Année de publication : 2021

Graça Raposo, Guillaume van Niel, Philip D Stahl (2021 Jun 14)
Extracellular vesicles and homeostasis-An emerging field in bioscience research.
FASEB bioAdvances : 456-458 : DOI : 10.1096/fba.2021-00009

Résumé

To keep abreast of developments in the biological sciences and in parallel fields such as medical education, () has created a special collections category, special collections (SC), that target, among other topics, emerging disciplines in the biomedical sciences. This SC is focused on the emerging field of extracellular vesicles (EVs) and homeostasis. Leading investigators in the biology of EVs around the globe have contributed to this collection of articles that cover the gamut of research activities from biogenesis and secretion to physiological function.

Kaushik Inamdar, Feng-Ching Tsai, Rayane Dibsy, Aurore de Poret, John Manzi, Peggy Merida, Remi Muller, Pekka Lappalainen, Philippe Roingeard, Johnson Mak, Patricia Bassereau, Cyril Favard, Delphine Muriaux (2021 Jun 11)
Full assembly of HIV-1 particles requires assistance of the membrane curvature factor IRSp53.
eLife : DOI : 10.7554/eLife.67321

Résumé

During HIV-1 particle formation, the requisite plasma membrane curvature is thought to be solely driven by the retroviral Gag protein. Here, we reveal that the cellular I-BAR protein IRSp53 is required for the progression of HIV-1 membrane curvature to complete particle assembly. siRNA-mediated knockdown of IRSp53 gene expression induces a decrease in viral particle production and a viral bud arrest at half completion. Single-molecule localization microscopy at the cell plasma membrane shows a preferential localization of IRSp53 around HIV-1 Gag assembly sites. In addition, we observe the presence of IRSp53 in purified HIV-1 particles. Finally, HIV-1 Gag protein preferentially localizes to curved membranes induced by IRSp53 I-BAR domain on giant unilamellar vesicles. Overall, our data reveal a strong interplay between IRSp53 I-BAR and Gag at membranes during virus assembly. This highlights IRSp53 as a crucial host factor in HIV-1 membrane curvature and its requirement for full HIV-1 particle assembly.

Angela Bellini, Ulrike Pötschger, Virginie Bernard, Eve Lapouble, Sylvain Baulande, Peter F Ambros, Nathalie Auger, Klaus Beiske, Marie Bernkopf, David R Betts, Jaydutt Bhalshankar, Nick Bown, Katleen de Preter, Nathalie Clément, Valérie Combaret, Jaime Font de Mora, Sally L George, Irene Jiménez, Marta Jeison, Barbara Marques, Tommy Martinsson, Katia Mazzocco, Martina Morini, Annick Mühlethaler-Mottet, Rosa Noguera, Gaelle Pierron, Maria Rossing, Sabine

Taschner-Mandl, Nadine Van Roy, Ales Vicha, Louis Chesler, Walentyna Balwierz, Victoria Castel, Martin Elliott, Per Kogner, Geneviève Laureys, Roberto Luksch, Josef Malis, Maja Popovic-Beck, Shifra Ash, Olivier Delattre, Dominique Valteau-Couanet, Deborah A Tweddle, Ruth Ladenstein, Gudrun Schleiermacher (2021 Jun 11)

Frequency and Prognostic Impact of Amplifications and Mutations in the European Neuroblastoma Study Group (SIOPEN) High-Risk Neuroblastoma Trial (HR-NBL1).

Journal of clinical oncology : official journal of the American Society of Clinical Oncology : JCO2100086 : DOI : 10.1200/JCO.21.00086

Résumé

In neuroblastoma (NB), the ALK receptor tyrosine kinase can be constitutively activated through activating point mutations or genomic amplification. We studied genetic alterations in high-risk (HR) patients on the HR-NBL1/SIOPEN trial to determine their frequency, correlation with clinical parameters, and prognostic impact.

GAUTIER Margot, THIRIANTCécile, DELATTRE Olivier, JANOUEIX-LEROSEY Isabelle (2021 Jun 10)

Plasticity in Neuroblastoma Cell Identity Defines a Noradrenergic-to-Mesenchymal Transition (NMT)

Cancers (Basel) : 13(12):2904. : DOI : 10.3390/cancers13122904

Résumé

Neuroblastoma, a pediatric cancer of the peripheral sympathetic nervous system, is characterized by an important clinical heterogeneity, and high-risk tumors are associated with a poor overall survival. Neuroblastoma cells may present with diverse morphological and biochemical properties in vitro, and seminal observations suggested that interconversion between two phenotypes called N-type and S-type may occur. In 2017, two main studies provided novel insights into these subtypes through the characterization of the transcriptomic and epigenetic landscapes of a panel of neuroblastoma cell lines. In this review, we focus on the available data that define neuroblastoma cell identity and propose to use the term noradrenergic (NOR) and mesenchymal (MES) to refer to these identities. We also address the question of transdifferentiation between both states and suggest that the plasticity between the NOR identity and the MES identity defines a noradrenergic-to-mesenchymal transition, reminiscent of but different from the well-established epithelial-to-mesenchymal transition.

Daniel Lévy, Aurélie Di Cicco, Aurélie Bertin, Manuela Dezi (2021 Jun 7)

[Cryo-electron microcopy for a new vision of the cell and its components]

Medecine/Sciences : 379-385 : DOI : 10.1051/medsci/2021034

Résumé

Cryo-electron microscopy (cryo-EM) is a technique for imaging biological samples that plays a central role in structural biology, with high impact on research fields such as cell and developmental biology, bioinformatics, cell physics and applied mathematics. It allows the determination of structures of purified proteins within cells. This review describes the main recent advances in cryo-EM, illustrated by examples of proteins of biomedical interest, and the avenues for future development.

Eugenio de la Mora, Manuela Dezi, Aurélie Di Cicco, Joëlle Bigay, Romain Gautier, John Manzi, Joël Polidori, Daniel Castaño Díez, Bruno Mesmin, Bruno Antonny, Daniel Lévy. (2021 Jun 7)
Nanoscale architecture of a VAP-A-OSBP tethering complex at membrane contact sites
Nature Communications : DOI : 10.1038/s41467-021-23799-1

Résumé

Membrane contact sites (MCS) are subcellular regions where two organelles appose their membranes to exchange small molecules, including lipids. Structural information on how proteins form MCS is scarce. We designed an in vitro MCS with two membranes and a pair of tethering proteins suitable for cryo-tomography analysis. It includes VAP-A, an ER transmembrane protein interacting with a myriad of cytosolic proteins, and oxysterol-binding protein (OSBP), a lipid transfer protein that transports cholesterol from the ER to the trans Golgi network. We show that VAP-A is a highly flexible protein, allowing formation of MCS of variable intermembrane distance. The tethering part of OSBP contains a central, dimeric, and helical T-shape region. We propose that the molecular flexibility of VAP-A enables the recruitment of partners of different sizes within MCS of adjustable thickness, whereas the T geometry of the OSBP dimer facilitates the movement of the two lipid-transfer domains between membranes.

Zhou J, Gelot C, Pantelidou C, Li A, Yücel H, Davis RE, Farkkila A, Kochupurakkal B, Syed A, Shapiro GI, Tainer JA, Blagg BSJ, Ceccaldi R*, D'Andrea AD*. * co-last and co-corresponding authors. (2021 Jun 2)
A first-in-class Polymerase Theta Inhibitor selectively targets Homologous Recombination-Deficient Tumors.
Nature Cancer : 598-610 : DOI : 10.1038/s43018-021-00203-xs

Résumé

DNA polymerase theta (POLθ or POLQ) is synthetic lethal with homologous recombination (HR) deficiency and is thus a candidate target for HR-deficient cancers. Through high-throughput small-molecule screens, we identified the antibiotic novobiocin (NVB) as a specific POLθ inhibitor that selectively kills HR-deficient tumor cells in vitro and in vivo. NVB

directly binds to the POLθ ATPase domain, inhibits its ATPase activity and phenocopies POLθ depletion. NVB kills HR-deficient breast and ovarian tumors in genetically engineered mouse models and xenograft and patient-derived xenograft models. Increased POLθ levels predict NVB sensitivity, and HR-deficient tumor cells with acquired resistance to poly(ADP-ribose) polymerase (PARP) inhibitors
(PARPi) are sensitive to NVB in vitro and in vivo. Mechanistically, NVB-mediated cell death in PARPi-resistant cells arises from increased double-strand break end resection, leading to accumulation of single-stranded DNA intermediates and nonfunctional foci of the recombinase RAD51. Our results demonstrate that NVB may be useful alone or in combination with PARPi for treating HR-deficient tumors, including those with acquired PARPi resistance.

Peter Peneder, Adrian M Stütz, Didier Surdez, Manuela Krumbholz, Sabine Semper, Mathieu Chicard, Nathan C Sheffield, Gaelle Pierron, Eve Lapouble, Marcus Tötzl, Bekir Ergüner, Daniele Barreca, André F Rendeiro, Abbas Agaimy, Heidrun Boztug, Gernot Engstler, Michael Dworzak, Marie Bernkopf, Sabine Taschner-Mandl, Inge M Ambros, Ola Myklebost, Perrine Marec-Bérard, Susan Ann Burchill, Bernadette Brennan, Sandra J Strauss, Jeremy Whelan, Gudrun Schleiermacher, Christiane Schaefer, Uta Dirksen, Caroline Hutter, Kjetil Boye, Peter F Ambros, Olivier Delattre, Markus Metzler, Christoph Bock, Eleni M Tomazou (2021 May 29)
Multimodal analysis of cell-free DNA whole-genome sequencing for pediatric cancers with low mutational burden.
Nature communications : 3230 : DOI : 10.1038/s41467-021-23445-w

Résumé

Sequencing of cell-free DNA in the blood of cancer patients (liquid biopsy) provides attractive opportunities for early diagnosis, assessment of treatment response, and minimally invasive disease monitoring. To unlock liquid biopsy analysis for pediatric tumors with few genetic aberrations, we introduce an integrated genetic/epigenetic analysis method and demonstrate its utility on 241 deep whole-genome sequencing profiles of 95 patients with Ewing sarcoma and 31 patients with other pediatric sarcomas. Our method achieves sensitive detection and classification of circulating tumor DNA in peripheral blood independent of any genetic alterations. Moreover, we benchmark different metrics for cell-free DNA fragmentation analysis, and we introduce the LIQUORICE algorithm for detecting circulating tumor DNA based on cancer-specific chromatin signatures. Finally, we combine several fragmentation-based metrics into an integrated machine learning classifier for liquid biopsy analysis that exploits widespread epigenetic deregulation and is tailored to cancers with low mutation rates. Clinical associations highlight the potential value of cfDNA fragmentation patterns as prognostic biomarkers in Ewing sarcoma. In summary, our study provides a comprehensive analysis of circulating tumor DNA beyond recurrent genetic aberrations, and it renders the benefits of liquid biopsy more readily accessible for childhood cancers.

Ashley L Arthur, Amy Crawford, Anne Houdusse, Margaret A Titus (2021 May 27)
VASP mediated actin dynamics activate and recruit a filopodia myosin.
eLife : DOI : 10.7554/eLife.68082

Résumé

Filopodia are thin, actin-based structures that cells use to interact with their environments. Filopodia initiation requires a suite of conserved proteins but the mechanism remains poorly understood. The actin polymerase VASP and a MyTH-FERM (MF) myosin, DdMyo7 in amoeba, are essential for filopodia initiation. DdMyo7 is localized to dynamic regions of the actin-rich cortex. Analysis of VASP mutants and treatment of cells with anti-actin drugs shows that myosin recruitment and activation in requires localized VASP-dependent actin polymerization. Targeting of DdMyo7 to the cortex alone is not sufficient for filopodia initiation; VASP activity is also required. The actin regulator locally produces a cortical actin network that activates myosin and together they shape the actin network to promote extension of parallel bundles of actin during filopodia formation. This work reveals how filopodia initiation requires close collaboration between an actin binding protein, the state of the actin cytoskeleton and MF myosin activity.

Anne Houdusse, Margaret A Titus (2021 May 25)
The many roles of myosins in filopodia, microvilli and stereocilia.
Current biology : CB : R586-R602 : DOI : S0960-9822(21)00518-2

Résumé

Filopodia, microvilli and stereocilia represent an important group of plasma membrane protrusions. These specialized projections are supported by parallel bundles of actin filaments and have critical roles in sensing the external environment, increasing cell surface area, and acting as mechanosensors. While actin-associated proteins are essential for actin-filament elongation and bundling in these protrusions, myosin motors have a surprising role in the formation and extension of filopodia and stereocilia and in the organization of microvilli. Actin regulators and specific myosins collaborate in controlling the length of these structures. Myosins can transport cargoes along the length of these protrusions, and, in the case of stereocilia and microvilli, interactions with adaptors and cargoes can also serve to anchor adhesion receptors to the actin-rich core via functionally conserved motor-adaptor complexes. This review highlights recent progress in understanding the diverse roles myosins play in filopodia, microvilli and stereocilia.

Linh Le, Julia Sirés-Campos, Graça Raposo, Cédric Delevoye, Michael S Marks (2021 May 22)
Melanosome biogenesis in the pigmentation of mammalian skin.
Integrative and comparative biology : DOI : icab078

Résumé

Melanins, the main pigments of the skin and hair in mammals, are synthesized within membrane-bound organelles of melanocytes called melanosomes. Melanosome structure and function are determined by a cohort of resident transmembrane proteins, many of which are expressed only in pigment cells, that localize specifically to melanosomes. Defects in the genes that encode melanosome-specific proteins or components of the machinery required for their transport in and out of melanosomes underlie various forms of ocular or oculocutaneous albinism, characterized by hypopigmentation of the hair, skin and eyes and by visual impairment. We review major components of melanosomes, including the enzymes that catalyze steps in melanin synthesis from tyrosine precursors, solute transporters that allow these enzymes to function, and structural proteins that underlie melanosome shape and melanin deposition. We then review the molecular mechanisms by which these components are biosynthetically delivered to newly forming melanosomes-many of which are shared by other cell types that generate cell type-specific lysosome-related organelles. We also highlight unanswered questions that need to be addressed by future investigation.

Hai-Feng Zhang, Christopher S Hughes, Wei Li, Jian-Zhong He, Didier Surdez, Amal M El-Naggar, Hongwei Cheng, Anna Prudova, Alberto Delaidelli, Gian Luca Negri, Xiaojun Li, Maj Sofie Orum-Madsen, Michael M Lizardo, Htoo Zarni Oo, Shane Colborne, Taras Shyp, Renata Scopim-Ribeiro, Colin A Hammond, Anne-Chloe Dhez, Sofya Langman, Jonathan Km Lim, Sonia Hy Kung, Amy Li, Anne Steino, Mads Daugaard, Seth J Parker, Ramon I Klein Geltink, Rimas J Orentas, Li-Yan Xu, Gregg B Morin, Olivier Delattre, Dimiter S Dimitrov, Poul H Sorensen (2021 May 22)
Proteomic screens for suppressors of anoikis identify IL1RAP as a promising surface target in Ewing sarcoma.
Cancer discovery : DOI : candisc.1690.2020

Résumé

Cancer cells must overcome anoikis (detachment-induced death) to successfully metastasize. Using proteomic screens, we found that distinct oncoproteins upregulate IL-1 receptor accessory protein (IL1RAP) to suppress anoikis. IL1RAP is directly induced by oncogenic fusions of Ewing sarcoma (EwS), a highly metastatic childhood sarcoma. IL1RAP inactivation triggers anoikis and impedes metastatic dissemination of EwS cells. Mechanistically, IL1RAP binds the cell surface system Xc- transporter to enhance exogenous cystine uptake, thereby replenishing cysteine and the glutathione antioxidant. Under cystine depletion, IL1RAP induces cystathionine gamma lyase (CTH) to activate the transsulfuration pathway for de novo cysteine synthesis. Therefore IL1RAP maintains cyst(e)ine and glutathione pools which are vital for redox homeostasis and anoikis resistance. IL1RAP is minimally expressed in pediatric and adult normal tissues, and human anti-IL1RAP antibodies induce potent antibody-dependent cellular cytotoxicity of EwS cells. Therefore, we define IL1RAP as a new cell surface target in EwS, which is potentially exploitable for immunotherapy.

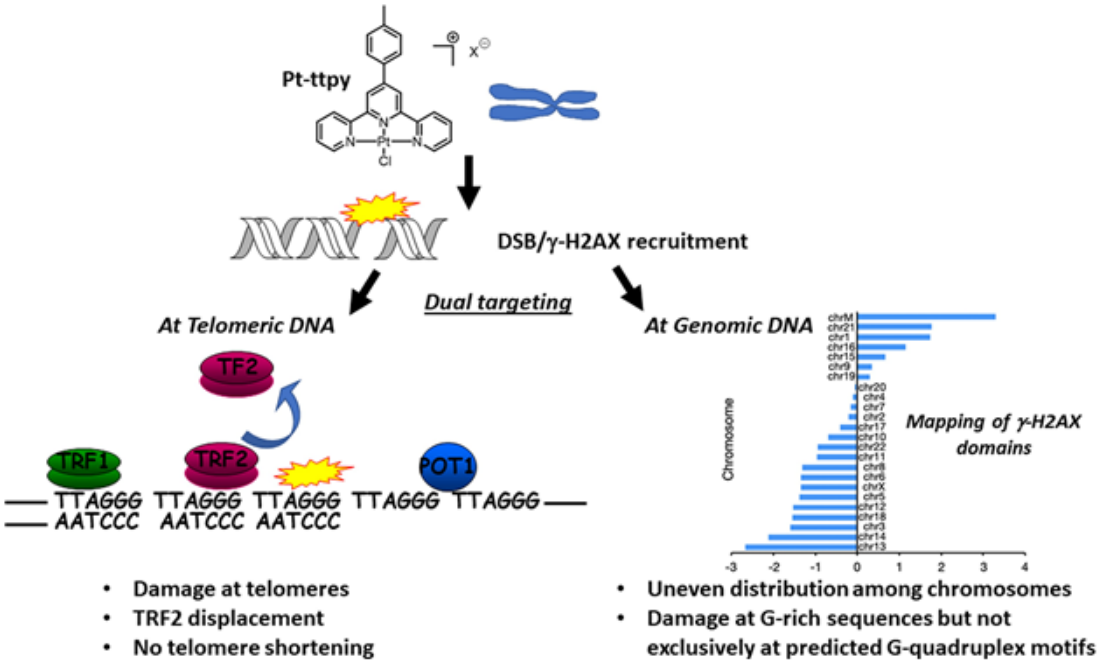
Samar Ali, Emilia Puig Lombardi, Deepanjan Ghosh, Tao Jia, Géraldine Vitry, Lina Saker, Joël

Poupon, Marie-Paule Teulade-Fichou, Alain Nicolas, Arturo Londono-Vallejo, Sophie Bombard (2021 May 22)

Pt-ttpy, a G-quadruplex binding platinum complex, induces telomere dysfunction and G-rich regions DNA damage.

Metallomics : integrated biometal science : 13 : mfab029 : DOI : 10.1093/mtomcs/mfab029

Résumé



Pt-ttpy (tolyl terpyridin-Pt complex) covalently binds to G-quadruplex (G4) structures in vitro and to telomeres in cellulo via its Pt moiety. Here, we identified its targets in the human genome, in comparison to Pt-tpy, its derivative without G4 affinity, and cisplatin. Pt-ttpy, but not Pt-tpy, induces the release of the shelterin protein TRF2 from telomeres concomitantly to the formation of DNA damage foci at telomeres but also at other chromosomal locations. γ-H2AX chromatin immunoprecipitation (ChIP-seq) after treatment with Pt-ttpy or cisplatin revealed accumulation in G- and A-rich tandemly repeated sequences, but not particularly in potential G4 forming sequences. Collectively, Pt-ttpy presents dual targeting efficiency on DNA, by inducing telomere dysfunction and genomic DNA damage at specific loci.

Silvia Benito-Martinez, Laura Salavessa, Graça Raposo, Michael S Marks, Cédric Delevoye (2021 May 22)

Melanin transfer and fate within keratinocytes in human skin pigmentation.

Integrative and comparative biology : DOI : icab094

Résumé

Human skin and hair pigmentation play important roles in social behavior but also in photoprotection from the harmful effects of ultraviolet light. The main pigments in mammalian skin, the melanins, are synthesized within specialized organelles called melanosomes in melanocytes, which sit at the basal layer of the epidermis and the hair bulb. The melanins are then transferred from melanocytes to keratinocytes, where they accumulate perinuclearly in membrane-bound organelles as a « cap » above the nucleus. The mechanism of transfer, the nature of the pigmented organelles within keratinocytes, and the mechanism governing their intracellular positioning are all debated and poorly understood, but likely play an important role in the photoprotective properties of melanin in the skin. Here, we detail our current understanding of these processes and present a guideline for future experimentation in this area.

Catalina Lodillinsky, Laetitia Fuhrmann, Marie Irondelle, Olena Pylypenko, Xiao-Yan Li, Hélène Bonsang-Kitzis, Fabien Reyal, Sophie Vacher, Claire Calmel, Olivier De Wever, Ivan Bièche, Marie-Lise Lacombe, Ana Maria Eiján, Anne Houdusse, Anne Vincent-Salomon, Stephen J Weiss, Philippe Chavrier, Mathieu Boissan (2021 May 20)

Metastasis-suppressor NME1 controls the invasive switch of breast cancer by regulating MT1-MMP surface clearance.

Oncogene : DOI : 10.1038/s41388-021-01826-1

Résumé

Membrane Type 1 Matrix Metalloprotease (MT1-MMP) contributes to the invasive progression of breast cancers by degrading extracellular matrix tissues. Nucleoside diphosphate kinase, NME1/NM23-H1, has been identified as a metastasis suppressor; however, its contribution to local invasion in breast cancer is not known. Here, we report that NME1 is up-regulated in ductal carcinoma in situ (DCIS) as compared to normal breast epithelial tissues. NME1 levels drop in microinvasive and invasive components of breast tumor cells relative to synchronous DCIS foci. We find a strong anti-correlation between NME1 and plasma membrane MT1-MMP levels in the invasive components of breast tumors, particularly in aggressive histological grade III and triple-negative breast cancers. Knockout of NME1 accelerates the invasive transition of breast tumors in the intraductal xenograft model. At the mechanistic level, we find that MT1-MMP, NME1 and dynamin-2, a GTPase known to require GTP production by NME1 for its membrane fission activity in the endocytic pathway, interact in clathrin-coated vesicles at the plasma membrane. Loss of NME1 function increases MT1-MMP surface levels by inhibiting endocytic clearance. As a consequence, the ECM degradation and invasive potentials of breast cancer cells are enhanced. This study identifies the down-modulation of NME1 as a potent driver of the in situ-to invasive transition during breast cancer progression.