Investigating the Repurposing Potential of Bevacizumab for Additional Cancer Types

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Problem definition

- Key scientific question:
  - Using scRNA-seq data from cancer cell lines, how could we explore the use of Bevacizumab in additional cancers?

- Bevacizumab FDA-approved indications:
  - Ovarian, cervical, kidney, glioblastoma, lung (NSCLC), colorectal, and hepatic cancer

About Bevacizumab

- Mechanism of action:
  - anti-VEGF antibody
  - Inhibits angiogenesis
- VEGFA and VEGFB subtypes of VEGF regulate angiogenesis, but Bevacizumab only binds to VEGFA.
- VEGFA expression is regulated by Hypoxia-inducible factor-1α (HIF-1α)
- HIF-1α is overexpressed in various cancer types, including cervical, ovarian, lung, kidney and thyroid cancer.

About the Dataset

- Expression profile of 198 cancer cell lines from 22 cancer types by single-cell RNA-seq with 10X chromium (GEO accession: GSE157220

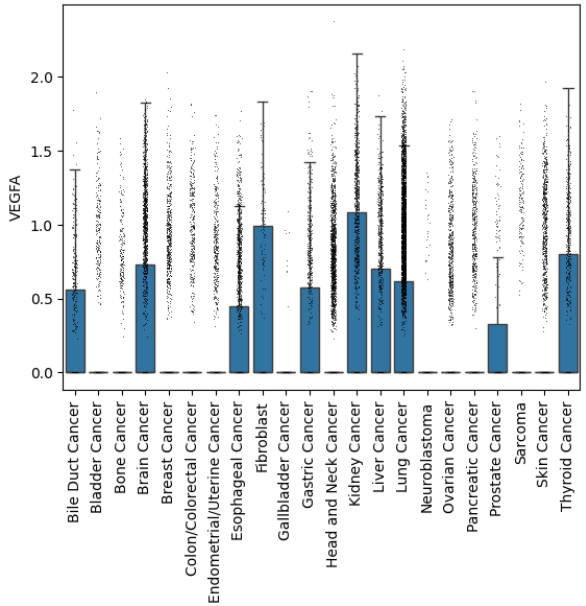
- The authors found that differential activation of specific cellular programs between different cell lines and cellular heterogeneity resembles those of human tumor cells, making cell lines appropriate models for the study of cellular heterogeneity in tumors.

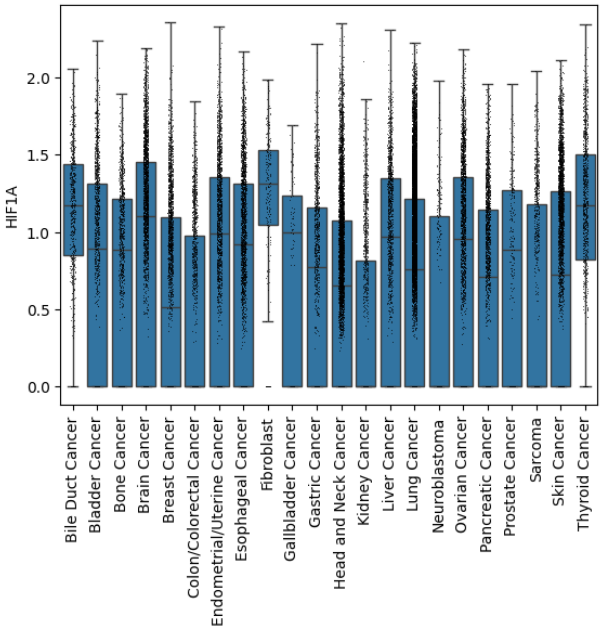
- By comparing scRNA-seq data of cancer types and finding ones that are similar to cancer types that respond to Bevacizumab, we could find potential additional indications for this drug.

Methods

- Data preprocessing including QC, normalization, and dimensionality reduction was performed using the scanpy library in python
- Comparing expression of the VEGFA gene (Bevacizumab target) and its regulator HIF-1α in different cancer types and cell lines
- Clustering to find and analyze cancer subtypes
- Pathway activity inference using the python implementation of decouplR to find cancer types under hypoxia and with activated angiogenesis

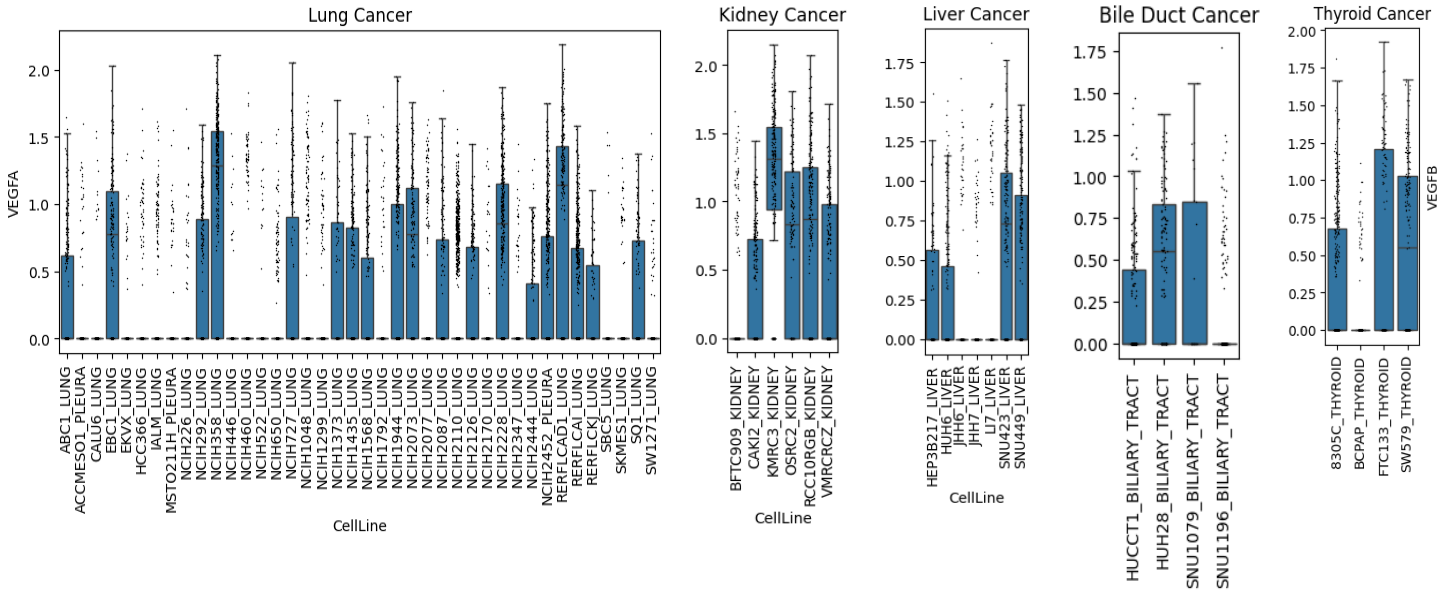
Results





- Results show that other than cancer types with Bevacizumab indication, bile duct cancer, esophageal cancer, gastric cancer, prostate cancer, and thyroid cancer show high expressions of VEGFA. Fibroblasts also demonstrate high VEFGA expression but are not specific to a single cancer type.
- All cancer types show high HIF-1α expression, but bile duct cancer and thyroid cancer show higher expression. It could be concluded from these results that high HIF-1α expression might be the reason behind high VEGFA expression in bile duct cancer and thyroid cancer.

Results



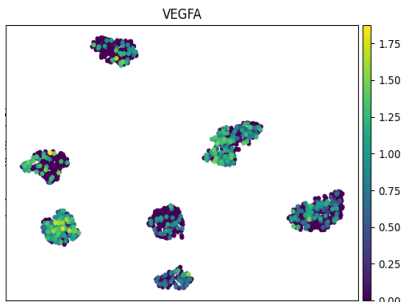
Similar to lung cancer, kidney cancer, and liver cancer with Bevaciumab indication, most bile duct cancer and thyroid cancer cell lines are VEGFA positive.

Results

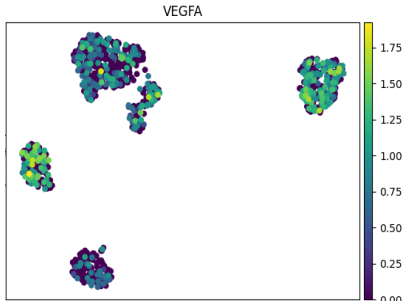
Similar to liver cancer with Bevacizumab, some cell clusters in thyroid cancer and bile duct cancer express both VEGFA and HIF-1α.

As not all clusters express VEGFA, if Bevacizumab were to be tested in these two cancer types, screening tests should be performed to detect VEGFA-positive patients.

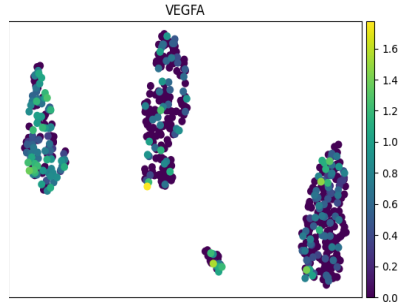
Liver Cancer



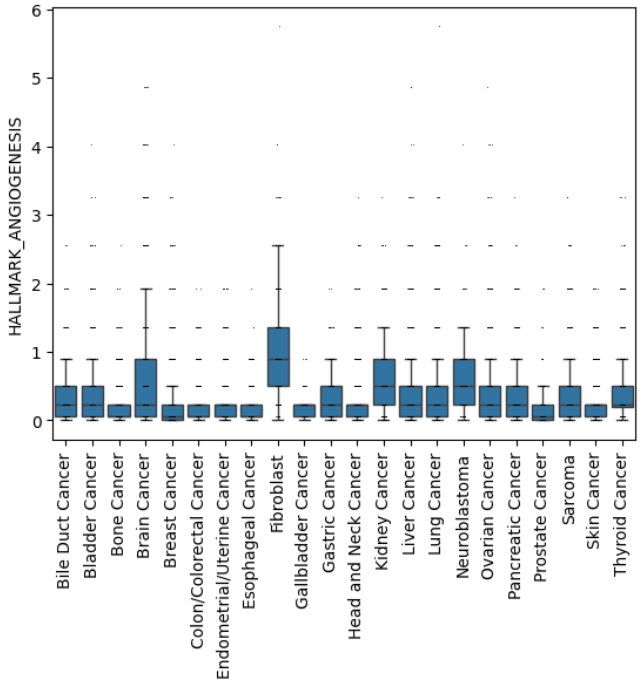
Thyroid Cancer

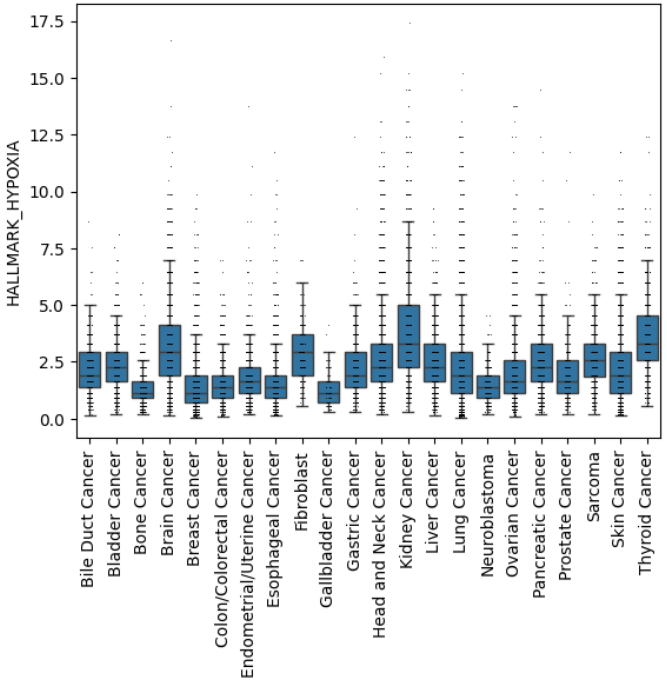


Bile Duct Cancer



Results





Inference of biological process activity was performed using decouplR to find cancer types with high angiogenesis and expression of hypoxia-related genes. The hypothesis is that cancer types under hypoxia and activating angiogenesis-related programs need more blood supply and therefore are more prone to VEGFA inactivation by Bevacizumab.
According to these results, The only VEGFA-positive cancer type (other than previously approved indications for Bevacizumab) with high activities of these two processes is thyroid cancer and can be further investigated for Bevacizumab repurposing.

Conclusion and Discussion

- According to the results, thyroid cancer cell lines present high VEGFA (Bevacizumab target) and HIF-1α (VEGFA expression regulator) expression, along with high angiogenesis and hypoxia-relate gene expression. Therefore, they show higher metabolism rates and are possibly prone to Bevacizumab.
- Various studies have shown that VEGFA is overexpressed in thyroid cancer cells (1, 2, 3, 4).
- In a study on the effect of Bevacizumab pretreatment before radioimmunotherapy on a mouse model of thyroid cancer, Bevacizumab increased tumor response to radioimmunotherapy (5).
- BRAF is a gene mutated in 52% of thyroid cancer patients, according to TCGA data analyzed by cBioPortal. In a paper recently published in Nature (6), It was found that HIF-1α is the main transcriptional contributor to the metabolic rewiring of BRAF-driven thyroid tumors. Therefore, BRAF-mutated thyroid cancer patients could potentially respond to Bevacizumab.
- A clinical trial was performed in 2008-2014 with 15 participants to test the effectiveness of Bevacizumab+Doxorubicin for the treatment of patients With Anaplastic Thyroid Cancer and was terminated due to lack of response. However, according to the results of the presented study, Bevaciumab is only effective in specific subtypes, perhaps with BRAF mutation.

Next Steps

- Using available genomics and transcriptomics data from TCGA, it should be investigated whether VEGFA is upregulated in BRAF-mutated thyroid cancer cells. In addition, scRNA-seq experiments should be performed on thyroid cancer cells with BRAF mutation to analyze the activity of different transcriptional programs. Also, in vitro and in vivo toxicity tests should be performed to confirm effectiveness of Bevacizumab.
- At last, if the above tests are positive, a clinical trial on patients with BRAF-mutated thyroid cancer tumors should be tested to investigate the effectiveness of Bevacizumab.

Acknowledgments

This study was part of the F1L internship emulator, and I thank Dr Dean Lee, the coordinator of this program, for this valuable experience. As working as a computational biologist in the industry is an option that I am considering for the future, this was a great opportunity for me to practice analyzing single-cell data and think creatively to solve an industry-related scientific question.

In addition, as a guide for how to analyze single-cell data, I mostly used the book "Single-cell Best Practices" by Professor Fabian Theis and colleagues, an amazing book that I strongly suggest everyone trying to learn singe-cell analysis to read.

References

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