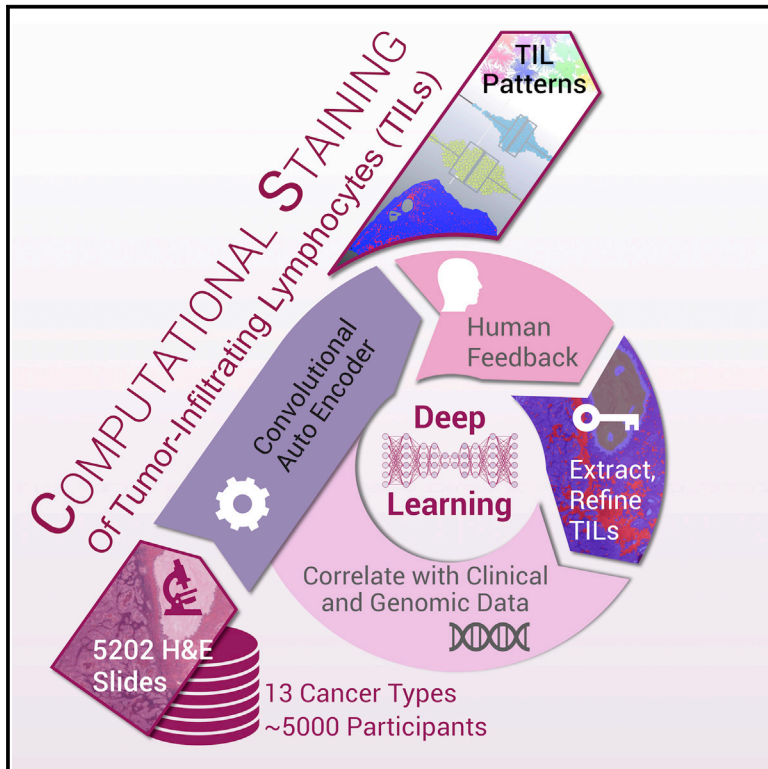


Cell Reports

Spatial Organization and Molecular Correlation of Tumor-Infiltrating Lymphocytes Using Deep Learning on Pathology Images

Graphical Abstract



Authors

Joel Saltz, Rajarsi Gupta, Le Hou, ..., Alexander J. Lazar, Ashish Sharma, Vésteinn Thorsson

Correspondence

joel.saltz@stonybrookmedicine.edu (J.S.),
vesteinn.thorsson@systemsbiology.org (V.T.)

In Brief

Tumor-infiltrating lymphocytes (TILs) were identified from standard pathology cancer images by a deep-learning-derived “computational stain” developed by Saltz et al. They processed 5,202 digital images from 13 cancer types. Resulting TIL maps were correlated with TCGA molecular data, relating TIL content to survival, tumor subtypes, and immune profiles.

Highlights

- Deep learning based computational stain for staining tumor-infiltrating lymphocytes (TILs)
- TIL patterns generated from 4,759 TCGA subjects (5,202 H&E slides), 13 cancer types
- Computationally stained TILs correlate with pathologist eye and molecular estimates
- TIL patterns linked to tumor and immune molecular features, cancer type, and outcome



Spatial Organization and Molecular Correlation of Tumor-Infiltrating Lymphocytes Using Deep Learning on Pathology Images

Joel Saltz,^{1,*} Rajarsi Gupta,^{1,4} Le Hou,² Tahsin Kurc,¹ Pankaj Singh,³ Vu Nguyen,² Dimitris Samaras,² Kenneth R. Shroyer,⁴ Tianhao Zhao,⁴ Rebecca Batiste,⁴ John Van Arnam,⁵ The Cancer Genome Atlas Research Network, Ilya Shmulevich,⁶ Arvind U.K. Rao,^{3,7} Alexander J. Lazar,⁸ Ashish Sharma,⁹ and Vésteinn Thorsson^{6,10,*}

¹Department of Biomedical Informatics, Stony Brook Medicine, Stony Brook, NY 11794, USA

²Department of Computer Science, Stony Brook University, Stony Brook, NY 11794, USA

³Department of Bioinformatics and Computational Biology, University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

⁴Department of Pathology, Stony Brook Medicine, Stony Brook, NY 11794, USA

⁵Department of Pathology and Laboratory Medicine, Perelman School at the University of Pennsylvania, Philadelphia, PA 19104, USA

⁶Institute for Systems Biology, Seattle, WA 98109, USA

⁷Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

⁸Departments of Pathology, Genomic Medicine, and Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

⁹Department of Biomedical Informatics, Emory University, Atlanta, GA 30322, USA

¹⁰Lead Contact

*Correspondence: joel.saltz@stonybrookmedicine.edu (J.S.), vesteinn.thorsson@systemsbiology.org (V.T.)

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SUMMARY

Beyond sample curation and basic pathologic characterization, the digitized H&E-stained images of TCGA samples remain underutilized. To highlight this resource, we present mappings of tumor-infiltrating lymphocytes (TILs) based on H&E images from 13 TCGA tumor types. These TIL maps are derived through computational staining using a convolutional neural network trained to classify patches of images. Affinity propagation revealed local spatial structure in TIL patterns and correlation with overall survival. TIL map structural patterns were grouped using standard histopathological parameters. These patterns are enriched in particular T cell subpopulations derived from molecular measures. TIL densities and spatial structure were differentially enriched among tumor types, immune subtypes, and tumor molecular subtypes, implying that spatial infiltrate state could reflect particular tumor cell aberration states. Obtaining spatial lymphocytic patterns linked to the rich genomic characterization of TCGA samples demonstrates one use for the TCGA image archives with insights into the tumor-immune microenvironment.

INTRODUCTION

Although studies in humans have shown that chronic inflammation can promote tumorigenesis (Trinchieri, 2012), the host immune system is equally capable of controlling tumor growth

through the activation of adaptive and innate immune mechanisms (Galon et al., 2013). Such intra-tumoral processes are often referred to collectively as immunoediting, where this selective pressure can result in the emergence of tumor cells that escape immune surveillance and, ultimately, to tumor progression. At the same time, many observations suggest that high densities of tumor-infiltrating lymphocytes (TILs) correlate with favorable clinical outcomes (Mlecnik et al., 2011a) such as longer disease-free survival or improved overall survival (OS) in multiple cancer types (Angell and Galon, 2013). Recent studies further suggest that the importance of *spatial* context and the nature of cellular heterogeneity of the tumor microenvironment, in terms of the immune infiltrate involving the tumor center and/or invasive margin, can also correlate with cancer prognosis (Fridman et al., 2012). Prognostic factors, most notably the *Immunoscore*, that quantify such spatial TIL densities in different tumor regions have high prognostic value that can significantly supplement and sometimes even supersede the standard TNM classification and staging in certain settings (Galon et al., 2006; Broussard and Disis, 2011; Mlecnik et al., 2011b). Given this and the central role of immunotherapy treatments in contemporary cancer care, these assessments of tumor-associated lymphocytes are increasingly important both in the clinical assessment of pathology slides, as well as in translational research into the role of these lymphocytic populations.

Tissue diagnostic studies are carried out and interpreted by pathologists for virtually all cancer patients, and the overwhelming majority of these are stained with hematoxylin and eosin (H&E). The TCGA Pan Cancer Atlas dataset includes representative H&E diagnostic whole-slide images (WSIs) that enable spatial quantification and analysis of TILs and association with the wealth of molecular characterization conducted through the TCGA. Previously, this rich trove of imaging data has primarily been used solely to qualify samples for TCGA analysis and



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