects in megakaryocyte maturation and proplatelet formation in -mutant mice. We have, thus, discovered an α-tubulin isotype with specific and essential roles in platelet biogenesis.

Morgan Pellerano, Delphine Naud-Martin, Florence Mahuteau-Betzer, Marie Morille, May Catherine Morris (2019 Feb 15)

Fluorescent biosensor for detection of the R248Q aggregation-prone mutant of p53.

Chembiochem : a European journal of chemical biology : 20 : 605-613 : DOI : 10.1002/cbic.201800531

Summary

The p53 tumour suppressor and guardian of the genome undergoes missense mutations which lead to functional inactivation in 50% human cancers. These mutations occur mostly in the DNA-binding domain of the protein and several of these induce conformational changes which lead to amyloid-like protein aggregation. Here we describe a fluorescent biosensor that reports on the R248Q mutant of p53 in vitro and in living cells, engineered through conjugation of an environmentally-sensitive probe onto a peptide derived from the primary aggregation segment of p53.This biosensor was characterized both in vitro and by fluorescence microscopy following facilitated delivery into cultured cells. We show that this biosensor preferentially reports on the p53 R248Q mutant in PC9 lung cancer cell line

compared to other lung cancer cell lines harbouring either wildtype or no p53.

Bertin Aurélie, Lomakin Alexis (2019 Feb 15)
Meeting report – Building the Cell 2018
journal of cell science : 132 : DOI : 10.1242/jcs.229765

Summary

Cell biologists from all around the world gathered in Paris on the 26 to 28 September 2018 to participate in the 3rd international meeting ‘Building the Cell’. It was organized by Hélène Barelli, Arnaud Echard, Thierry Galli, Florence Niedergang, Manuel Théry and Marie Hélène Verlhac on behalf of the French Society for Cell Biology (SBCF) at the Institut Pasteur. Around 230 participants joined the meeting for stimulating talks, discussions, poster sessions, and a gala dinner on the Seine that included a music performance by the rock group ‘Membrane Band’. The unifying theme of the meeting was the development of creative multidisciplinary approaches to understand cellular life at different scales in a dynamic and quantitative manner. Here, we summarize the results presented at the meeting and the emerging ideas from the different sessions.

The 3rd international meeting ‘Building the Cell’ (Fig. 1; Fig. 2) was divided into ten different sessions that covered a variety of topics including intracellular trafficking, cell division, cytoskeletal dynamics and cell mechanics, cancer and stem cell biology, embryonic development and tissue morphogenesis, neurobiology, and aggregates and phase transitions. A broad spectrum of modern approaches and experimental systems ranging from synthetic biology and stem cell technologies to 3D organoids and animal models was presented. The meeting highlighted some of the latest and novel findings in cell biology, often coupled to major methodological developments in quantitative microscopy and computational modelling, as well as cell and tissue micro-engineering.

Marine Gros, Sebastian Amigorena (2019 Feb 13)
Regulation of Antigen Export to the Cytosol During Cross-Presentation.
Frontiers in immunology : 41 : DOI : 10.3389/fimmu.2019.00041

Summary

Cross-priming refers to the induction of primary cytotoxic CD8 T cell responses to antigens that are not expressed in antigen presenting cells (APCs) responsible for T cell priming. Cross-priming is achieved through cross-presentation of exogenous antigens derived from tumors, extracellular pathogens or infected neighboring cells on Major Histocompatibility Complex (MHC) class I molecules. Despite extensive research efforts to understand the intracellular pathways involved in antigen cross-presentation, certain critical steps remain elusive and controversial. Here we review recent advances on antigen cross-presentation, focusing on the mechanisms involved in antigen export to the cytosol, a crucial step of this pathway.