Année de publication : 2020

Sebastien Gauthier, Iwona Pranke, Vincent Jung, Loredana Martignetti, Véronique Stoven, Thao Nguyen-Khoa, Michaela Semeraro, Alexandre Hinzpeter, Aleksander Edelman, Ida Chiara Guerrera, Isabelle Sermet-Gaudelus (2020 Sep 15)

Urinary Exosomes of Patients with Cystic Fibrosis Unravel CFTR-Related Renal Disease.

International journal of molecular sciences : DOI : E6625

Résumé

The prevalence of chronic kidney disease is increased in patients with cystic fibrosis (CF). The study of urinary exosomal proteins might provide insight into the pathophysiology of CF kidney disease. Urine samples were collected from 19 CF patients (among those 7 were treated by cystic fibrosis transmembrane conductance regulator (CFTR) modulators), and 8 healthy subjects. Urine exosomal protein content was determined by high resolution mass spectrometry. A heatmap of the differentially expressed proteins in urinary exosomes showed a clear separation between control and CF patients. Seventeen proteins were upregulated in CF patients (including epidermal growth factor receptor (EGFR); proteasome subunit beta type-6, transglutaminases, caspase 14) and 118 were downregulated (including glutathione S-transferases, superoxide dismutase, klotho, endosomal sorting complex required for transport, and matrisome proteins). Gene set enrichment analysis revealed 20 gene sets upregulated and 74 downregulated. Treatment with CFTR modulators yielded no significant modification of the proteomic content. These results highlight that CF kidney cells adapt to the CFTR defect by upregulating proteasome activity and that autophagy and endosomal targeting are impaired. Increased expression of EGFR and decreased expression of klotho and matrisome might play a central role in this CF kidney signature by inducing oxidation, inflammation, accelerated senescence, and abnormal tissue repair. Our study unravels novel insights into consequences of CFTR dysfunction in the urinary tract, some of which may have clinical and therapeutic implications.

Année de publication : 2017

Mathurin Dorel, Eric Viara, Emmanuel Barillot, Andrei Zinovyev, Inna Kuperstein (2017 Apr 18)

NaviCom: a web application to create interactive molecular network portraits using multi-level omics data.

Database : the journal of biological databases and curation : DOI : 10.1093/database/bax026

Résumé

Human diseases such as cancer are routinely characterized by high-throughput molecular technologies, and multi-level omics data are accumulated in public databases at increasing rate. Retrieval and visualization of these data in the context of molecular network maps can provide insights into the pattern of regulation of molecular functions reflected by an omics profile. In order to make this task easy, we developed NaviCom, a Python package and web

platform for visualization of multi-level omics data on top of biological network maps. NaviCom is bridging the gap between cBioPortal, the most used resource of large-scale cancer omics data and NaviCell, a data visualization web service that contains several molecular network map collections. NaviCom proposes several standardized modes of data display on top of molecular network maps, allowing addressing specific biological questions. We illustrate how users can easily create interactive network-based cancer molecular portraits via NaviCom web interface using the maps of Atlas of Cancer Signalling Network (ACSN) and other maps. Analysis of these molecular portraits can help in formulating a scientific hypothesis on the molecular mechanisms deregulated in the studied disease.

Laura Cantini, Michele Caselle, Antoine Forget, Andrei Zinovyev, Emmanuel Barillot, Loredana Martignetti (2017 Apr 15)
A review of computational approaches detecting microRNAs involved in cancer.
Frontiers in bioscience (Landmark edition) : 1774-1791

Résumé

MicroRNAs (miRNAs) are small non-coding RNAs playing an essential role in gene expression regulation. Multiple studies have demonstrated that miRNAs are dysregulated in cancer initiation and progression, pointing out their potential as biomarkers for diagnosis, prognosis and response to treatment. With the introduction of high-throughput technologies several computational approaches have been proposed to identify cancer-associated miRNAs. Here, we present a systematic and comprehensive overview of the current knowledge concerning the computational detection of miRNAs involved in tumor onset and subtyping, with possible theranostic employment. An overview of the state of art in this field is thus proposed with the aim of supporting researchers, especially experimentalists and pathologists, in choosing the optimal approach for their case of study.

Catherine M Phelan, Karoline B Kuchenbaecker, Jonathan P Tyrer, Siddhartha P Kar, Kate Lawrenson, Stacey J Winham, Joe Dennis, Ailith Pirie, Marjorie J Riggan, Ganna Chornokur, Madalene A Earp, Paulo C Lyra, Janet M Lee, Simon Coetzee, Jonathan Beesley, Lesley McGuffog, Penny Soucy, Ed Dicks, Andrew Lee, Daniel Barrowdale, Julie Lecarpentier, Goska Leslie, Cora M Aalfs, Katja K H Aben, Marcia Adams, Julian Adlard, Irene L Andrulis, Hoda Anton-Culver, Natalia Antonenkova, , Gerasimos Aravantinos, Norbert Arnold, Banu K Arun, Brita Arver, Jacopo Azzollini, Judith Balmaña, Susana N Banerjee, Laure Barjhoux, Rosa B Barkardottir, Yukie Bean, Matthias W Beckmann, Alicia Beeghly-Fadiel, Javier Benitez, Marina Bermisheva, Marcus Q Bernardini, Michael J Birrer, Line Bjorge, Amanda Black, Kenneth Blankstein, Marinus J Blok, Clara Bodelon, Natalia Bogdanova, Anders Bojesen, Bernardo Bonanni, Åke Borg, Angela R Bradbury, James D Brenton, Carole Brewer, Louise Brinton, Per Broberg, Angela Brooks-Wilson, Fiona Bruinsma, Joan Brunet, Bruno Buecher, Ralf Butzow, Saundra S Buys, Trinidad Caldes, Maria A Caligo, Ian Campbell, Rikki Cannioto, Michael E Carney, Terence Cescon, Salina B Chan, Jenny

Chang-Claude, Stephen Chanock, Xiao Qing Chen, Yoke-Eng Chiew, Jocelyne Chiquette, Wendy K Chung, Kathleen B M Claes, Thomas Conner, Linda S Cook, Jackie Cook, Daniel W Cramer, Julie M Cunningham, Aimee A D'Aloisio, Mary B Daly, Francesca Damiola, Sakaeva Dina Damirovna, Agnieszka Dansonka-Mieszkowska, Fanny Dao, Rosemarie Davidson, Anna DeFazio, Capucine Delnatte, Kimberly F Doheny, Orland Diez, Yuan Chun Ding, Jennifer Anne Doherty, Susan M Domchek, Cecilia M Dorfling, Thilo Dörk, Laure Dossus, Mercedes Duran, Matthias Dürst, Bernd Dworniczak, Diana Eccles, Todd Edwards, Ros Eeles, Ursula Eilber, Bent Ejlertsen, Arif B Ekici, Steve Ellis, Mingajeva Elvira, , Kevin H Eng, Christoph Engel, D Gareth Evans, Peter A Fasching, Sarah Ferguson, Sandra Fert Ferrer, James M Flanagan, Zachary C Fogarty, Renée T Fortner, Florentia Fostira, William D Foulkes, George Fountzilas, Brooke L Fridley, Tara M Friebel, Eitan Friedman, Debra Frost, Patricia A Ganz, Judy Garber, María J García, Vanesa Garcia-Barberan, Andrea Gehrig, , Aleksandra Gentry-Maharaj, Anne-Marie Gerdes, Graham G Giles, Rosalind Glasspool, Gord Glendon, Andrew K Godwin, David E Goldgar, Teodora Goranova, Martin Gore, Mark H Greene, Jacek Gronwald, Stephen Gruber, Eric Hahnen, Christopher A Haiman, Niclas Håkansson, Ute Hamann, Thomas V O Hansen, Patricia A Harrington, Holly R Harris, Jan Hauke, , Alexander Hein, Alex Henderson, Michelle A T Hildebrandt, Peter Hillemanns, Shirley Hodgson, Claus K Høgdall, Estrid Høgdall, Frans B L Hogervorst, Helene Holland, Maartje J Hooning, Karen Hosking, Ruea-Yea Huang, Peter J Hulick, Jillian Hung, David J Hunter, David G Huntsman, Tomasz Huzarski, Evgeny N Imyanitov, Claudine Isaacs, Edwin S Iversen, Louise Izatt, Angel Izquierdo, Anna Jakubowska, Paul James, Ramunas Janavicius, Mats Jernetz, Allan Jensen, Uffe Birk Jensen, Esther M John, Sharon Johnatty, Michael E Jones, Päivi Kannisto, Beth Y Karlan, Anthony Karnezis, Karin Kast, , Catherine J Kennedy, Elza Khusnutdinova, Lambertus A Kiemeney, Johanna I Kiiski, Sung-Won Kim, Susanne K Kjaer, Martin Köbel, Reidun K Kopperud, Torben A Kruse, Jolanta Kupryjanczyk, Ava Kwong, Yael Laitman, Diether Lambrechts, Nerea Larrañaga, Melissa C Larson, Conxi Lazaro, Nhu D Le, Loic Le Marchand, Jong Won Lee, Shashikant B Lele, Arto Leminen, Dominique Leroux, Jenny Lester, Fabienne Lesueur, Douglas A Levine, Dong Liang, Clemens Liebrich, Jenna Lilyquist, Loren Lipworth, Jolanta Lissowska, Karen H Lu, Jan Lubiński, Craig Luccarini, Lene Lundvall, Phuong L Mai, Gustavo Mendoza-Fandiño, Siranoush Manoukian, Leon F A G Massuger, Taymaa May, Sylvie Mazoyer, Jessica N McAlpine, Valerie McGuire, John R McLaughlin, Iain McNeish, Hanne Meijers-Heijboer, Alfons Meindl, Usha Menon, Arjen R Mensenkamp, Melissa A Merritt, Roger L Milne, Gillian Mitchell, Francesmary Modugno, Joanna Moes-Sosnowska, Melissa Moffitt, Marco Montagna, Kirsten B Moysich, Anna Marie Mulligan, Jacob Musinsky, Katherine L Nathanson, Lotte Nedergaard, Roberta B Ness, Susan L Neuhausen, Heli Nevanlinna, Dieter Niederacher, Robert L Nussbaum, Kunle Odunsi, Edith Olah, Olufunmilayo I Olopade, Håkan Olsson, Curtis Olswold, David M O'Malley, Kai-Ren Ong, N Charlotte Onland-Moret, , Nicholas Orr, Sandra Orsulic, Ana Osorio, Domenico Palli, Laura Papi, Tjoung-Won Park-Simon, James Paul, Celeste L Pearce, Inge Søkilde Pedersen, Petra H M Peeters, Bernard Peissel, Ana Peixoto, Tanja Pejovic, Liisa M Pelttari, Jennifer B Permuth, Paolo Peterlongo, Lidia Pezzani, Georg Pfeiler, Kelly-Anne Phillips, Marion Piedmonte, Malcolm C Pike,

Anna M Piskorz, Samantha R Poblete, Timea Pocza, Elizabeth M Poole, Bruce Poppe, Mary E Porteous, Fabienne Prieur, Darya Prokofyeva, Elizabeth Pugh, Miquel Angel Pujana, Pascal Pujol, Paolo Radice, Johanna Rantala, Christine Rappaport-Fuerhauser, Gad Rennert, Kerstin Rhiem, Patricia Rice, Andrea Richardson, Mark Robson, Gustavo C Rodriguez, Cristina Rodríguez-Antona, Jane Romm, Matti A Rookus, Mary Anne Rossing, Joseph H Rothstein, Anja Rudolph, Ingo B Runnebaum, Helga B Salvesen, Dale P Sandler, Minouk J Schoemaker, Leigha Senter, V Wendy Setiawan, Gianluca Severi, Priyanka Sharma, Tameka Shelford, Nadeem Siddiqui, Lucy E Side, Weiva Sieh, Christian F Singer, Hagay Sobol, Honglin Song, Melissa C Southey, Amanda B Spurdle, Zsofia Stadler, Doris Steinemann, Dominique Stoppa-Lyonnet, Lara E Sucheston-Campbell, Grzegorz Sukiennicki, Rebecca Sutphen, Christian Sutter, Anthony J Swerdlow, Csilla I Szabo, Lukasz Szafron, Yen Y Tan, Jack A Taylor, Muy-Kheng Tea, Manuel R Teixeira, Soo-Hwang Teo, Kathryn L Terry, Pamela J Thompson, Liv Cecilie Vestrheim Thomsen, Darcy L Thull, Laima Tihomirova, Anna V Tinker, Marc Tischkowitz, Silvia Tognazzo, Amanda Ewart Toland, Alicia Tone, Britton Trabert, Ruth C Travis, Antonia Trichopoulou, Nadine Tung, Shelley S Tworoger, Anne M van Altena, David Van Den Berg, Annemarie H van der Hout, Rob B van der Luijt, Mattias Van Heetvelde, Els Van Nieuwenhuysen, Elizabeth J van Rensburg, Adriaan Vanderstichele, Raymonda Varon-Mateeva, Ana Vega, Digna Velez Edwards, Ignace Vergote, Robert A Vierkant, Joseph Vijai, Athanassios Vratimos, Lisa Walker, Christine Walsh, Dorothea Wand, Shan Wang-Gohrke, Barbara Wappenschmidt, Penelope M Webb, Clarice R Weinberg, Jeffrey N Weitzel, Nicolas Wentzensen, Alice S Whittemore, Juul T Wijnen, Lynne R Wilkens, Alicja Wolk, Michelle Woo, Xifeng Wu, Anna H Wu, Hannah Yang, Drakoulis Yannoukakos, Argyrios Ziogas, Kristin K Zorn, Steven A Narod, Douglas F Easton, Christopher I Amos, Joellen M Schildkraut, Susan J Ramus, Laura Ottini, Marc T Goodman, Sue K Park, Linda E Kelemen, Harvey A Risch, Mads Thomassen, Kenneth Offit, Jacques Simard, Rita Katharina Schmutzler, Dennis Hazelett, Alvaro N Monteiro, Fergus J Couch, Andrew Berchuck, Georgia Chenevix-Trench, Ellen L Goode, Thomas A Sellers, Simon A Gayther, Antonis C Antoniou, Paul D P Pharoah (2017 Mar 28)

Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer.

Nature genetics : DOI : 10.1038/ng.3826

Résumé

To identify common alleles associated with different histotypes of epithelial ovarian cancer (EOC), we pooled data from multiple genome-wide genotyping projects totaling 25,509 EOC cases and 40,941 controls. We identified nine new susceptibility loci for different EOC histotypes: six for serous EOC histotypes (3q28, 4q32.3, 8q21.11, 10q24.33, 18q11.2 and 22q12.1), two for mucinous EOC (3q22.3 and 9q31.1) and one for endometrioid EOC (5q12.3). We then performed meta-analysis on the results for high-grade serous ovarian cancer with the results from analysis of 31,448 BRCA1 and BRCA2 mutation carriers, including 3,887 mutation carriers with EOC. This identified three additional susceptibility loci at 2q13, 8q24.1 and 12q24.31. Integrated analyses of genes and regulatory biofeatures at

each locus predicted candidate susceptibility genes, including OBFC1, a new candidate susceptibility gene for low-grade and borderline serous EOC.

Veronique Dieras, Simona Pop, Frederique Berger, Marie-Eglantine Dujaric, Philippe Beuzeboc, Laurence Escalup, François Clement Bidard, Paul Henri Cottu, Christophe LE Tourneau, Sophie Piperno-Neumann, Valerie Laurence, Mathieu Robain, Bernard Asselain, Jean-Yves Pierga (2017 Mar 19)
First-line Bevacizumab and Paclitaxel for HER2-negative Metastatic Breast Cancer: A French Retrospective Observational Study.
Anticancer research : 1403-1407

Résumé

To assess outcomes in patients treated with first-line bevacizumab-containing therapy for human epidermal growth factor receptor (HER)2-negative metastatic breast cancer (mBC) at a single centre with a homogenous standard-of-care.

Manuela Portoso, Roberta Ragazzini, Živa Brenčič, Arianna Moiani, Audrey Michaud, Ivaylo Vassilev, Michel Wassef, Nicolas Servant, Bruno Sargueil, Raphaël Margueron (2017 Feb 8)
PRC2 is dispensable for HOTAIR-mediated transcriptional repression.
The EMBO journal : DOI : e201695335

Résumé

Long non-coding RNAs (lncRNAs) play diverse roles in physiological and pathological processes. Several lncRNAs have been suggested to modulate gene expression by guiding chromatin-modifying complexes to specific sites in the genome. However, besides the example of Xist, clear-cut evidence demonstrating this novel mode of regulation remains sparse. Here, we focus on HOTAIR, a lncRNA that is overexpressed in several tumor types and previously proposed to play a key role in gene silencing through direct recruitment of Polycomb Repressive Complex 2 (PRC2) to defined genomic loci. Using genetic tools and a novel RNA-tethering system, we investigated the interplay between HOTAIR and PRC2 in gene silencing. Surprisingly, we observed that forced overexpression of HOTAIR in breast cancer cells leads to subtle transcriptomic changes that appear to be independent of PRC2. Mechanistically, we found that artificial tethering of HOTAIR to chromatin causes transcriptional repression, but that this effect does not require PRC2. Instead, PRC2 recruitment appears to be a consequence of gene silencing. We propose that PRC2 binding to RNA might serve functions other than chromatin targeting.

Maud Borensztein, Laurène Syx, Katia Ancelin, Patricia Diabangouaya, Christel Picard, Tao Liu, Jun-Bin Liang, Ivaylo Vassilev, Rafael Galupa, Nicolas Servant, Emmanuel Barillot, Azim Surani,

Chong-Jian Chen, Edith Heard (2017 Jan 31)

Xist-dependent imprinted X inactivation and the early developmental consequences of its failure.

Nature structural & molecular biology : DOI : 10.1038/nsmb.3365

Résumé

The long noncoding RNA Xist is expressed from only the paternal X chromosome in mouse preimplantation female embryos and mediates transcriptional silencing of that chromosome. In females, absence of Xist leads to postimplantation lethality. Here, through single-cell RNA sequencing of early preimplantation mouse embryos, we found that the initiation of imprinted X-chromosome inactivation absolutely requires Xist. Lack of paternal Xist leads to genome-wide transcriptional misregulation in the early blastocyst and to failure to activate the extraembryonic pathway that is essential for postimplantation development. We also demonstrate that the expression dynamics of X-linked genes depends on the strain and parent of origin as well as on the location along the X chromosome, particularly at the first 'entry' sites of Xist. This study demonstrates that dosage-compensation failure has an effect as early as the blastocyst stage and reveals genetic and epigenetic contributions to orchestrating transcriptional silencing of the X chromosome during early embryogenesis.

Année de publication : 2016

Yuvia A Pérez Rico, Valentina Boeva, Allison C Mallory, Angelo Bitetti, Sara Majello, Emmanuel Barillot, Alena Shkumatava (2016 Dec 15)

Comparative analyses of super-enhancers reveal conserved elements in vertebrate genomes.

Genome research : DOI : gr.203679.115

Résumé

Super-enhancers (SEs) are key transcriptional drivers of cellular, developmental and disease states in mammals, yet the conservational and regulatory features of these enhancer elements in non-mammalian vertebrates are unknown. To define SEs in zebrafish and enable sequence and functional comparisons to mouse and human SEs, we used genome-wide histone H3 lysine 27 acetylation (H3K27ac) occupancy as a primary SE delineator. Our study determined the set of SEs in pluripotent state cells and adult zebrafish tissues and revealed both similarities and differences between zebrafish and mammalian SEs. Although the total number of SEs was proportional to the genome size, the genomic distribution of zebrafish SEs differed from that of the mammalian SEs. Despite the evolutionary distance separating zebrafish and mammals and the low overall SE sequence conservation, ~42% of zebrafish SEs were located in close proximity to orthologs that also were associated with SEs in mouse and human. Compared to their non-associated counterparts, higher sequence conservation was revealed for those SEs that have maintained orthologous gene associations. Functional dissection of two of these SEs identified conserved sequence elements and tissue-specific expression patterns, while chromatin accessibility analyses predicted transcription factors

governing the function of pluripotent state zebrafish SEs. Our zebrafish annotations and comparative studies show the extent of SE usage and their conservation across vertebrates, permitting future gene regulatory studies in several tissues.

Daniela Chmiest, Nanaocha Sharma, Natacha Zanin, Christine Viaris de Lesegno, Massiullah Shafaq-Zadah, Vonick Sibut, Florent Dingli, Philippe Hupé, Stephan Wilmes, Jacob Piehler, Damarys Loew, Ludger Johannes, Gideon Schreiber, Christophe Lamaze (2016 Dec 6)
Spatiotemporal control of interferon-induced JAK/STAT signalling and gene transcription by the retromer complex.
Nature communications : 13476 : DOI : 10.1038/ncomms13476

Résumé

Type-I interferons (IFNs) play a key role in the immune defences against viral and bacterial infections, and in cancer immunosurveillance. We have established that clathrin-dependent endocytosis of the type-I interferon (IFN-α/β) receptor (IFNAR) is required for JAK/STAT signalling. Here we show that the internalized IFNAR1 and IFNAR2 subunits of the IFNAR complex are differentially sorted by the retromer at the early endosome. Binding of the retromer VPS35 subunit to IFNAR2 results in IFNAR2 recycling to the plasma membrane, whereas IFNAR1 is sorted to the lysosome for degradation. Depletion of VPS35 leads to abnormally prolonged residency and association of the IFNAR subunits at the early endosome, resulting in increased activation of STAT1- and IFN-dependent gene transcription. These experimental data establish the retromer complex as a key spatiotemporal regulator of IFNAR endosomal sorting and a new factor in type-I IFN-induced JAK/STAT signalling and gene transcription.

Yosr Hamdi, Penny Soucy, Karoline B Kuchenbaeker, Tomi Pastinen, Arnaud Droit, Audrey Lemaçon, Julian Adlard, Kristiina Aittomäki, Irene L Andrulis, Adalgeir Arason, Norbert Arnold, Banu K Arun, Jacopo Azzollini, Anita Bane, Laure Barjhoux, Daniel Barrowdale, Javier Benitez, Pascaline Berthet, Marinus J Blok, Kristie Bobolis, Valérie Bonadona, Bernardo Bonanni, Angela R Bradbury, Carole Brewer, Bruno Buecher, Saundra S Buys, Maria A Caligo, Jocelyne Chiquette, Wendy K Chung, Kathleen B M Claes, Mary B Daly, Francesca Damiola, Rosemarie Davidson, Miguel De la Hoya, Kim De Leeneer, Orland Diez, Yuan Chun Ding, Riccardo Dolcetti, Susan M Domchek, Cecilia M Dorfling, Diana Eccles, Ros Eeles, Zakaria Einbeigi, Bent Ejlertsen, , Christoph Engel, D Gareth Evans, Lidia Feliubadalo, Lenka Foretova, Florentia Fostira, William D Foulkes, George Fountzilas, Eitan Friedman, Debra Frost, Pamela Ganschow, Patricia A Ganz, Judy Garber, Simon A Gayther, , Anne-Marie Gerdes, Gord Glendon, Andrew K Godwin, David E Goldgar, Mark H Greene, Jacek Gronwald, Eric Hahnen, Ute Hamann, Thomas V O Hansen, Steven Hart, John L Hays, , Frans B L Hogervorst, Peter J Hulick, Evgeny N Imyanitov, Claudine Isaacs, Louise Izatt, Anna Jakubowska, Paul James, Ramunas Janavicius, Uffe Birk Jensen, Esther M John, Vijai Joseph, Walter Just, Katarzyna Kaczmarek, Beth Y Karlan, , Carolien M Kets, Judy

Kirk, Mieke Kriege, Yael Laitman, Maïté Laurent, Conxi Lazaro, Goska Leslie, Jenny Lester, Fabienne Lesueur, Annelie Liljegren, Niklas Loman, Jennifer T Loud, Siranoush Manoukian, Milena Mariani, Sylvie Mazoyer, Lesley McGuffog, Hanne E J Meijers-Heijboer, Alfons Meindl, Austin Miller, Marco Montagna, Anna Marie Mulligan, Katherine L Nathanson, Susan L Neuhausen, Heli Nevanlinna, Robert L Nussbaum, Edith Olah, Olufunmilayo I Olopade, Kai-Ren Ong, Jan C Oosterwijk, Ana Osorio, Laura Papi, Sue Kyung Park, Inge Sokilde Pedersen, Bernard Peissel, Pedro Perez Segura, Paolo Peterlongo, Catherine M Phelan, Paolo Radice, Johanna Rantala, Christine Rappaport-Fuerhauser, Gad Rennert, Andrea Richardson, Mark Robson, Gustavo C Rodriguez, Matti A Rookus, Rita Katharina Schmutzler, Nicolas Sevenet, Payal D Shah, Christian F Singer, Thomas P Slavin, Katie Snape, Johanna Sokolowska, Ida Marie Heeholm Sønderstrup, Melissa Southey, Amanda B Spurdle, Zsofia Stadler, Dominique Stoppa-Lyonnet, Grzegorz Sukiennicki, Christian Sutter, Yen Tan, Muy-Kheng Tea, Manuel R Teixeira, Alex Teulé, Soo-Hwang Teo, Mary Beth Terry, Mads Thomassen, Laima Tihomirova, Marc Tischkowitz, Silvia Tognazzo, Amanda Ewart Toland, Nadine Tung, Ans M W van den Ouweland, Rob B van der Luijt, Klaartje van Engelen, Elizabeth J van Rensburg, Raymonda Varon-Mateeva, Barbara Wappenschmidt, Juul T Wijnen, Timothy Rebbeck, Georgia Chenevix-Trench, Kenneth Offit, Fergus J Couch, Silje Nord, Douglas F Easton, Antonis C Antoniou, Jacques Simard (2016 Nov 1)
Association of breast cancer risk in BRCA1 and BRCA2 mutation carriers with genetic variants showing differential allelic expression: identification of a modifier of breast cancer risk at locus 11q22.3.
Breast cancer research and treatment : 117-134 : DOI : 10.1007/s10549-016-4018-2

Résumé

Cis-acting regulatory SNPs resulting in differential allelic expression (DAE) may, in part, explain the underlying phenotypic variation associated with many complex diseases. To investigate whether common variants associated with DAE were involved in breast cancer susceptibility among BRCA1 and BRCA2 mutation carriers, a list of 175 genes was developed based of their involvement in cancer-related pathways.

Angelica Macauda, Diego Calvetti, Giuseppe Maccari, Kari Hemminki, Asta Försti, Hartmut Goldschmidt, Niels Weinhold, Richard Houlston, Vibeke Andersen, Ulla Vogel, Gabriele Buda, Judit Varkonyi, Anna Sureda, Joaquin Martinez Lopez, Marzena Watek, Aleksandra Butrym, Maria Eugenia Sarasquete, Marek Dudziński, Artur Jurczyszyn, Agnieszka Druzd-Sitek, Marcin Kruszewski, Edyta Subocz, Mario Petrini, Elzbieta Iskierka-Jażdżewska, Malgorzata Raźny, Gergely Szombath, Herlander Marques, Daria Zawirska, Dominik Chraniuk, Janusz Halka, Svend Erik Hove Jacobsen, Grzegorz Mazur, Ramón García Sanz, Charles Dumontet, Victor Moreno, Anna Stępień, Katia Beider, Matteo Pelosini, Rui Manuel Reis, Malgorzata Krawczyk-Kulis, Marcin Rymko, Hervé Avet-Loiseau, Fabienne Lesueur, Norbert Grząśko, Olga Ostrovsky, Krzysztof Jamroziak, Annette J Vangsted, Andrés Jerez, Waldemar Tomczak, Jan Maciej Zaucha, Katalin

Kadar, Juan Sainz, Arnon Nagler, Stefano Landi, Federica Gemignani, Federico Canzian (2016 Oct 9)

Identification of miRSNPs associated with the risk of multiple myeloma.

International journal of cancer : 526-534 : DOI : 10.1002/ijc.30465

Résumé

Multiple myeloma (MM) is a malignancy of plasma cells usually infiltrating the bone marrow, associated with the production of a monoclonal immunoglobulin (M protein) which can be detected in the blood and/or urine. Multiple lines of evidence suggest that genetic factors are involved in MM pathogenesis, and several studies have identified single nucleotide polymorphisms (SNPs) associated with the susceptibility to the disease. SNPs within miRNA-binding sites in target genes (miRSNPs) may alter the strength of miRNA-mRNA interactions, thus deregulating protein expression. MiRSNPs are known to be associated with risk of various types of cancer, but they have never been investigated in MM. We performed an in silico genome-wide search for miRSNPs predicted to alter binding of miRNAs to their target sequences. We selected 12 miRSNPs and tested their association with MM risk. Our study population consisted of 1,832 controls and 2,894 MM cases recruited from seven European countries and Israel in the context of the IMMEnSE (International Multiple Myeloma rESEarch) consortium. In this population two SNPs showed an association with $p < 0.05$: rs286595 (located in gene MRLP22) and rs14191881 (located in gene TCF19). Results from IMMEnSE were meta-analyzed with data from a previously published genome-wide association study (GWAS). The SNPs rs13409 (located in the 3'UTR of the POU5F1 gene), rs1419881 (TCF19), rs1049633, rs1049623 (both in DDR1) showed significant associations with MM risk. In conclusion, we sought to identify genetic polymorphisms associated with MM risk starting from genome-wide prediction of miRSNPs. For some mirSNPs, we have shown promising associations with MM risk.

Loic Verlingue, Aurélien Dugourd, Gautier Stoll, Emmanuel Barillot, Laurence Calzone, Arturo Londoño-Vallejo (2016 Sep 11)

A comprehensive approach to the molecular determinants of lifespan using a Boolean model of geroconversion.

Aging cell : DOI : 10.1111/acel.12504

Résumé

Altered molecular responses to insulin and growth factors (GF) are responsible for late-life shortening diseases such as type-2 diabetes mellitus (T2DM) and cancers. We have built a network of the signaling pathways that control S-phase entry and a specific type of senescence called geroconversion. We have translated this network into a Boolean model to study possible cell phenotype outcomes under diverse molecular signaling conditions. In the context of insulin resistance, the model was able to reproduce the variations of the senescence level observed in tissues related to T2DM's main morbidity and mortality. Furthermore, by calibrating the pharmacodynamics of mTOR inhibitors, we have been able to reproduce the dose-dependent effect of rapamycin on liver degeneration and lifespan

expansion in wild-type and HER2-neu mice. Using the model, we have finally performed an in silico prospective screen of the risk-benefit ratio of rapamycin dosage for healthy lifespan expansion strategies. We present here a comprehensive prognostic and predictive systems biology tool for human aging.

Yan Ren, Juan Jesus Lence-Anta, Celia Pereda, Mae Chappa, Milagro Velasco, Idalmis Infante, Marlene Bustillo, Sylvia Turcios, Axelle Leufroy, Thierry Guérin, Laurent Noël, Fabienne Lesueur, Stéphane Maillard, Ernora Clero, Constance Xhaard, Rodrigue S Allodji, Carole Rubino, Regla Rodriguez, Rosa Ortiz, Florent de Vathaire (2016 Sep 10)

Foxe1 Polymorphism Interacts with Dietary Iodine Intake in Differentiated Thyroid Cancer Risk in the Cuban Population.

Thyroid : official journal of the American Thyroid Association

Résumé

The incidence of differentiated thyroid cancer (DTC) is low in Cuba and the contribution of dietary factors to DTC in this population has not been investigated so far. Our aim was to evaluate the relationship between dietary iodine intake and DTC with regard to the interaction with environmental factors or some common single nucleotide polymorphisms (SNPs), based on a case-control study carried out in Cuba.

Wael Jdey, Sylvain Thierry, Christophe Russo, Flavien Devun, Muthana Al Abo, Patricia Noguiez-Hellin, Jian-Sheng Sun, Emmanuel Barillot, Andrei Zinovyev, Inna Kuperstein, Yves Pommier, Marie Dutreix (2016 Aug 26)

Drug Driven Synthetic Lethality: bypassing tumor cell genetics with a combination of Dbait and PARP inhibitors.

Clinical cancer research : an official journal of the American Association for Cancer Research : DOI : clincanres.1193.2016

Résumé

Cancer treatments using tumor defects in DNA repair pathways have shown promising results but are restricted to small subpopulations of patients. The most advanced drugs in this field are Poly(ADP-Ribose) Polymerase (PARP) inhibitors (PARPi), which trigger synthetic lethality in tumors with Homologous Recombination (HR) deficiency. Using AsiDNA, an inhibitor of HR and Non Homologous End Joining, together with PARPi should allow bypassing the genetic restriction for PARPi efficacy.

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Fine-Scale Mapping at 9p22.2 Identifies Candidate Causal Variants That Modify Ovarian Cancer Risk in BRCA1 and BRCA2 Mutation Carriers.

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Résumé

Population-based genome wide association studies have identified a locus at 9p22.2 associated with ovarian cancer risk, which also modifies ovarian cancer risk in BRCA1 and BRCA2 mutation carriers. We conducted fine-scale mapping at 9p22.2 to identify potential causal variants in BRCA1 and BRCA2 mutation carriers. Genotype data were available for 15,252 (2,462 ovarian cancer cases) BRCA1 and 8,211 (631 ovarian cancer cases) BRCA2 mutation carriers. Following genotype imputation, ovarian cancer associations were assessed for 4,873 and 5,020 SNPs in BRCA1 and BRCA 2 mutation carriers respectively, within a retrospective cohort analytical framework. In BRCA1 mutation carriers one set of eight correlated candidate causal variants for ovarian cancer risk modification was identified (top SNP rs10124837, HR: 0.73, 95%CI: 0.68 to 0.79, p-value 2× 10-16). These variants were located up to 20 kb upstream of BNC2. In BRCA2 mutation carriers one region, up to 45 kb

upstream of BNC2, and containing 100 correlated SNPs was identified as candidate causal (top SNP rs62543585, HR: 0.69, 95%CI: 0.59 to 0.80, p-value 1.0 × 10-6). The candidate causal in BRCA1 mutation carriers did not include the strongest associated variant at this locus in the general population. In sum, we identified a set of candidate causal variants in a region that encompasses the BNC2 transcription start site. The ovarian cancer association at 9p22.2 may be mediated by different variants in BRCA1 mutation carriers and in the general population. Thus, potentially different mechanisms may underlie ovarian cancer risk for mutation carriers and the general population.