quantitative tools are desperately needed to refine and uncover novel biologically and clinically meaningful insights from the spatial distribution of cells of the tumor immune microenvironment.

Methods We compiled over 60 prostate cancer and melanoma FFPE tumor sections and performed Opal multiplex immunohistochemistry for a diversity of T-cell and other immune markers, including CD3, CD4, CD8, FOXP3 and PDL1, as well as a prostate cancer (AMACR) or melanoma (SOX10) marker and DAPI. Following spectral imaging on the Vectra Polaris, we performed cell and tissue segmentation and phenotyping with the inForm or HALO image analysis software. The detected X, Y coordinates of cells and marker intensities were used for subsequent method development.

Results We developed SPIAT (Spatial Image Analysis of Tissues)[1], an R package with a suite of data processing, quality control, visualization, data handling and data analysis tools for spatial data. SPIAT includes our novel algorithms for the identification of cell clusters, tumor margins and cell gradients, the calculation of neighborhood proportions and algorithms for the prediction of cell phenotypes. By interfacing with packages used in ecology, geographic data analysis and spatial statistics, we have begun to robustly address fundamental questions in the analysis of cell spatial data, such as metrics to measure mixing between cell types, the identification of tumor borders and statistical approaches to compare samples.

Conclusions SPIAT is compatible with multiplex immunohistochemistry, spatial transcriptomics and data generated from other spatial platforms, and continues to be actively developed. We expect SPIAT to become a user-friendly and speedy go-to package for the spatial analysis of cells in tissues, as well as promote the use of quantitative metrics in the spatial analysis of the tumor immune microenvironment.

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669 COMPUTATIONAL ANALYSIS OF MUTUAL FEEDBACK REGULATIONS BETWEEN IDO1 AND PD-L1

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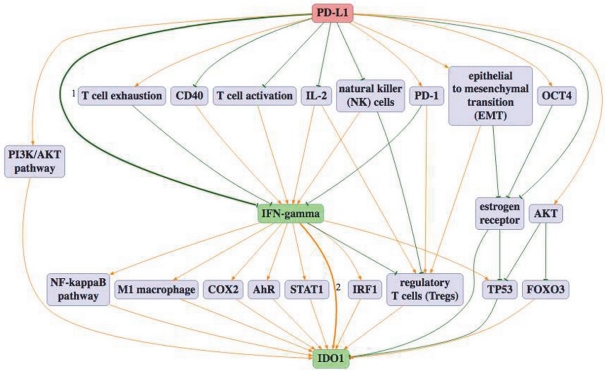
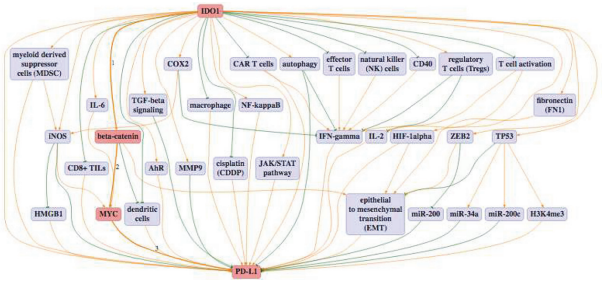
Background PD-L1 is a validated biomarker for anti-PD-1/PD-L1 therapies and its expression can be regulated by IDO1, and vice verse IDO1 can regulate PD-L1 expression indirectly through various signaling pathways. Concurrent inhibition of IDO1 and PD-1/PD-L1 may have enhanced anti-tumor effects.

Methods In this study, computational models were established to identify factors involved in interactions between these two therapeutic targets. Abstracts published on IDO1, PD-1, PD-L1, anti-PD1/PD-L1 were downloaded from PubMed, and analyzed by natural language processing and text mining. The information on interactions among gene, compound/therapy, cell/animal model, pathway and disease was extracted. Two gene networks, IDO1->PD-L1 and PD-L1->IDO1, were constructed (figures 1 and 2, respectively).



Abstract 669 Figure 1 The PD-L1/IDO1 network
Organ curve with an arrow indicates a positive interaction between nodes. Green curve with a bar indicates a negative interaction between nodes



Abstract 669 Figure 2 The IDO1/PD-L1 network
Organ curve with an arrow indicates a positive interaction between nodes. Green curve with a bar indicates a negative interaction between nodes

Results The PD-L1/IDO1 network is primarily mediated through IFN-gamma and Tregs. PD-L1 inhibits IFN-gamma production through down-regulation of NK cells, IL-2 and CD40 and activation of PD-1. In turn, diminished production of IFN-gamma inactivates AhR, IRF1, STAT1, COX2, NF-kappaB and M1 macrophages, leading to down-regulation of IDO1. On the other hand, PD-L1 could induce IDO1 expression through up-regulation of Tregs and PI3K/AKT pathway (figure 1). The key factors involved in the IDO1/PD-L1 network comprise MYC, EMT and IFN-gamma. MYC and EMT contribute to the positive feedback from IDO1 to PD-L1. IDO1 up-regulates IL-6, iNOS and beta-catenin, leading to activation of MYC and subsequent induction of PD-L1. IDO1 could also up-regulate PD-L1 through activation of MDSC, AhR, JAK/STAT, HIF1-alpha and NF-kappaB. However, IDO1 down-regulates IFN-gamma, which is a leading factor inducing PD-L1 expression (figure 2).

Conclusions As the network analyses revealed, IDO1 and PD-L1 are involved in complex mutual feedback regulations. Inhibition of IDO1 could either up- or down-regulate PD-L1, and enhance or reduce efficacy of anti-PD-1/PD-L1. The factors involved in the mutual feedback regulations could serve as biomarkers to determine and monitor the efficacy of combining IDO1 and PD-1/PD-L1 inhibitors, as well as additional therapeutic targets. The literature-based modeling approach facilitates the development of combination strategies especially when the experimental evident is lacking.

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