Année de publication : 2019

Julian Musa, Florencia Cidre-Aranaz, Marie-Ming Aynaud, Martin F Orth, Maximilian M L Knott, Olivier Mirabeau, Gal Mazor, Mor Varon, Tilman L B Hölting, Sandrine Grossetête, Moritz Gartlgruber, Didier Surdez, Julia S Gerke, Shunya Ohmura, Aruna Marchetto, Marlene Dallmayer, Michaela C Baldauf, Stefanie Stein, Giuseppina Sannino, Jing Li, Laura Romero-Pérez, Frank Westermann, Wolfgang Hartmann, Uta Dirksen, Melissa Gymrek, Nathaniel D Anderson, Adam Shlien, Barak Rotblat, Thomas Kirchner, Olivier Delattre, Thomas G P Grünewald (2019 Sep 13)
Cooperation of cancer drivers with regulatory germline variants shapes clinical outcomes.
Nature communications : 4128 : DOI : 10.1038/s41467-019-12071-2

Résumé

Pediatric malignancies including Ewing sarcoma (EwS) feature a paucity of somatic alterations except for pathognomonic driver-mutations that cannot explain overt variations in clinical outcome. Here, we demonstrate in EwS how cooperation of dominant oncogenes and regulatory germline variants determine tumor growth, patient survival and drug response. Binding of the oncogenic EWSR1-FLI1 fusion transcription factor to a polymorphic enhancer-like DNA element controls expression of the transcription factor MYBL2 mediating these phenotypes. Whole-genome and RNA sequencing reveals that variability at this locus is inherited via the germline and is associated with variable inter-tumoral MYBL2 expression. High MYBL2 levels sensitize EwS cells for inhibition of its upstream activating kinase CDK2 in vitro and in vivo, suggesting MYBL2 as a putative biomarker for anti-CDK2-therapy. Collectively, we establish cooperation of somatic mutations and regulatory germline variants as a major determinant of tumor progression and highlight the importance of integrating the regulatory genome in precision medicine.

Scepanovic P, Hodel F, Mondot S, Partula V, Byrd A, Hammer C, Alanio C, Bergstedt J, Patin E, Touvier M, Lantz O, Albert ML, Duffy D, Quintana-Murci L, Fellay J; Milieu Intérieur Consortium. (2019 Sep 13)
xA comprehensive assessment of demographic, environmental, and host genetic associations with gut microbiome diversity in healthy individuals.
: 13;7(1) : 130 : DOI : 10.1186/s40168-019-0747-x

Résumé

Eric Victor van Leen, Florencia di Pietro, Yohanns Bellaïche (2019 Sep 12)
Oriented cell divisions in epithelia: from force generation to force anisotropy by tension, shape and vertices.
Current opinion in cell biology : 9-16 : DOI : S0955-0674(19)30070-5

Résumé

Mitotic spindle orientation has been linked to asymmetric cell divisions, tissue morphogenesis and homeostasis. The canonical pathway to orient the mitotic spindle is composed of the cortical recruitment factor NuMA and the molecular motor dynein, which exerts pulling forces on astral microtubules to orient the spindle. Recent work has defined a novel role for NuMA as a direct contributor to force generation. In addition, the exploration of geometrical and physical cues combined with the study of classical polarity pathways has led to deeper insights into the upstream regulation of spindle orientation. Here, we focus on how cell shape, junctions and mechanical tension act to orient spindle pulling forces in epithelia, and discuss different roles for spindle orientation in epithelia.

Kenneth W Witwer, Clotilde Théry (2019 Sep 7)
Extracellular vesicles or exosomes? On primacy, precision, and popularity influencing a choice of nomenclature.
Journal of extracellular vesicles : 1648167 : DOI : 10.1080/20013078.2019.1648167

Résumé

Moitrier Sarah, Pricoupenko Nastassia, Kerjouan Adèle, Oddou Christiane, Destaing Olivier, Battistella Aude, Silberzan Pascal, Bonnet Isabelle (2019 Sep 3)
Local light-activation of the Src oncoprotein in an epithelial monolayer promotes collective extrusion
Communications Physics : 2 : 98 : DOI : 10.1038/s42005-019-0198-5

Résumé

Transformed isolated cells are usually extruded from normal epithelia and subsequently eliminated. However, multicellular tumors outcompete healthy cells, highlighting the importance of collective effects. Here, we investigate this situation in vitro by controlling in space and time the activity of the Src oncoprotein within a normal Madin–Darby Canine Kidney (MDCK) epithelial cell monolayer. Using an optogenetics approach with cells expressing a synthetic light-sensitive version of Src (optoSrc), we reversibly trigger the oncogenic activity by exposing monolayers to well-defined light patterns. We show that small populations of activated optoSrc cells embedded in the non-transformed monolayer collectively extrude as a tridimensional aggregate and remain alive, while the surrounding normal cells migrate towards the exposed area. This phenomenon requires an interface between normal and transformed cells and is partially reversible. Traction forces show that Src- activated cells either actively extrude or are pushed out by the surrounding cells in a non- autonomous way.

Angrand G., Quillévéré A., Loaëc N., Daskalogianni C., Granzhan A., Teulade-Fichou M.P.,

Fahraeus R., Prado Martins R., Blondel M. (2019 Sep 1)

Sneaking Out for Happy Hour: Yeast-Based Approaches to Explore and Modulate Immune Response and Immune Evasion

Genes : 10 : 667-689 : DOI : 10.3390/genes10090667

Résumé

Many pathogens (virus, bacteria, fungi, or parasites) have developed a wide variety of mechanisms to evade their host immune system. The budding yeast Saccharomyces cerevisiae has successfully been used to decipher some of these immune evasion strategies. This includes the cis-acting mechanism that limits the expression of the oncogenic Epstein–Barr virus (EBV)-encoded EBNA1 and thus of antigenic peptides derived from this essential but highly antigenic viral protein. Studies based on budding yeast have also revealed the molecular bases of epigenetic switching or recombination underlying the silencing of all except one members of extended families of genes that encode closely related and highly antigenic surface proteins. This mechanism is exploited by several parasites (that include pathogens such as Plasmodium, Trypanosoma, Candida, or Pneumocystis) to alternate their surface antigens, thereby evading the immune system. Yeast can itself be a pathogen, and pathogenic fungi such as Candida albicans, which is phylogenetically very close to S. cerevisiae, have developed stealthiness strategies that include changes in their cell wall composition, or epitope-masking, to control production or exposure of highly antigenic but essential polysaccharides in their cell wall. Finally, due to the high antigenicity of its cell wall, yeast has been opportunistically exploited to create adjuvants and vectors for vaccination.

François Legoux, Déborah Bellet, Celine Daviaud, Yara El Morr, Aurelie Darbois, Kristina Niort, Emanuele Procopio, Marion Salou, Jules Gilet, Bernhard Ryffel, Aurélie Balvay, Anne Foussier, Manal Sarkis, Ahmed El Marjou, Frederic Schmidt, Sylvie Rabot, Olivier Lantz (2019 Aug 31)

Microbial metabolites control the thymic development of mucosal-associated invariant T cells.

Science (New York, N.Y.) : DOI : eaaw2719

Résumé

How the microbiota modulate immune functions remains poorly understood. Mucosal-associated invariant T (MAIT) cells are implicated in mucosal homeostasis and absent in germ-free mice. Here, we show that commensal bacteria govern murine MAIT intrathymic development, as MAIT cells did not recirculate to the thymus. MAIT development required expression in bacteria, indicating that production of the MAIT antigen 5-(2-oxopropylideneamino)-6-d-ribitylaminouracil (5-OP-RU) was necessary. 5-OP-RU rapidly traveled from mucosal surfaces to the thymus, where it was captured by the major histocompatibility complex class Ib molecule MR1. This led to increased numbers of the earliest MAIT precursors and the expansion of more mature receptor-related orphan receptor γt-positive MAIT cells. Thus, a microbiota-derived metabolite controls development of mucosally targeted T cells, in a process blurring the distinction between exogenous and self-

antigens.

Charlotte Laurent, Laure Ricard, Olivier Fain, Irene Buvat, Amir Adedjouma, Michael Soussan, Arsène Mekinian (2019 Aug 29)

PET/MRI in large-vessel vasculitis: clinical value for diagnosis and assessment of disease activity.

Scientific reports : 12388 : DOI : 10.1038/s41598-019-48709-w

Résumé

Diagnosis of large vessel vasculitis (LVV) and evaluation of its inflammatory activity can be challenging. Our aim was to investigate the value of hybrid positron-emission tomography/magnetic resonance imaging (PET/MRI) in LVV. All consecutive patients with LVV from the Department of Internal Medicine who underwent PET/MRI were included. Three PET/MRI patterns were defined: (i) « inflammatory, » with positive PET (>liver uptake) and abnormal MRI (stenosis and/or wall thickening); (ii) « fibrous », negative PET (≤liver uptake) and abnormal MRI; and (iii) « normal ». Thirteen patients (10 female; median age: 67-years [range: 23-87]) underwent 18 PET/MRI scans. PET/MRI was performed at diagnosis (n = 4), at relapse (n = 7), or during remission (n = 7). Among the 18 scans, eight (44%) showed an inflammatory pattern and three (17%) a fibrous pattern; the other seven were normal. The distribution of the three patterns did not differ between patients with Takayasu arteritis (TA, n = 10 scans) and those with giant cell arteritis (GCA, n = 8 scans). PET/MRI findings were normal in 2/10 (20%) TA scans vs. 5/8 (62%) GCA scans (p = 0.3). Median SUV was 4.7 [2.1-8.6] vs. 2 [1.8-2.6] in patients with active disease vs. remission, respectively (p = 0.003). PET/MRI is a new hybrid imaging modality allowing comprehensive and multimodal analysis of vascular wall inflammation and the vascular lumen. This technique offers promising perspectives for the diagnosis and monitoring of LVV.

Roberta Ragazzini, Raquel Pérez-Palacios, Irem H Baymaz, Seynabou Diop, Katia Ancelin, Dina Zielinski, Audrey Michaud, Maëlle Givelet, Mate Borsos, Setareh Aflaki, Patricia Legoix, Pascal W T C Jansen, Nicolas Servant, Maria-Elena Torres-Padilla, Deborah Bourc'his, Pierre Fouchet, Michiel Vermeulen, Raphaël Margueron (2019 Aug 28)

EZHIP constrains Polycomb Repressive Complex 2 activity in germ cells.

Nature communications : 3858 : DOI : 10.1038/s41467-019-11800-x

Résumé

The Polycomb group of proteins is required for the proper orchestration of gene expression due to its role in maintaining transcriptional silencing. It is composed of several chromatin modifying complexes, including Polycomb Repressive Complex 2 (PRC2), which deposits H3K27me2/3. Here, we report the identification of a cofactor of PRC2, EZHIP (EZH1/2 Inhibitory Protein), expressed predominantly in the gonads. EZHIP limits the enzymatic activity of PRC2 and lessens the interaction between the core complex and its accessory subunits, but does not interfere with PRC2 recruitment to chromatin. Deletion of Ezhip in

mice leads to a global increase in H3K27me2/3 deposition both during spermatogenesis and at late stages of oocyte maturation. This does not affect the initial number of follicles but is associated with a reduction of follicles in aging. Our results suggest that mature oocytes Ezhip-/- might not be fully functional and indicate that fertility is strongly impaired in Ezhip-/- females. Altogether, our study uncovers EZHIP as a regulator of chromatin landscape in gametes.

Simon Durand, Cécile Pierre-Eugène, Olivier Mirabeau, Caroline Louis-Brennetot, Valérie Combaret, Léo Colmet-Daage, Orphée Blanchard, Angela Bellini, Estelle Daudigeos-Dubus, Virginie Raynal, Gudrun Schleiermacher, Sylvain Baulande, Olivier Delattre, Isabelle Janoueix-Lerosey (2019 Aug 28)

ALK mutation dynamics and clonal evolution in a neuroblastoma model exhibiting two ALK mutations.

Oncotarget : 4937-4950 : DOI : 10.18632/oncotarget.27119

Résumé

The gene is a major oncogene of neuroblastoma cases exhibiting ALK activating mutations. Here, we characterized two neuroblastoma cell lines established from a stage 4 patient at diagnosis either from the primary tumor (PT) or from the bone marrow (BM). Both cell lines exhibited similar genomic profiles. All cells in the BM-derived cell line exhibited an ALK F1174L mutation, whereas this mutation was present in only 5% of the cells in the earliest passages of the PT-derived cell line. The BM-derived cell line presented with a higher proliferation rate and injections in Nude mice resulted in tumor formation only for the BM-derived cell line. Next, we observed that the F1174L mutation frequency in the PT-derived cell line increased with successive passages. Further Whole Exome Sequencing revealed a second ALK mutation, L1196M, in this cell line. Digital droplet PCR documented that the allele fractions of both mutations changed upon passages, and that the F1174L mutation reached 50% in late passages, indicating clonal evolution. treatment of the PT-derived cell line exhibiting the F1174L and L1196M mutations with the alectinib inhibitor resulted in an enrichment of the L1196M mutation. Using xenografts, we documented a better efficacy of alectinib compared to crizotinib on tumor growth and an enrichment of the L1196M mutation at the end of both treatments. Finally, single-cell RNA-seq analysis was consistent with both mutations resulting in ALK activation. Altogether, this study provides novel insights into ALK mutation dynamics in a neuroblastoma model harbouring two ALK mutations.

Ariane Ramaekers, Annelies Claeys, Martin Kapun, Emmanuèle Mouchel-Vielh, Delphine Potier, Simon Weinberger, Nicola Grillenzoni, Delphine Dardalhon-Cuménal, Jiekun Yan, Reinhard Wolf, Thomas Flatt, Erich Buchner, Bassem A Hassan (2019 Aug 27)

Altering the Temporal Regulation of One Transcription Factor Drives Evolutionary Trade-Offs between Head Sensory Organs.

Developmental cell : 780-792.e7 : DOI : S1534-5807(19)30658-6

Résumé

Size trade-offs of visual versus olfactory organs is a pervasive feature of animal evolution. This could result from genetic or functional constraints. We demonstrate that head sensory organ size trade-offs in Drosophila are genetically encoded and arise through differential subdivision of the head primordium into visual versus non-visual fields. We discover that changes in the temporal regulation of the highly conserved eyeless/Pax6 gene expression during development is a conserved mechanism for sensory trade-offs within and between Drosophila species. We identify a natural single nucleotide polymorphism in the cis-regulatory region of eyeless in a binding site of its repressor Cut that is sufficient to alter its temporal regulation and eye size. Because eyeless/Pax6 is a conserved regulator of head sensory placode subdivision, we propose that its temporal regulation is key to define the relative size of head sensory organs.

Markus Frederik Schliffka, Jean-Léon Maître (2019 Aug 25)
Stay hydrated: basolateral fluids shaping tissues.
Current opinion in genetics & development : 70-77 : DOI : S0959-437X(19)30021-8

Résumé

During development, embryos perform a mesmerizing choreography, which is crucial for the correct shaping, positioning and function of all organs. The cellular properties powering animal morphogenesis have been the focus of much attention. In contrast, much less consideration has been given to the invisible engine constituted by the intercellular fluid. Cells are immersed in fluid, of which the composition and physical properties have a considerable impact on development. In this review, we revisit recent studies from the perspective of the fluid, focusing on basolateral fluid compartments and taking the early mouse and zebrafish embryos as models. These examples illustrate how the hydration levels of tissues are spatio-temporally controlled and influence embryonic development.

Abegão L.M.G., Fonseca R.D., Santos F.A., Rodrigues J.J., Kamada K., Mendonça C.R., Piguel S., De Boni L. (2019 Aug 23)
First molecular electronic hyperpolarizability of series of π-conjugated oxazole dyes in solution: an experimental and theoretical study
RSC Adv. : 9 : 26476-26482 : DOI : 10.1039/C9RA05246A

Résumé

In this work, we report the experimental and theoretical first molecular electronic hyperpolarizability (βHRS) of eleven π-conjugated oxazoles compounds in toluene medium. The Hyper-Rayleigh Scattering (HRS) technique allowed the determination of the experimental dynamic βHRS values, by exciting the compounds with a picosecond pulse trains from a Q-switched and mode-locked Nd:YAG laser tuned at 1064 nm. Theoretical predictions based on time-dependent density functional theory level using the Gaussian 09

program package were performed with three different functionals (B3LYP, CAM-B3LYP, and M06-2X), to calculate both static and dynamic theoretical βHRS values. Good accordance was found between the experimental and theoretical values, in particular for the CAM-B3LYP and M06-2X functionals.

François Legoux, Jules Gilet, Emanuele Procopio, Klara Echasserieau, Karine Bernardeau, Olivier Lantz (2019 Aug 22)

Molecular mechanisms of lineage decisions in metabolite-specific T cells.

Nature immunology : 1244-1255 : DOI : 10.1038/s41590-019-0465-3

Résumé

Mucosal-associated invariant T cells (MAIT cells) recognize the microbial metabolite 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) presented by the MHC class Ib molecule, MR1. MAIT cells acquire effector functions during thymic development, but the mechanisms involved are unclear. Here we used single-cell RNA-sequencing to characterize the developmental path of 5-OP-RU-specific thymocytes. In addition to the known MAIT1 and MAIT17 effector subsets selected on bone-marrow-derived hematopoietic cells, we identified 5-OP-RU-specific thymocytes that were selected on thymic epithelial cells and differentiated into CD44 naive T cells. MAIT cell positive selection required signaling through the adapter, SAP, that controlled the expression of the transcription factor, ZBTB16. Pseudotemporal ordering of single cells revealed transcriptional trajectories of 5-OP-RU-specific thymocytes selected on either thymic epithelial cells or hematopoietic cells. The resulting model illustrates T cell lineage decisions.

Antonela Merlotti, Alvaro López Malizia, Paula Michea, Pierre-Emmanuel Bonte, Christel Goudot, María Sol Carregal, Nicolás Nuñez, Christine Sedlik, Ana Ceballos, Vassili Soumelis, Sebastián Amigorena, Jorge Geffner, Eliane Piaggio, Juan Sabatte (2019 Aug 21)

Aberrant fucosylation enables breast cancer clusterin to interact with dendritic cell-specific ICAM-grabbing non-integrin (DC-SIGN).

Oncoimmunology : e1629257 : DOI : 10.1080/2162402X.2019.1629257

Résumé

Clusterin is a glycoprotein able to mediate different physiological functions such as control of complement activation, promotion of unfolded protein clearance and modulation of cell survival. Clusterin is overexpressed in many types of cancers and a large body of evidence suggests that it promotes carcinogenesis and tumor progression. We have previously described a novel clusterin glycoform present in human semen, but not in serum, highly enriched in terminal fucose motifs. Here we show that human luminal breast cancer (LBC) clusterin also bears terminal fucosylated glycans, conferring clusterin the ability to interact with DC-SIGN, a C-type lectin receptor expressed by myeloid cells. This clusterin glycosylation pattern was absent or diminished in non-involved juxtatumoral tissue, suggesting that fucosylated clusterin might represent a cancer associated glycoform. We

also found that DC-SIGN is expressed by luminal breast cancer intratumoral macrophages. Moreover, experiments performed using semen fucosylated clusterin and monocyte derived macrophages showed that the interaction of semen clusterin with DC-SIGN promoted a proangiogenic profile, characterized by a high production of VEGF, IL-8 and TNF-α. Our results reveal an unexpected complexity on the structure and function of secretory clusterin produced by tumors and suggest that fucosylated clusterin produced by luminal breast cancer cells might play a role in tumor progression by promoting the release of pro-angiogenic factors by intratumoral macrophages.