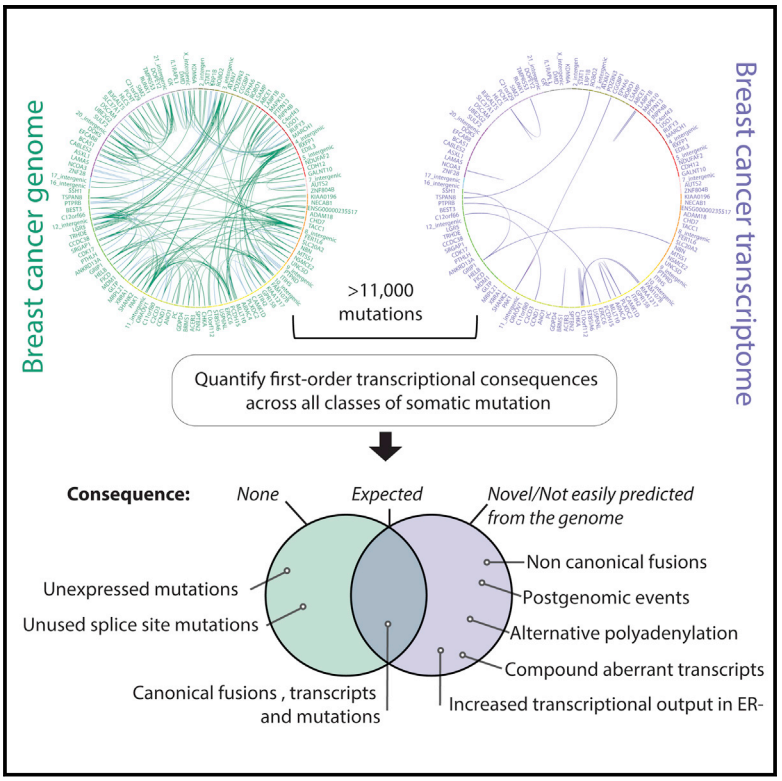
Resource

Cell Reports

Direct Transcriptional Consequences of Somatic Mutation in Breast Cancer

Graphical Abstract



Highlights

- Greater transcriptional activity in cancer than stromal cells, particularly when ER-ve
- Intron mutations only infrequently affect splicing, even at essential splice sites
- Distinctive RNA effects of sense-to-antisense and gene-to-intergenic rearrangements
- Exhaustive pipeline for identifying aberrant transcripts from RNA-sequencing data

Authors

Adam Shlien, Keiran Raine, Fabio Fuligni, ..., Kornelia Polyak, Michael R. Stratton, Peter J. Campbell

Correspondence

adam.shlien@sickkids.ca (A.S.), pc8@sanger.ac.uk (P.J.C.)

In Brief

Shlien et al. quantify first-order transcriptional consequences across all classes of somatic mutation in well-annotated breast cancers. They find that cancer cells are more transcriptionally active than stromal cells, especially in ER-negative cancers. Rearrangements that break genes or place them in opposite orientation are an unexpectedly potent source of fusions.

Shlien et al., 2016, Cell Reports *16*, 2032–2046
August 16, 2016 © 2016 The Authors.
http://dx.doi.org/10.1016/j.celrep.2016.07.028

CellPress

OPEN ACCESS
CellPress

Cell Reports
Resource

Direct Transcriptional Consequences of Somatic Mutation in Breast Cancer

Adam Shlien,[1,16,*] Keiran Raine,[1] Fabio Fuligni,[15] Roland Arnold,[15] Serena Nik-Zainal,[1] Serge Dronov,[1,17] Lira Mamanova,[1] Andrej Rosic,[15] Young Seok Ju,[1] Susanna L. Cooke,[1] Manasa Ramakrishna,[1] Elli Papaemmanuil,[1] Helen R. Davies,[1] Patrick S. Tarpey,[1] Peter Van Loo,[1,2] David C. Wedge,[1] David R. Jones,[1] Sancha Martin,[1] John Marshall,[1] Elizabeth Anderson,[1] Claire Hardy,[1] ICGC Breast Cancer Working Group, Oslo Breast Cancer Research Consortium, Violetta Barbashina,[3] Samuel A.J.R. Aparicio,[4] Torill Sauer,[5] Øystein Garred,[5] Anne Vincent-Salomon,[6] Odette Mariani,[6] Sandrine Boyault,[7] Aquila Fatima,[8] Anita Langerød,[9,10] Åke Borg,[11] Gilles Thomas,[7,17] Andrea L. Richardson,[8] Anne-Lise Børresen-Dale,[9,10] Kornelia Polyak,[12] Michael R. Stratton,[1] and Peter J. Campbell[1,13,14,*]

[1]Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton, Cambridgeshire CB10 1SA, UK
[2]Department of Human Genetics, University of Leuven, 3000 Leuven, Belgium
[3]Breakthrough Breast Cancer, The Institute of Cancer Research, London SM2 5NG, UK
[4]British Columbia Cancer Agency, Vancouver, BC V5Z 1L3, Canada
[5]Department of Pathology, Oslo University Hospital, 0450 Oslo, Norway
[6]Institut Curie, 75005 Paris, France
[7]Synergie Lyon Cancer, Centre Léon Bérard, 69008 Lyon, France
[8]Dana-Farber Cancer Institute, Boston, MA 02215, USA
[9]Department of Genetics, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, 0379 Oslo, Norway
[10]K.G. Jebsen Center for Breast Cancer Research, Institute for Clinical Medicine, Faculty of Medicine, University of Oslo, 0316 Oslo, Norway
[11]Department of Oncology, Lund University, SE-221 00 Lund, Sweden
[12]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
[13]Department of Haematology, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
[14]Department of Haematology, University of Cambridge, Cambridge CB2 1TN, UK
[15]Department of Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada
[16]Present address: Department of Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada
[17]Deceased
*Correspondence: adam.shlien@sickkids.ca (A.S.), pc8@sanger.ac.uk (P.J.C.)
http://dx.doi.org/10.1016/j.celrep.2016.07.028

SUMMARY

Disordered transcriptomes of cancer encompass direct effects of somatic mutation on transcription, coordinated secondary pathway alterations, and increased transcriptional noise. To catalog the rules governing how somatic mutation exerts direct transcriptional effects, we developed an exhaustive pipeline for analyzing RNA sequencing data, which we integrated with whole genomes from 23 breast cancers. Using X-inactivation analyses, we found that cancer cells are more transcriptionally active than intermixed stromal cells. This is especially true in estrogen receptor (ER)-negative tumors. Overall, 59% of substitutions were expressed. Nonsense mutations showed lower expression levels than expected, with patterns characteristic of nonsense-mediated decay. 14% of 4,234 rearrangements caused transcriptional abnormalities, including exon skips, exon reusage, fusions, and premature polyadenylation. We found productive, stable transcription from sense-to-antisense gene fusions and gene-to-intergenic rearrangements, suggesting that these mutation classes drive more transcriptional disruption than previously suspected. Systematic integration of transcriptome with genome data reveals the rules by which transcriptional machinery interprets somatic mutation.

INTRODUCTION

Somatic mutation underpins the development of cancer, and most solid tumors have thousands to tens of thousands of point mutations, coupled with tens to hundreds of genomic rearrangements and copy-number changes (Garraway and Lander, 2013; Stratton et al., 2009). Small numbers of these, known as driver mutations, dysregulate the fundamental cellular processes involved in normal tissue homeostasis, and they confer a selective advantage to the clone. A critical point is that Darwinian selection acts on *phenotype*, and so, for a somatic mutation to drive cancer, it must manifest a phenotypic effect. Transcription is the primary conduit by which changes in the genomic code are translated into cellular phenotype, with the corollary that it is a necessary criterion of driver mutations that they directly induce a change in transcript structure. Altered transcript structure can take many forms, including the creation of fusion genes by genomic rearrangement, interference with RNA splicing at mutated splice sites, alteration of the codon sequence for missense substitutions, and over- or under-expression of genes through copy-number alterations or mutation in regulatory regions.

This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Download English Version:

https://daneshyari.com/en/article/2039918

Download Persian Version:

https://daneshyari.com/article/2039918

Daneshyari.com