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Preview

Preview of "Interpretable systems biomarkers predict response to immune-checkpoint inhibitors"

Justin Guinney[1,2,*]
[1]Tempus Labs, Chicago, IL, USA
[2]University of Washington, Seattle, WA, USA
*Correspondence: jguinney@gmail.com
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Lapuente-Santana et al. (2021) developed Estimate Systems Immune Response (EaSIeR), a method for assessing the immune response to cancer using systems biology traits.

Immune checkpoint blockade (ICB) has become an important pillar in the treatment of cancer. While some patients achieve robust and durable tumor regression, the unfortunate reality is that most patients do not receive long-term clinical benefit.[1] Research on antitumor immunity has revealed multiple tumor cell intrinsic and extrinsic factors contributing to ICB response,[2] although robust mechanistic models are still lacking.[3] Tumor intrinsic factors such as tumor mutation burden (TMB), neo-antigen presentation, and deficient mismatch repair (dMMR)—hallmarks of tumor immunogenicity—are approved today for use as clinical biomarkers in most indications. Extrinsic factors—found principally within the tumor microenvironment (TME)—are increasingly recognized as critical to the immune response. A complex milieu of immune cells and non-immune stromal cells such as endothelial cells and fibroblasts, the TME can exert both activating and inhibitory influences on the adaptive and innate immune response to cancer.[4] Deepening our understanding of the cellular components of the TME and their complex interplay will be critical in developing better biomarkers of response and expanding the pool of patients who might benefit from ICB therapy.

While single-cell RNA sequencing has become an important tool in decoding the TME, technical and cost considerations continue to limit its use. Consequently, bulk transcriptomic data remain an important, unbiased resource for modeling the immune response to cancer. Recent studies have successfully used bulk RNA sequencing data from The Cancer Genome Atlas (TCGA) and other sources to identify recurrent gene expression patterns within the human immunome, leading to the development of several cancer immune subtypes.[5–7] These subtypes represent global structures of the immunome and are an amalgamation of many pathways and immune responses that may be private to a subtype or shared across them. In contrast to this global subtyping approach, other studies have focused on the development of gene signatures that reflect more targeted behaviors of the immune response, such as cytolic activity,[8] T cell dysfunction and exclusion,[9] and cytokine inflammation and immune suppression.[10] While these global and targeted approaches capture important properties of the immune response, they fall short of providing a mechanistic and fine-grained understanding of the immune response to cancer.

To address this shortcoming, Lapuente-Santana et al., developed Estimate Systems Immune Response (EaSIeR), an algorithm designed to identify systems biology traits underlying the immune response to cancer. Structured as a supervised machine learning problem, EaSIeR uses as its inputs (predictors) five systems-biology-based *views* derived from prior knowledge: (1) immune-cell fractions within the TME, (2) signatures of intracellular pathway signaling, (3) transcription-factor (TF) target gene activity, (4) inter-cellular ligand receptor pair activity, and (5) inter-cellular cell-cell pair activity. The learning outputs are 14 gene signatures that encompass a variety of immune response phenotypes (e.g., see targeted gene signatures as described above). However, instead of training 14 individual models—one for each immune signature—EaSIeR employs multi-task learning (MTL), a machine learning approach that conjointly learns multiple predictive models (tasks). MTL has been shown to work well when the training outputs are themselves noisy and when the tasks share a common objective function.[11]

By framing the problem as a predictive modeling problem, Lapuente-Santana et al. *learn* a set of systems biology traits that optimally predict the immune response. The coefficients of the trained models quantitatively describe the contribution of each view's traits to the model, while the different models' predictive performances reveal which views—and combination of views—are most informative. Lapuente-Santana et al. applied EaSIeR to 18 solid tumor types from TCGA, producing a large, tumor-specific compendium of systems biology traits. Interestingly, Lapuente-Santana et al. showed that while the immune cell type composition is the most informative view, combining each of the views into a single ensemble model results in the highest predictive performance, suggesting that systems biology views provide complementary information and capture different properties of the immune response.

Lapuente-Santana et al. next tested whether their model can predict patient response to ICB therapy. First applying EaSIeR to two melanoma cohorts, they showed that combining systems-based views is better than the immune response tasks themselves at predicting therapeutic response. Considering that the models themselves were trained with the immune response phenotypes, this result is counter-intuitive, and Lapuente-Santana et al. provide no rationale for this

unexpected finding, although this likely suggests that systems-based traits may be more stable—and consequently more generalizable—across independent cohorts. Finally, Lapuente-Santana et al. hypothesized that TMB—as a proxy for tumor immunogenicity—is distinct from the immune response. Despite the strong dependency between immunogenicity and immune response, Lapuente-Santana et al. showed that TMB combined with EaSIeR results in better ICB response classification performance than either TMB or EaSIeR alone. This finding supports their hypothesis that EaSIeR captures components of the immune response that are independent of tumor immunogenicity.

Lapuente-Santana et al. are not the first to explore how systems-based traits correlate with immune phenotypes. For example, Thorrson et al., identified six *de novo* immune subtypes using TCGA expression data and characterized their association with cell type fractions, genomic alterations, transcriptional regulatory networks, and extracellular communication networks.[6] However, their gold standard for differences of immune response are their derived subtypes. In contrast, Lapuente-Santana et al. leveraged multiple axes of the immune response by integrating 14 functional immune signatures. Moreover, by using a multi-variable predictive modeling framework, EaSIeR aggregated multiple systems views within a single model, providing a quantitative measure of the views' contribution to the immune response.

The history of drug therapeutics is one where the clinical adoption of a drug often precedes a comprehensive understanding of its *in vivo* mechanisms; immunotherapy is no exception. In the quest to identify better biomarkers of response, develop rationale strategies for drug combinations, and overcome innate or acquired resistance to immunotherapy, sophisticated tools for modeling intra- and intercellular and mechanistic behaviors are urgently needed. Systems biology based approaches are well-suited to this task, and the EaSIeR algorithm described by Lapuente-Santana et al. is a promising step in this direction.

DECLARATION OF INTERESTS

Dr. Guinney is an employee at Tempus Labs.

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