Année de publication : 2018

Joo Sang Lee, Avinash Das, Livnat Jerby-Arnon, Rand Arafeh, Noam Auslander, Matthew Davidson, Lynn McGarry, Daniel James, Arnaud Amzallag, Seung Gu Park, Kuoyuan Cheng, Welles Robinson, Dikla Atias, Chani Stossel, Ella Buzhor, Gidi Stein, Joshua J Waterfall, Paul S Meltzer, Talia Golan, Sridhar Hannenhalli, Eyal Gottlieb, Cyril H Benes, Yardena Samuels, Emma Shanks, Eytan Ruppin (2018 Jul 1)

Harnessing synthetic lethality to predict the response to cancer treatment.

Nature communications : 2546 : DOI : 10.1038/s41467-018-04647-1

Résumé

While synthetic lethality (SL) holds promise in developing effective cancer therapies, SL candidates found via experimental screens often have limited translational value. Here we present a data-driven approach, ISLE (identification of clinically relevant synthetic lethality), that mines TCGA cohort to identify the most likely clinically relevant SL interactions (cSLi) from a given candidate set of lab-screened SLi. We first validate ISLE via a benchmark of large-scale drug response screens and by predicting drug efficacy in mouse xenograft models. We then experimentally test a select set of predicted cSLi via new screening experiments, validating their predicted context-specific sensitivity in hypoxic vs normoxic conditions and demonstrating cSLi's utility in predicting synergistic drug combinations. We show that cSLi can successfully predict patients' drug treatment response and provide patient stratification signatures. ISLE thus complements existing actionable mutation-based methods for precision cancer therapy, offering an opportunity to expand its scope to the whole genome.

Natalay Kouprina, Mikhail Liskovykh, Nicholas C O Lee, Vladimir N Noskov, Joshua J Waterfall, Robert L Walker, Paul S Meltzer, Eric J Topol, Vladimir Larionov (2018 Apr 11)

Analysis of the 9p21.3 sequence associated with coronary artery disease reveals a tendency for duplication in a CAD patient.

Oncotarget : 15275-15291 : DOI : 10.18632/oncotarget.24567

Résumé

Tandem segmental duplications (SDs) greater than 10 kb are widespread in complex genomes. They provide material for gene divergence and evolutionary adaptation, while formation of specific SDs is a hallmark of cancer and some human diseases. Most SDs map to distinct genomic regions termed 'duplication blocks'. SDs organization within these blocks is often poorly characterized as they are mosaics of ancestral duplicons juxtaposed with younger duplicons arising from more recent duplication events. Structural and functional analysis of SDs is further hampered as long repetitive DNA structures are underrepresented in existing BAC and YAC libraries. We applied Transformation-Associated Recombination (TAR) cloning, a versatile technique for large DNA manipulation, to selectively isolate the coronary artery disease (CAD) interval sequence within the 9p21.3 chromosome locus from a

patient with coronary artery disease and normal individuals. Four tandem head-to-tail duplicons, each ~50 kb long, were recovered in the patient but not in normal individuals. Sequence analysis revealed that the repeats varied by 10-15 SNPs between each other and by 82 SNPs between the human genome sequence (version hg19). SNPs polymorphism within the junctions between repeats allowed two junction types to be distinguished, Type 1 and Type 2, which were found at a 2:1 ratio. The junction sequences contained an Alu element, a sequence previously shown to play a role in duplication. Knowledge of structural variation in the CAD interval from more patients could help link this locus to cardiovascular diseases susceptibility, and maybe relevant to other cases of regional amplification, including cancer.

Joshua J Waterfall, Paul S Meltzer (2018 Mar 14)
A Non-canonical Polycomb Dependency in Synovial Sarcoma.
Cancer cell : 344-346 : DOI : S1535-6108(18)30066-7

Résumé

Disruptions in the antagonistic balance between the chromatin-modifying Polycomb and Trithorax group proteins drive many malignancies. In this issue of Cancer Cell, Banito et al. describe how the SS18-SSX oncogenic fusion protein in synovial sarcoma directly co-opts these complexes to drive gene dysregulation and sustain the transformed state.

Année de publication : 2017

Jittiporn Chaisaingmongkol, Anuradha Budhu, Hien Dang, Siritida Rabibhadana, Benjarath Pupacdi, So Mee Kwon, Marshonna Forgues, Yotsawat Pomyen, Vajarabhongsa Bhudhisawasdi, Nirush Lertprasertsuke, Anon Chotirosniramit, Chawalit Pairojkul, Chirayu U Auewarakul, Thaniya Sricharunrat, Kannika Phornphutkul, Suleeporn Sangrajrang, Maggie Cam, Ping He, Stephen M Hewitt, Kris Ylaya, Xiaolin Wu, Jesper B Andersen, Snorri S Thorgeirsson, Joshua J Waterfall, Yuelin J Zhu, Jennifer Walling, Holly S Stevenson, Daniel Edelman, Paul S Meltzer, Christopher A Loffredo, Natsuko Hama, Tatsuhiro Shibata, Robert H Wiltrout, Curtis C Harris, Chulabhorn Mahidol, Mathuros Ruchirawat, Xin W Wang, (2017 Jun 27)
Common Molecular Subtypes Among Asian Hepatocellular Carcinoma and Cholangiocarcinoma.
Cancer cell : 57-70.e3 : DOI : S1535-6108(17)30205-2

Résumé

Intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma (HCC) are clinically disparate primary liver cancers with etiological and biological heterogeneity. We identified common molecular subtypes linked to similar prognosis among 199 Thai ICC and HCC patients through systems integration of genomics, transcriptomics, and metabolomics. While ICC and HCC share recurrently mutated genes, including TP53, ARID1A, and ARID2, mitotic

checkpoint anomalies distinguish the C1 subtype with key drivers PLK1 and ECT2, whereas the C2 subtype is linked to obesity, T cell infiltration, and bile acid metabolism. These molecular subtypes are found in 582 Asian, but less so in 265 Caucasian patients. Thus, Asian ICC and HCC, while clinically treated as separate entities, share common molecular subtypes with similar actionable drivers to improve precision therapy.

Année de publication : 2016

J Keith Killian, Lambert C J Dorssers, Britton Trabert, Ad J M Gillis, Michael B Cook, Yonghong Wang, Joshua J Waterfall, Holly Stevenson, William I Smith, Natalia Noyes, Parvathy Retnakumar, J Hans Stoop, J Wolter Oosterhuis, Paul S Meltzer, Katherine A McGlynn, Leendert H J Looijenga (2016 Nov 3)

Imprints and DPPA3 are bypassed during pluripotency- and differentiation-coupled methylation reprogramming in testicular germ cell tumors.

Genome research : 1490-1504

Résumé

Testicular germ cell tumors (TGCTs) share germline ancestry but diverge phenotypically and clinically as seminoma (SE) and nonseminoma (NSE), the latter including the pluripotent embryonal carcinoma (EC) and its differentiated derivatives, teratoma (TE), yolk sac tumor (YST), and choriocarcinoma. Epigenomes from TGCTs may illuminate reprogramming in both normal development and testicular tumorigenesis. Herein we investigate pure-histological forms of 130 TGCTs for conserved and subtype-specific DNA methylation, including analysis of relatedness to pluripotent stem cell (ESC, iPSC), primordial germ cell (PGC), and differentiated somatic references. Most generally, TGCTs conserve PGC-lineage erasure of maternal and paternal genomic imprints and DPPA3 (also known as STELLA); however, like ESCs, TGCTs show focal recurrent imprinted domain hypermethylation. In this setting of shared physiologic erasure, NSEs harbor a malignancy-associated hypermethylation core, akin to that of a diverse cancer compendium. Beyond these concordances, we found subtype epigenetic homology with pluripotent versus differentiated states. ECs demonstrate a striking convergence of both CpG and CpH (non-CpG) methylation with pluripotent states; the pluripotential methyl-CpH signature crosses species boundaries and is distinct from neuronal methyl-CpH. EC differentiation to TE and YST entails reprogramming toward the somatic state, with loss of methyl-CpH but de novo methylation of pluripotency loci such as NANOG Extreme methyl-depletion among SE reflects the PGC methylation nadir. Adjacent to TGCTs, benign testis methylation profiles are determined by spermatogenetic proficiency measured by Johnsen score. In sum, TGCTs share collective entrapment in a PGC-like state of genomic-imprint and DPPA3 erasure, recurrent hypermethylation of cancer-associated targets, and subtype-dependent pluripotent, germline, or somatic methylation.

Jun Li, Susan L Woods, Sue Healey, Jonathan Beesley, Xiaoqing Chen, Jason S Lee, Haran Sivakumaran, Nicci Wayte, Katia Nones, Joshua J Waterfall, John Pearson, Anne-Marie Patch,

Janine Senz, Manuel A Ferreira, Pardeep Kaurah, Robertson Mackenzie, Alireza Heravi-Moussavi, Samantha Hansford, Tamsin R M Lannagan, Amanda B Spurdle, Peter T Simpson, Leonard da Silva, Sunil R Lakhani, Andrew D Clouston, Mark Bettington, Florian Grimpen, Rita A Busuttil, Natasha Di Costanzo, Alex Boussioutas, Marie Jeanjean, George Chong, Aurélie Fabre, Sylviane Olschwang, Geoffrey J Faulkner, Evangelos Bellos, Lachlan Coin, Kevin Rioux, Oliver F Bathe, Xiaogang Wen, Hilary C Martin, Deborah W Neklason, Sean R Davis, Robert L Walker, Kathleen A Calzone, Itzhak Avital, Theo Heller, Christopher Koh, Marbin Pineda, Udo Rudloff, Martha Quezado, Pavel N Pichurin, Peter J Hulick, Scott M Weissman, Anna Newlin, Wendy S Rubinstein, Jone E Sampson, Kelly Hamman, David Goldgar, Nicola Poplawski, Kerry Phillips, Lyn Schofield, Jacqueline Armstrong, Cathy Kiraly-Borri, Graeme K Suthers, David G Huntsman, William D Foulkes, Fatima Carneiro, Noralane M Lindor, Stacey L Edwards, Juliet D French, Nicola Waddell, Paul S Meltzer, Daniel L Worthley, Kasmintan A Schrader, Georgia Chenevix-Trench (2016 Apr 19)

Point Mutations in Exon 1B of APC Reveal Gastric Adenocarcinoma and Proximal Polyposis of the Stomach as a Familial Adenomatous Polyposis Variant.

American journal of human genetics : 830-842 : DOI : S0002-9297(16)30036-2

Résumé

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is an autosomal-dominant cancer-predisposition syndrome with a significant risk of gastric, but not colorectal, adenocarcinoma. We mapped the gene to 5q22 and found loss of the wild-type allele on 5q in fundic gland polyps from affected individuals. Whole-exome and -genome sequencing failed to find causal mutations but, through Sanger sequencing, we identified point mutations in APC promoter 1B that co-segregated with disease in all six families. The mutations reduced binding of the YY1 transcription factor and impaired activity of the APC promoter 1B in luciferase assays. Analysis of blood and saliva from carriers showed allelic imbalance of APC, suggesting that these mutations lead to decreased allele-specific expression in vivo. Similar mutations in APC promoter 1B occur in rare families with familial adenomatous polyposis (FAP). Promoter 1A is methylated in GAPPS and sporadic FGPs and in normal stomach, which suggests that 1B transcripts are more important than 1A in gastric mucosa. This might explain why all known GAPPS-affected families carry promoter 1B point mutations but only rare FAP-affected families carry similar mutations, the colonic cells usually being protected by the expression of the 1A isoform. Gastric polyposis and cancer have been previously described in some FAP-affected individuals with large deletions around promoter 1B. Our finding that GAPPS is caused by point mutations in the same promoter suggests that families with mutations affecting the promoter 1B are at risk of gastric adenocarcinoma, regardless of whether or not colorectal polyps are present.

Rebecca Sorber, Yaroslav Teper, Abisola Abisoye-Ogunniyan, Joshua J Waterfall, Sean Davis, J Keith Killian, Marbin Pineda, Satyajit Ray, Matt R McCord, Holger Pflicke, Sandra Sczerba Burkett, Paul S Meltzer, Udo Rudloff (2016 Mar 11)

Whole Genome Sequencing of Newly Established Pancreatic Cancer Lines Identifies Novel Somatic Mutation (c.2587G>A) in Axon Guidance Receptor Plexin A1 as Enhancer of Proliferation and Invasion.
PloS one : e0149833 : DOI : 10.1371/journal.pone.0149833

Résumé

The genetic profile of human pancreatic cancers harbors considerable heterogeneity, which suggests a possible explanation for the pronounced inefficacy of single therapies in this disease. This observation has led to a belief that custom therapies based on individual tumor profiles are necessary to more effectively treat pancreatic cancer. It has recently been discovered that axon guidance genes are affected by somatic structural variants in up to 25% of human pancreatic cancers. Thus far, however, some of these mutations have only been correlated to survival probability and no function has been assigned to these observed axon guidance gene mutations in pancreatic cancer. In this study we established three novel pancreatic cancer cell lines and performed whole genome sequencing to discover novel mutations in axon guidance genes that may contribute to the cancer phenotype of these cells. We discovered, among other novel somatic variants in axon guidance pathway genes, a novel mutation in the PLXNA1 receptor (c.2587G>A) in newly established cell line SB.06 that mediates oncogenic cues of increased invasion and proliferation in SB.06 cells and increased invasion in 293T cells upon stimulation with the receptor's natural ligand semaphorin 3A compared to wild type PLXNA1 cells. Mutant PLXNA1 signaling was associated with increased Rho-GTPase and p42/p44 MAPK signaling activity and cytoskeletal expansion, but not changes in E-cadherin, vimentin, or metalloproteinase 9 expression levels. Pharmacologic inhibition of the Rho-GTPase family member CDC42 selectively abrogated PLXNA1 c.2587G>A-mediated increased invasion. These findings provide in-vitro confirmation that somatic mutations in axon guidance genes can provide oncogenic gain-of-function signals and may contribute to pancreatic cancer progression.

Année de publication : 2015

Lars Grøntved, Joshua J Waterfall, Dong Wook Kim, Songjoon Baek, Myong-Hee Sung, Li Zhao, Jeong Won Park, Ronni Nielsen, Robert L Walker, Yuelin J Zhu, Paul S Meltzer, Gordon L Hager, Sheue-yann Cheng (2015 Apr 29)
Transcriptional activation by the thyroid hormone receptor through ligand-dependent receptor recruitment and chromatin remodelling.
Nature communications : 7048 : DOI : 10.1038/ncomms8048

Résumé

A bimodal switch model is widely used to describe transcriptional regulation by the thyroid hormone receptor (TR). In this model, the unliganded TR forms stable, chromatin-bound complexes with transcriptional co-repressors to repress transcription. Binding of hormone dissociates co-repressors and facilitates recruitment of co-activators to activate transcription. Here we show that in addition to hormone-independent TR occupancy, ChIP-

seq against endogenous TR in mouse liver tissue demonstrates considerable hormone-induced TR recruitment to chromatin associated with chromatin remodelling and activated gene transcription. Genome-wide footprinting analysis using DNase-seq provides little evidence for TR footprints both in the absence and presence of hormone, suggesting that unliganded TR engagement with repressive complexes on chromatin is, similar to activating receptor complexes, a highly dynamic process. This dynamic and ligand-dependent interaction with chromatin is likely shared by all steroid hormone receptors regardless of their capacity to repress transcription in the absence of ligand.

Joshua J Waterfall, Paul S Meltzer (2015 Feb 26)
Avalanching mutations in biallelic mismatch repair deficiency syndrome.
Nature genetics : 194-6 : DOI : 10.1038/ng.3227

Résumé

Tumors from pediatric patients generally contain relatively few somatic mutations. A new study reports a striking exception in individuals in whom biallelic germline deficiency for mismatch repair is compounded by somatic loss of function in DNA proofreading polymerases, resulting in 'ultra-hypermutated' malignant brain tumors.

Année de publication : 2014

J Keith Killian, Markku Miettinen, Robert L Walker, Yonghong Wang, Yuelin Jack Zhu, Joshua J Waterfall, Natalia Noyes, Parvathy Retnakumar, Zhiming Yang, William I Smith, M Scott Killian, C Christopher Lau, Marbin Pineda, Jennifer Walling, Holly Stevenson, Carly Smith, Zengfeng Wang, Jerzy Lasota, Su Young Kim, Sosipatros A Boikos, Lee J Helman, Paul S Meltzer (2014 Dec 26)
Recurrent epimutation of SDHC in gastrointestinal stromal tumors.
Science translational medicine : 268ra177 : DOI : 10.1126/scitranslmed.3009961

Résumé

Succinate dehydrogenase (SDH) is a conserved effector of cellular metabolism and energy production, and loss of SDH function is a driver mechanism in several cancers. SDH-deficient gastrointestinal stromal tumors (dSDH GISTs) collectively manifest similar phenotypes, including hypermethylated epigenomic signatures, tendency to occur in pediatric patients, and lack of KIT/PDGFRA mutations. dSDH GISTs often harbor deleterious mutations in SDH subunit genes (SDHA, SDHB, SDHC, and SDHD, termed SDHx), but some are SDHx wild type (WT). To further elucidate mechanisms of SDH deactivation in SDHx-WT GIST, we performed targeted exome sequencing on 59 dSDH GISTs to identify 43 SDHx-mutant and 16 SDHx-WT cases. Genome-wide DNA methylation and expression profiling exposed SDHC promoter-specific CpG island hypermethylation and gene silencing in SDHx-WT dSDH GISTs [15 of 16 cases (94%)]. Six of 15 SDHC-epimutant GISTs occurred in the setting of the multitumor syndrome Carney triad. We observed neither SDHB promoter hypermethylation nor large deletions on chromosome 1q in any SDHx-WT cases. Deep genome sequencing of a 130-kbp

(kilo-base pair) window around SDHC revealed no recognizable sequence anomalies in SDHC-epimutant tumors. More than 2000 benign and tumor reference tissues, including stem cells and malignancies with a hypermethylator epigenotype, exhibit solely a non-epimutant SDHC promoter. Mosaic constitutional SDHC promoter hypermethylation in blood and saliva from patients with SDHC-epimutant GIST implicates a postzygotic mechanism in the establishment and maintenance of SDHC epimutation. The discovery of SDHC epimutation provides a unifying explanation for the pathogenesis of dSDH GIST, whereby loss of SDH function stems from either SDHx mutation or SDHC epimutation.

Joshua J Waterfall, Paul S Meltzer (2014 Dec 18)
Building through breaking: the development of cancer neochromosomes.
Cancer cell : 593-5 : DOI : 10.1016/j.ccell.2014.10.013

Résumé

In this issue of Cancer Cell, Garsed and colleagues combine chromosome flow sorting and deep sequencing to characterize the structure of oncogene-containing neochromosomes in liposarcoma and provide evidence that they are generated by a combination of multiple dynamic and destructive processes.

Joshua J Waterfall, J Keith Killian, Paul S Meltzer (2014 Aug 12)
The role of mutation of metabolism-related genes in genomic hypermethylation.
Biochemical and biophysical research communications : 16-23 : DOI : 10.1016/j.bbrc.2014.08.003

Résumé

Genetic mutations, metabolic dysfunction, and epigenetic misregulation are commonly considered to play distinct roles in tumor development and maintenance. However, intimate relationships between these mechanisms are now emerging. In particular, mutations in genes for the core metabolic enzymes IDH, SDH, and FH are significant drivers of diverse tumor types. In each case, the resultant accumulation of particular metabolites inhibits TET enzymes responsible for oxidizing 5-methylcytosine, leading to pervasive DNA hypermethylation.

Année de publication : 2013

Joshua J Waterfall, Evgeny Arons, Robert L Walker, Marbin Pineda, Laura Roth, J Keith Killian, Ogan D Abaan, Sean R Davis, Robert J Kreitman, Paul S Meltzer (2013 Nov 19)
High prevalence of MAP2K1 mutations in variant and IGHV4-34-expressing hairy-cell leukemias.
Nature genetics : 8-10 : DOI : 10.1038/ng.2828

Résumé

To understand the genetic mechanisms driving variant and IGHV4-34-expressing hairy-cell leukemias, we performed whole-exome sequencing of leukemia samples from ten affected individuals, including six with matched normal samples. We identified activating mutations in the MAP2K1 gene (encoding MEK1) in 5 of these 10 samples and in 10 of 21 samples in a validation set (overall frequency of 15/31), suggesting potential new strategies for treating individuals with these diseases.

J Keith Killian, Su Young Kim, Markku Miettinen, Carly Smith, Maria Merino, Maria Tsokos, Martha Quezado, William I Smith, Mona S Jahromi, Paraskevi Xekouki, Eva Szarek, Robert L Walker, Jerzy Lasota, Mark Raffeld, Brandy Klotzle, Zengfeng Wang, Laura Jones, Yuelin Zhu, Yonghong Wang, Joshua J Waterfall, Maureen J O'Sullivan, Marina Bibikova, Karel Pacak, Constantine Stratakis, Katherine A Janeway, Joshua D Schiffman, Jian-Bing Fan, Lee Helman, Paul S Meltzer (2013 Apr 4)
Succinate dehydrogenase mutation underlies global epigenomic divergence in gastrointestinal stromal tumor.
Cancer discovery : 648-57 : DOI : 10.1158/2159-8290.CD-13-0092

Résumé

Gastrointestinal stromal tumors (GIST) harbor driver mutations of signal transduction kinases such as KIT, or, alternatively, manifest loss-of-function defects in the mitochondrial succinate dehydrogenase (SDH) complex, a component of the Krebs cycle and electron transport chain. We have uncovered a striking divergence between the DNA methylation profiles of SDH-deficient GIST (n = 24) versus KIT tyrosine kinase pathway-mutated GIST (n = 39). Infinium 450K methylation array analysis of formalin-fixed paraffin-embedded tissues disclosed an order of magnitude greater genomic hypermethylation relative to SDH-deficient GIST versus the KIT-mutant group (84.9 K vs. 8.4 K targets). Epigenomic divergence was further found among SDH-mutant paraganglioma/pheochromocytoma (n = 29), a developmentally distinct SDH-deficient tumor system. Comparison of SDH-mutant GIST with isocitrate dehydrogenase-mutant glioma, another Krebs cycle-defective tumor type, revealed comparable measures of global hypo- and hypermethylation. These data expose a vital connection between succinate metabolism and genomic DNA methylation during tumorigenesis, and generally implicate the mitochondrial Krebs cycle in nuclear epigenomic maintenance.

Année de publication : 2012

Leighton J Core, Joshua J Waterfall, Daniel A Gilchrist, David C Fargo, Hojoong Kwak, Karen Adelman, John T Lis (2012 Oct 16)
Defining the status of RNA polymerase at promoters.
Cell reports : 1025-35 : DOI : 10.1016/j.celrep.2012.08.034

Résumé

Recent genome-wide studies in metazoans have shown that RNA polymerase II (Pol II) accumulates to high densities on many promoters at a rate-limited step in transcription. However, the status of this Pol II remains an area of debate. Here, we compare quantitative outputs of a global run-on sequencing assay and chromatin immunoprecipitation sequencing assays and demonstrate that the majority of the Pol II on Drosophila promoters is transcriptionally engaged; very little exists in a preinitiation or arrested complex. These promoter-proximal polymerases are inhibited from further elongation by detergent-sensitive factors, and knockdown of negative elongation factor, NELF, reduces their levels. These results not only solidify the notion that pausing occurs at most promoters, but demonstrate that it is the major rate-limiting step in early transcription at these promoters. Finally, the divergent elongation complexes seen at mammalian promoters are far less prevalent in Drosophila, and this specificity in orientation correlates with directional core promoter elements, which are abundant in Drosophila.