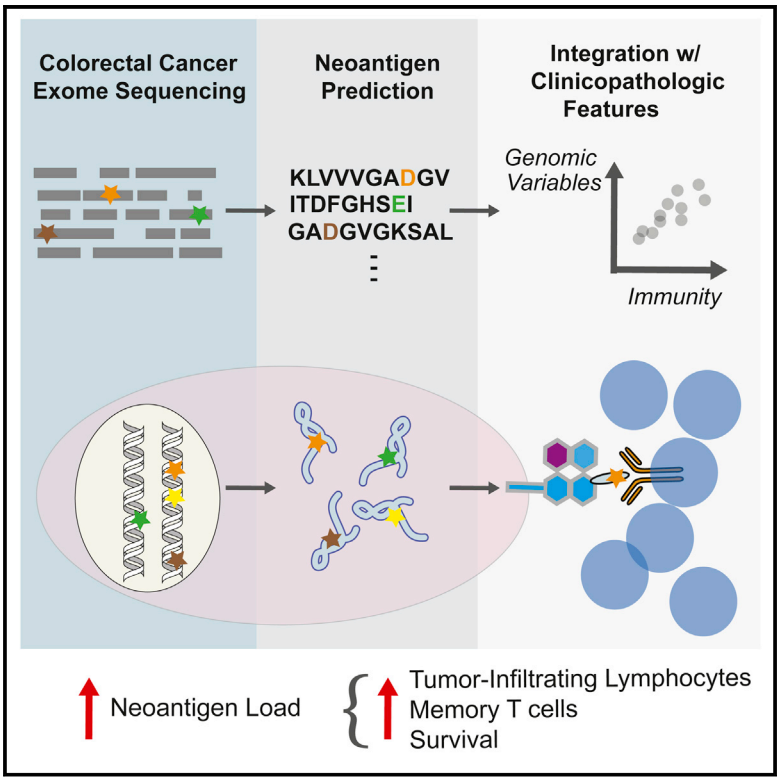
Article

Cell Reports

Genomic Correlates of Immune-Cell Infiltrates in Colorectal Carcinoma

Graphical Abstract



Authors

Marios Giannakis, Xinmeng Jasmine Mu, Sachet A. Shukla, ..., Charles S. Fuchs, Shuji Ogino, Levi A. Garraway

Correspondence

shuji_ogino@dfci.harvard.edu (S.O.), levi_garraway@dfci.harvard.edu (L.A.G.)

In Brief

Through whole-exome sequencing of annotated colorectal tumors, Giannakis et al. identify additional colorectal cancer driver genes and correlate high neoantigen load with increased lymphocytic infiltration and improved survival. They also find positive selection for HLA mutations in immune-cell-infiltrated tumors. These results may inform immunotherapeutic approaches in colorectal cancer.

Highlights

- Whole-exome sequencing of 619 colorectal cancers with clinicopathologic annotations
- Discovery of significantly mutated genes in colorectal cancer
- Neoantigen load correlation with infiltrating lymphocytes and memory T cells
- Positive selection for HLA mutations in immune-cell-infiltrated tumors

Giannakis et al., 2016, Cell Reports *15*, 857–865
April 26, 2016
http://dx.doi.org/10.1016/j.celrep.2016.03.075

CellPress

Cell Reports
Article

Genomic Correlates of Immune-Cell Infiltrates in Colorectal Carcinoma

Marios Giannakis,[1,2,3,16] Xinmeng Jasmine Mu,[1,2,3,16] Sachet A. Shukla,[1,3,16] Zhi Rong Qian,[1] Ofir Cohen,[1,3] Reiko Nishihara,[1,4,5,6] Samira Bahl,[3] Yin Cao,[5,7,8] Ali Amin-Mansour,[1,3] Mai Yamauchi,[1] Yasutaka Sukawa,[9] Chip Stewart,[3] Mara Rosenberg,[3] Kosuke Mima,[1] Kentaro Inamura,[1] Katsuhiko Nosho,[10] Jonathan A. Nowak,[11] Michael S. Lawrence,[3] Edward L. Giovannucci,[4,5,12] Andrew T. Chan,[7,8,12] Kimmie Ng,[1,2] Jeffrey A. Meyerhardt,[1,2] Eliezer M. Van Allen,[1,2,3] Gad Getz,[3,13] Stacey B. Gabriel,[3] Eric S. Lander,[3,14,15] Catherine J. Wu,[1,2,3,17] Charles S. Fuchs,[1,2,12,17] Shuji Ogino,[1,4,11,17,*] and Levi A. Garraway[1,2,3,17,*]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02215, USA
[2]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[3]Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA
[4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA
[5]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA
[6]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA
[7]Division of Gastroenterology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
[8]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
[9]Department of Gastroenterology and Hepatology, Division of Internal Medicine, School of Medicine, Keio University, Tokyo 108-8345, Japan
[10]Department of Gastroenterology, Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo 060-8543, Japan
[11]Division of MPE Molecular Pathological Epidemiology, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[12]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[13]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA 02114, USA
[14]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[15]Department of Systems Biology, Harvard Medical School, Boston, MA 02115, USA
[16]Co-first author
[17]Co-senior author
*Correspondence: shuji_ogino@dfci.harvard.edu (S.O.), levi_garraway@dfci.harvard.edu (L.A.G.)
http://dx.doi.org/10.1016/j.celrep.2016.03.075

SUMMARY

Large-scale genomic characterization of tumors from prospective cohort studies may yield new insights into cancer pathogenesis. We performed whole-exome sequencing of 619 incident colorectal cancers (CRCs) and integrated the results with tumor immunity, pathology, and survival data. We identified recurrently mutated genes in CRC, such as *BCL9L*, *RBM10*, *CTCF*, and *KLF5*, that were not previously appreciated in this disease. Furthermore, we investigated the genomic correlates of immune-cell infiltration and found that higher neoantigen load was positively associated with overall lymphocytic infiltration, tumor-infiltrating lymphocytes (TILs), memory T cells, and CRC-specific survival. The association with TILs was evident even within microsatellite-stable tumors. We also found positive selection of mutations in HLA genes and other components of the antigen-processing machinery in TIL-rich tumors. These results may inform immunotherapeutic approaches in CRC. More generally, this study demonstrates a framework for future integrative molecular epidemiology research in colorectal and other malignancies.

INTRODUCTION

Large-scale cancer sequencing efforts have advanced our understanding of the genomic landscape of many malignancies (Garraway and Lander, 2013). However, a common drawback of comprehensive genomic studies has been the lack of detailed demographic, epidemiologic, and clinical annotations for cancer cases (Cancer Genome Atlas Network, 2012). Together with tumor molecular profiling, such annotations can be used to discover potentially actionable tumor biomarkers, which may change medical practice through lifestyle or pharmacologic intervention (Liao et al., 2012). Another limitation of many tumor sequencing studies has been their limited statistical power to identify significantly mutated genes that have an intermediate or lower frequency of mutation (e.g., <5% frequency). This "long tail" of cancer driver genes can be explored by increasing the number of samples that are sequenced in each tumor type (Lawrence et al., 2014).

Over the past several decades, cancer epidemiologists have invested considerable effort in developing large and exquisitely annotated cohort studies. Two prominent examples include