Année de publication : 2021

Anke Steinmetz, Thomas Yvorra, Pascal Retailleau, Olivier Lantz, Frédéric Schmidt (2021 Jan 28)

Datasets and analyses of molecular dynamics simulations of covalent binary and ternary complexes of MHC class I-related molecule/T-cell receptor (MR1/TCR) agonists to understand complex formation and conditions of fluorescent labelling.

Data in brief : 106704 : DOI : 10.1016/j.dib.2020.106704

Résumé

Data of molecular dynamics (MD) simulations were obtained for mucosal-associated invariant T (MAIT) cell ligands complexed with MR1 or MR1/TCR. Ligands included in the simulations were natural ligands 5-(2-oxoethylideneamino)-6-D-ribitylaminouracil (5-OE-RU), 5-(2-oxopropylideneamino)-6-(D-ribitylamino)uracil (5-OP-RU), their C5′ ethinylated analogs in S or R configuration, as well as the corresponding fluorophore-reacted products. All-atom models of the binary and ternary complexes were constructed using PDB entry 4NQE and docked poses [1]. Missing loops, N- and C-termini were completed by homology modelling, the loop conformations optimized, and the models energy minimized prior to setup for MD simulations. A standard pre-equilibration protocol was applied before the production phase of 120 ns simulation as NPT ensemble at 300 K and 1 atm applying an explicit solvent model with OPLS3 force field parameters. Atomic coordinates and energies were recorded every 60 ps and 12 ps, respectively. The corresponding raw data files of the MD simulations are part of this dataset. All simulations were analysed with respect to root mean square deviations (rmsd) and root mean square fluctuations (rmsf) of the coordinates of protein and ligand atoms, stability of protein secondary structure, protein-ligand contacts, ligand torsion profiles, and ligand properties. More detailed statistics of non-covalent interaction counts were also collected. Radial distribution functions (rdf) were calculated when relevant. Visualization of the trajectories permits appreciation of the molecular dynamics of both, ligands and proteins and their interactions, thereby supporting drug design of MAIT cell ligands; furthermore, additional analysis of e.g. conformational changes or interactions not reported in the primary publication [1] can be performed on the data. The raw data may also be used as starting point for extension of the simulations or more sophisticated MD techniques.

Lieske H Schrijver, Antonis C Antoniou, Håkan Olsson, Thea M Mooij, Marie-José Roos-Blom, Leyla Azarang, Julian Adlard, Munaza Ahmed, Daniel Barrowdale, Rosemarie Davidson, Alan Donaldson, Ros Eeles, D Gareth Evans, Debra Frost, Alex Henderson, Louise Izatt, Kai-Ren Ong, Valérie Bonadona, Isabelle Coupier, Laurence Faivre, Jean-Pierre Fricker, Paul Gesta, Klaartje van Engelen, Agnes Jager, Fred H Menko, Marian J E Mourits, Christian F Singer, Yen Y Tan, Lenka Foretova, Marie Navratilova, Rita K Schmutzler, Carolina Ellberg, Anne-Marie Gerdes, Trinidad Caldes, Jacques Simard, Edith Olah, Anna Jakubowska, Johanna Rantala, Ana Osorio, John L Hopper, Kelly-Anne Phillips, Roger L Milne, Mary Beth Terry, Catherine Noguès, Christoph Engel, Karin Kast, David E Goldgar, Flora E van Leeuwen, Douglas F Easton, Nadine Andrieu, Matti A

Rookus, (2021 Jan 25)
Oral contraceptive use and ovarian cancer risk for BRCA1/2 mutation carriers: an international cohort study.
American journal of obstetrics and gynecology : DOI : S0002-9378(21)00038-7

Résumé

Ovarian cancer risk in BRCA1 and BRCA2 mutation carriers has been shown to decrease with longer duration of oral contraceptive use. Although the effects of using oral contraceptives in the general population are well established (approximately 50% risk reduction in ovarian cancer), the estimated risk reduction in mutation carriers is much less precise because of potential bias and small sample sizes. In addition, only a few studies on oral contraceptive use have examined the associations of duration of use, time since last use, starting age, and calendar year of start with risk of ovarian cancer.

Samyuktha Suresh, Solène Huard, Thierry Dubois (2021 Jan 24)
CARM1/PRMT4: Making Its Mark beyond Its Function as a Transcriptional Coactivator.
Trends in cell biology : DOI : 10.1016/j.tcb.2020.12.010

Résumé

Coactivator-associated arginine methyltransferase 1 (CARM1), identified 20 years ago as a coregulator of transcription, is an enzyme that catalyzes arginine methylation of proteins. Beyond its well-established involvement in the regulation of transcription, the physiological functions of CARM1 are still poorly understood. However, recent studies have revealed novel roles of CARM1 in autophagy, metabolism, paraspeckles, and early development. In addition, CARM1 is emerging as an attractive therapeutic target and a drug response biomarker for certain types of cancer. Here, we provide a comprehensive overview of the structure of CARM1 and its post-translational modifications, its various functions, apart from transcriptional coactivation, and its involvement in cancer.

Karaki S, Blanc C, Tran T, Galy-Fauroux I, Mougel A, Dransart E, Anson M, Tanchot C, Gibault L, Lepimpec-Barthes F, Darmotte D, Fabre E, Golub* R, Johannes* L, Tartour* E (2021 Jan 24)
CXCR6 deficiency impairs cancer vaccine efficacy and CD8+ resident memory T-cell recruitment in head and neck and lung tumors
J Immunother CancerBMJ Journals : DOI : 10.1136/jitc-2020-001948

Résumé

Background Resident memory T lymphocytes (T_{RM}) are located in tissues and play an important role in immunosurveillance against tumors. The presence of T_{RM} prior to treatment or their induction is associated to the response to anti-Programmed cell death protein 1

(PD-1)/Programmed death-ligand 1 (PD-L1) immunotherapy and the efficacy of cancer vaccines. Previous work by our group and others has shown that the intranasal route of vaccination allows more efficient induction of these cells in head and neck and lung mucosa, resulting in better tumor protection. The mechanisms of in vivo migration of these cells remains largely unknown, apart from the fact that they express the chemokine receptor CXCR6.

Methods We used *CXCR6*-deficient mice and an intranasal tumor vaccination model targeting the Human Papillomavirus (HPV) E7 protein expressed by the TC-1 lung cancer epithelial cell line. The role of CXCR6 and its ligand, CXCL16, was analyzed using multiparametric cytometric techniques and Luminex assays.

Human biopsies obtained from patients with lung cancer were also included in this study.

Results We showed that CXCR6 was preferentially expressed by $CD8^+$ T_{RM} after vaccination in mice and also on intratumoral $CD8^+$ T_{RM} derived from human lung cancer. We also demonstrate that vaccination of Cxcr6-deficient mice induces a defect in the lung recruitment of antigen-specific $CD8^+$ T cells, preferentially in the T_{RM} subsets. In addition, we found that intranasal vaccination with a cancer vaccine is less effective in these *Cxcr6*-deficient mice compared with wild-type mice, and this loss of efficacy is associated with decreased recruitment of local antitumor $CD8^+$ T_{RM}. Interestingly, intranasal, but not intramuscular vaccination induced higher and more sustained concentrations of CXCL16, compared with other chemokines, in the bronchoalveolar lavage fluid and pulmonary parenchyma.

Conclusions This work demonstrates the in vivo role of CXCR6-CXCL16 axis in the migration of $CD8^+$ resident memory T cells in lung mucosa after vaccination, resulting in the control of tumor growth. This work reinforces and explains why the intranasal route of vaccination is the most appropriate strategy for inducing these cells in the head and neck and pulmonary mucosa, which remains a major objective to overcome resistance to anti-PD-1/PD-L1, especially in cold tumors.

Andrés Ernesto Zucchetti, Noémie Paillon, Olga Markova, Stéphanie Dogniaux, Claire Hivroz, Julien Husson (2021 Jan 20)

Influence of external forces on actin-dependent T cell protrusions during immune synapse formation.

Biology of the cell : 250-263 : DOI : 10.1111/boc.202000133

Résumé

We have previously observed that in response to antigenic activation, T cells produce actin-rich protrusions that generate forces involved in T cell activation. These forces are influenced by the mechanical properties of antigen-presenting cells (APCs). However, how external forces, which can be produced by APCs, influence the dynamic of the actin protrusion remains unknown. In this study, we quantitatively characterised the effects of external forces

in the dynamic of the protrusion grown by activated T cells.

Anna Bigas, Ivan Zanoni, Matthew R Hepworth, Stephanie C Eisenbarth, Seth Lucian Masters, Jonathan Kipnis, Carola G Vinuesa, Kim L Good-Jacobson, Stuart G Tangye, Sayuri Yamazaki, Claire Hivroz, Elia Tait Wojno, Ziv Shulman, Marco Colonna (2021 Jan 19)
JEM career launchpad.
The Journal of experimental medicine : DOI : e20202509

Résumé

Tomasz Chelmicki, Emeline Roger, Aurélie Teissandier, Mathilde Dura, Lorraine Bonneville, Sofia Rucli, François Dossin, Camille Fouassier, Sonia Lameiras, Deborah Bourc'his (2021 Jan 14)
mA RNA methylation regulates the fate of endogenous retroviruses.
Nature : 312-316 : DOI : 10.1038/s41586-020-03135-1

Résumé

Endogenous retroviruses (ERVs) are abundant and heterogenous groups of integrated retroviral sequences that affect genome regulation and cell physiology throughout their RNA-centred life cycle. Failure to repress ERVs is associated with cancer, infertility, senescence and neurodegenerative diseases. Here, using an unbiased genome-scale CRISPR knockout screen in mouse embryonic stem cells, we identify mA RNA methylation as a way to restrict ERVs. Methylation of ERV mRNAs is catalysed by the complex of methyltransferase-like METTL3-METTL14 proteins, and we found that depletion of METTL3-METTL14, along with their accessory subunits WTAP and ZC3H13, led to increased mRNA abundance of intracisternal A-particles (IAPs) and related ERVK elements specifically, by targeting their 5′ untranslated region. Using controlled auxin-dependent degradation of the METTL3-METTL14 enzymatic complex, we showed that IAP mRNA and protein abundance is dynamically and inversely correlated with mA catalysis. By monitoring chromatin states and mRNA stability upon METTL3-METTL14 double depletion, we found that mA methylation mainly acts by reducing the half-life of IAP mRNA, and this occurs by the recruitment of the YTHDF family of mA reader proteins. Together, our results indicate that RNA methylation provides a protective effect in maintaining cellular integrity by clearing reactive ERV-derived RNA species, which may be especially important when transcriptional silencing is less stringent.

Florian Constanty, Alena Shkumatava (2021 Jan 14)
lncRNAs in development and differentiation: from sequence motifs to functional characterization.
Development (Cambridge, England) : DOI : dev182741

Résumé

The number of long noncoding RNAs (lncRNAs) with characterized developmental and cellular functions continues to increase, but our understanding of the molecular mechanisms underlying lncRNA functions, and how they are dictated by RNA sequences, remains limited. Relatively short, conserved sequence motifs embedded in lncRNA transcripts are often important determinants of lncRNA localization, stability and interactions. Identifying such RNA motifs remains challenging due to the substantial length of lncRNA transcripts and the rapid evolutionary turnover of lncRNA sequences. Nevertheless, the recent discovery of specific RNA elements, together with their experimental interrogation, has enabled the first step in classifying heterogeneous lncRNAs into sub-groups with similar molecular mechanisms and functions. In this Review, we focus on lncRNAs with roles in development, cell differentiation and normal physiology in vertebrates, and we discuss the sequence elements defining their functions. We also summarize progress on the discovery of regulatory RNA sequence elements, as well as their molecular functions and interaction partners.

Andreia Mendes, Julien P Gigan, Christian Rodriguez Rodrigues, Sébastien A Choteau, Doriane Sanseau, Daniela Barros, Catarina Almeida, Voahirana Camosseto, Lionel Chasson, Adrienne W Paton, James C Paton, Rafael J Argüello, Ana-Maria Lennon-Duménil, Evelina Gatti, Philippe Pierre (2021 Jan 14)

Proteostasis in dendritic cells is controlled by the PERK signaling axis independently of ATF4.

Life science alliance : DOI : e202000865

Résumé

In stressed cells, phosphorylation of eukaryotic initiation factor 2α (eIF2α) controls transcriptome-wide changes in mRNA translation and gene expression known as the integrated stress response. We show here that DCs are characterized by high eIF2α phosphorylation, mostly caused by the activation of the ER kinase PERK (EIF2AK3). Despite high p-eIF2α levels, DCs display active protein synthesis and no signs of a chronic integrated stress response. This biochemical specificity prevents translation arrest and expression of the transcription factor ATF4 during ER-stress induction by the subtilase cytotoxin (SubAB). PERK inactivation, increases globally protein synthesis levels and regulates IFN-β expression, while impairing LPS-stimulated DC migration. Although the loss of PERK activity does not impact DC development, the cross talk existing between actin cytoskeleton dynamics; PERK and eIF2α phosphorylation is likely important to adapt DC homeostasis to the variations imposed by the immune contexts.

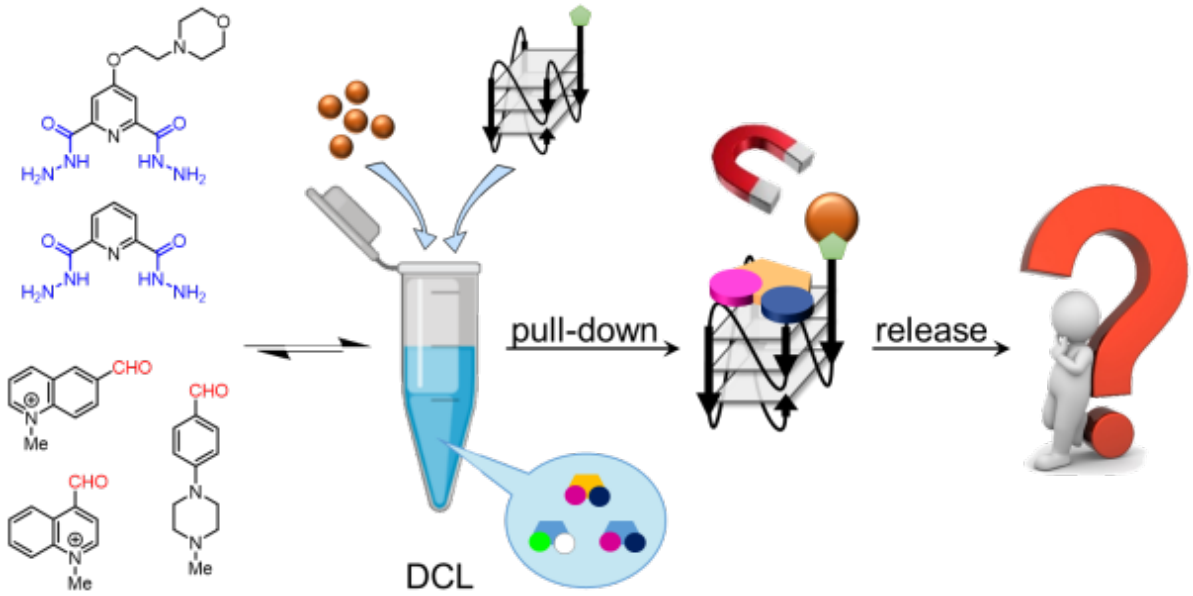
Oksana Reznichenko, Anne Cucchiarini, Valérie Gabelica, Anton Granzhan (2021 Jan 14)

Quadruplex DNA-guided ligand selection from dynamic combinatorial libraries of acylhydrazones

Organic and Biomolecular Chemistry : 19 : 379-386 : DOI : 10.1039/D0OB01908A

Résumé

Dynamic combinatorial libraries of acylhydrazones were prepared from diacylhydrazides and several cationic or neutral aldehydes in the presence of 5-methoxyanthranilic acid catalyst. Pull-down experiments with magnetic beads functionalized with a G-quadruplex (G4)-forming oligonucleotide led to the identification of putative ligands, which were resynthesized or emulated by close structural analogues. G4-binding properties of novel derivatives were assessed by fluorimetric titrations, mass spectrometry and thermal denaturation experiments, giving evidence of strong binding (K_d < 10 nM) for two compounds.



Marina Murillo-Pineda, Luis P Valente, Marie Dumont, João F Mata, Daniele Fachinetti, Lars E T Jansen (2021 Jan 14)

Induction of spontaneous human neocentromere formation and long-term maturation.

The Journal of cell biology : DOI : e202007210

Résumé

Human centromeres form primarily on α-satellite DNA but sporadically arise de novo at naive ectopic loci, creating neocentromeres. Centromere inheritance is driven primarily by chromatin containing the histone H3 variant CENP-A. Here, we report a chromosome engineering system for neocentromere formation in human cells and characterize the first experimentally induced human neocentromere at a naive locus. The spontaneously formed neocentromere spans a gene-poor 100-kb domain enriched in histone H3 lysine 9 trimethylated (H3K9me3). Long-read sequencing revealed this neocentromere was formed by purely epigenetic means and assembly of a functional kinetochore correlated with CENP-A seeding, eviction of H3K9me3 and local accumulation of mitotic cohesin and RNA polymerase

II. At formation, the young neocentromere showed markedly reduced chromosomal passenger complex (CPC) occupancy and poor sister chromatin cohesion. However, long-term tracking revealed increased CPC assembly and low-level transcription providing evidence for centromere maturation over time.

Marchand A., Beauvineau C., Teulade-Fichou M.P., Zenobi R. (2021 Jan 13)
Competition of ligands and the 18-mer binding domain of the RHAU helicase for G-quadruplexes – orthosteric or allosteric binding mechanism?
Chemistry – A European Journal : 23 : 1113-1121 : DOI : 10.1002/chem.202004040

Résumé

Stabilizing the DNA and RNA structures known as G-quadruplexes (G4s) using specific ligands is a strategy that has been proposed to fight cancer. However, although G-quadruplex:ligand (G4:L) interactions have often been investigated, whether or not ligands are able to disrupt G-quadruplex:protein (G4:P) interactions remains poorly studied. In this study, using native mass spectrometry, we have investigated ternary G4:L:P complexes formed by G4s, some of the highest affinity ligands, and the binding domain of the RHAU helicase. Our results suggest that RHAU binds not only preferentially to parallel G4s, but also to free external G-quartets. We also found that, depending on the G4, ligands could prevent the binding of the peptide, either by direct competition for the binding sites (orthosteric inhibition) or by inducing conformational changes (allosteric inhibition). Notably, the ligand Cu–ttpy (ttpy=4′-tolyl-2,2′:6′,2″-terpyridine) induced a conformational change that increased the binding of the peptide. This study illustrates that it is important to not only characterize drug–target interactions, but also how the binding to other partners is affected.

Giorgia Barucci, Deborah Bourc'his (2021 Jan 12)
Meiosis, a New Playground for Retrotransposon Evolution.
Developmental cell : 1-2 : DOI : S1534-5807(20)31018-2

Résumé

Retrotransposons provide both threats and evolutionary opportunities for their hosts. In this issue of Developmental Cell, Laureau et al. describe a fascinating host-retrotransposon relationship that may lead to retrotransposon domestication: Ty3/Gypsy exploit meiosis networks to sustain their transcription, while the host deploys RNA-binding proteins to prevent their translation.

Pavel Mozgunov, Xavier Paoletti, Thomas Jaki (2021 Jan 7)
A benchmark for dose-finding studies with unknown ordering.
Biostatistics (Oxford, England) : DOI : kxaa054

Résumé

An important tool to evaluate the performance of a dose-finding design is the nonparametric optimal benchmark that provides an upper bound on the performance of a design under a given scenario. A fundamental assumption of the benchmark is that the investigator can arrange doses in a monotonically increasing toxicity order. While the benchmark can be still applied to combination studies in which not all dose combinations can be ordered, it does not account for the uncertainty in the ordering. In this article, we propose a generalization of the benchmark that accounts for this uncertainty and, as a result, provides a sharper upper bound on the performance. The benchmark assesses how probable the occurrence of each ordering is, given the complete information about each patient. The proposed approach can be applied to trials with an arbitrary number of endpoints with discrete or continuous distributions. We illustrate the utility of the benchmark using recently proposed dose-finding designs for Phase I combination trials with a binary toxicity endpoint and Phase I/II combination trials with binary toxicity and continuous efficacy.

Andrey Kleshnin, Léa Monet, Marina Plays, Hugo Vaysset, Claire Rougeulle, Stéphan Vagner
(2021 Jan 6)
Amid darkness, light will prevail – a report on the 2020 annual SFC meeting on "Dark genome and Cancer"
Bulletin du cancer : DOI : S0007-4551(20)30510-5

Résumé

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