IMMUNO-ONCOLOGY BIOMARKER DISCOVERY AND VALIDATION

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Immune-evading pathways are currently being clinically targeted, but the therapies are not effective in all patients and all cancer types. Therefore, more efficient approaches are needed to predict responsiveness and also to discover and characterize novel targets as alternative or combination treatments. In this study, we used GENEVESTIGATOR® for biomarker validation and characterization of a gene signature predictive of reponse to immunotherapy.
GENEVESTIGATOR® is an analysis tool and database, containing high quality curated gene expression data. It allows the user to mine the data of thousands of experiments simultaneously, to identify genes having a very specific profile or indications associated with the transcriptional activity of selected genes.

SUMMARY

Suppressive immune checkpoint pathways are hijacked by tumors in order to evade the immune system. Cancer immunotehrapies targeting these pathways have established new standards of treatment in multiple tumor types. However, only a subset of patients exhibits durable responses to immunotherapy. New biomarkers are urgently needed in order to improve the selection of patients who will best respond to therapy, further elucidate drug mechanisms of action, and help tailor therapy regimens. This study shows how GENEVESTIGATOR® can be used for a rapid and efficient validation of biomarkers and characterization of gene signatures.

RESULTS AND DISCUSSION

Biomarker validation: compendium-wide 2-gene plot

Regulatory T (Treg) cells are implicated in tumour growth and metastasis and in the mechanism of action of checkpoint-blocking immunotherapy. A deep characterization of their transcriptional profile is crucial for identification of novel potential therapeutic targets. In *Figure 1*, the expression of CCR8 and MAGEH1, previously reported as markers of intra-tumoral Treg cells (*De Simone et al., Plitas et al., 2016*), is compared between various CD4 T-cell subsets compendium-wide. Their combined strength in destingusihing tumor derived T-reg cells from all other CD4-positve T-cell subsets, including Treg cells isolated from normal tissues and tumor-derived Th1 and Th1 cells, could be confidently confirmed.

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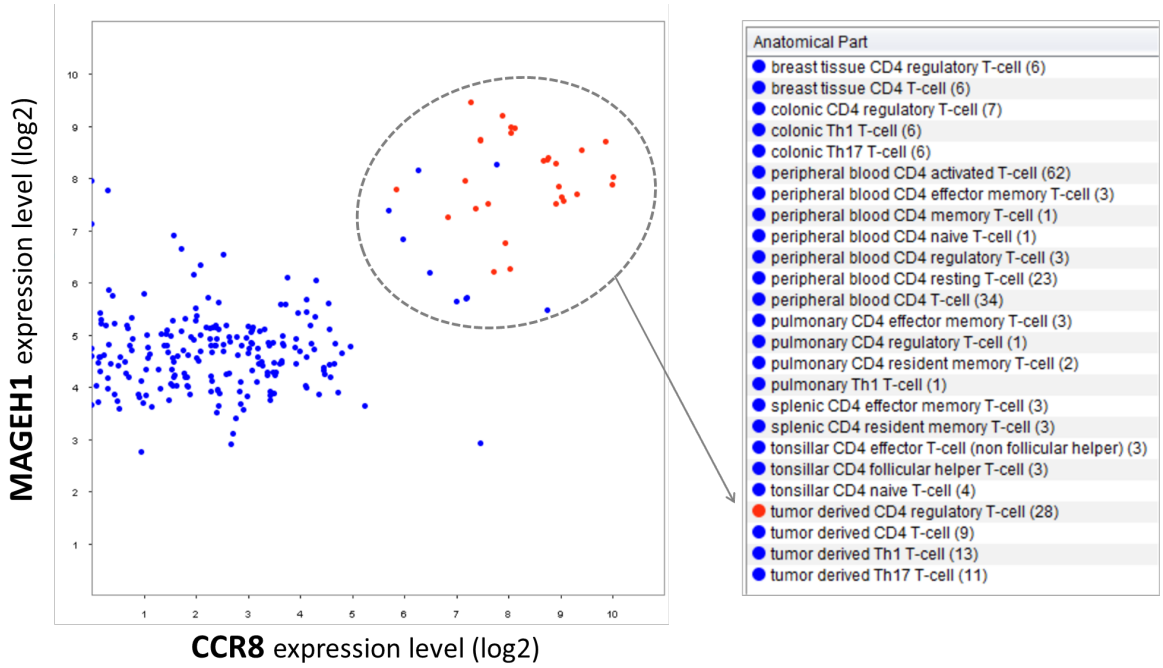

Figure 1: Compendium-wide expression of MAGEH1 and CCR8 across CD4-positive T-cell populations. The 2-Gene Plot tool in GENEVESTIGATOR® was used to plot the expression, measured by RNA-seq, of human genes CCR8 and MAGEH1, highlighting the differences between intra-tumoral Treg cells and other CD4 T-cell subtypes. Marked in red: Tregs isolated from primary tumor tissues of breast cancer, colorectal carcinoma and non-small cell lung cancer patients. Marked in blue: other CD4 T-cell subsets including, among others, Tregs from normal tissues, peripheral Tregs and tumor-derived Th1 and Th17 cells.

Gene signature predictive of response to immunotherapy

We investigated the gene signature of responders versus non-responders to anti-PD-1 therapy in melanoma samples at baseline. Using the GENEVESTIGATOR® Signature tool, we identified conditions showing a similar gene regulation pattern. The identified conditions are mostly inflammatory autoimmune diseases such as ulcerative colitis (UC), Crohn's disease and rheumatoid arthritis (RA) vs. control tissue. This suggests a pre-existing immune-recognition of the tumor in responders.

Figure 2: Baseline gene signature of responders vs. non-responders to Nivolumab and conditions showing a similar regulation pattern. A gene signature of responders vs. non-responders to immune checkpoint blockade treatment in melanoma samples at baseline was identified using data published by Riaz et al. (2017). The Signature tool in GENEVESTIGATOR® was used to identify conditions causing a similar gene regulation pattern, using human RNA-seq data. An extract of the resulting image showing the most similar conditions is presented here. Red: up-regulated gens. Green: down-regulated genes.

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Smart integrated systems with high quality curated data empower scientists to perform compendium-wide searches and analyses, advancing their research and accelerating novel scientific discoveries. The described case studies show how GENEVESTIGATOR® effectively takes advantage of the world's high-quality expression data, to help identifying new targets and biomarkers and characterize expression patterns of marker genes across diseases.

SELECTED DATA AND SETTINGS FOR GENEVESTIGATOR®

2-Gene Plot: HS_mRNASeq_HUMAN platform filtered for all CD4+ T-cell populations

Signature tool: DATA-HS_mRNASeq_HUMAN full platform

REFERENCES

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Plitas G et al., Regulatory T Cells Exhibit Distinct Features in Human Breast Cancer. Immunity. 2016

CONTACT INFORMATION

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