Spatially Coordinated Immune Evasion in Classical Hodgkin's Lymphoma

Nitya Thakkar
Neriman Tokcan, Broad Institute of MIT and Harvard

INTRODUCTION

Classical Hodgkin's Lymphoma (CHL) is the most common cancer diagnosed in adolescents. While many cancers have homogenous or less diverse tumor microenvironments, CHL tumors are unique in that comparatively they have a very diverse tumor microenvironment composed of around 1% tumor cells with the remainder as non-malignant cells (Figure 1). Previous studies have found these tumor cells are dependent on the tumor microenvironment for survival and to evolve their mechanisms of immune evasion (Trujillo et al. Cancer Research 32, 1057-1065, 1972; Eisinger et al. Nature 233, 104-18, 1971); however, even though it is so common in adolescents the current standard treatment has a high associated morbidity rate. Therefore, the goal of this project is to use spatial transcriptomic data (Figure 2, 3) to enable the discovery of interactions within the microenvironment. If we can determine which nonmalignant cells enable the survival of tumor cells and their mechanisms of immune evasion, we can develop new therapies to target those cells directly with fewer adverse effects on the patient.

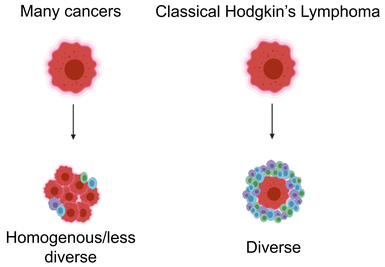


Figure 1: Tumor microenvironment: red tumor cells with non-malignant immune cells

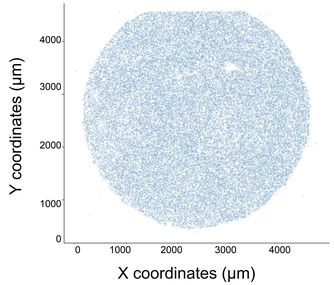


Figure 2: Spatial transcriptomic data puck example

Bulk Genomics	Single-Cell Genomics	Spatial Transcriptomics
Average gene expression of cells, spatial context lost	Expression of each individual cell, spatial context lost	Near individual expression of cells, retain positional context

Figure 3: Overview comparison: spatial transcriptomic data allows for near individual gene expression of cells and retention of positional context

METHODS

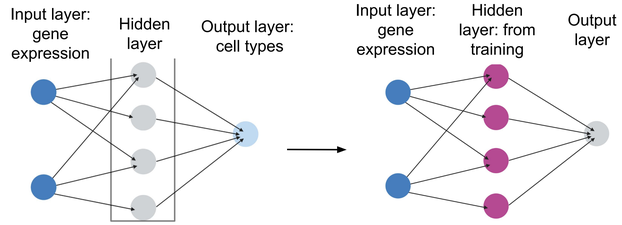
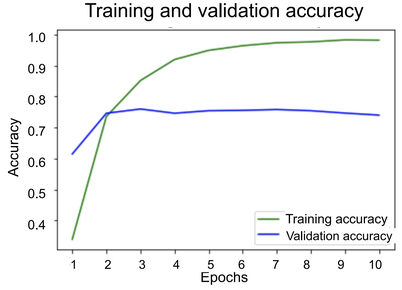


Figure 4: Neural network architecture overview

- Spatial data generated by biologists at the Broad Institute
- Created a feed forward network in tensorflow to predict cell types in spatial data from gene expression inputs, and trained on single-cell reference data generated by collaborators
- Tumor proximity analysis: categorized data based on distance to nearest tumor cell, recorded cell density in each region

RESULTS - Neural network



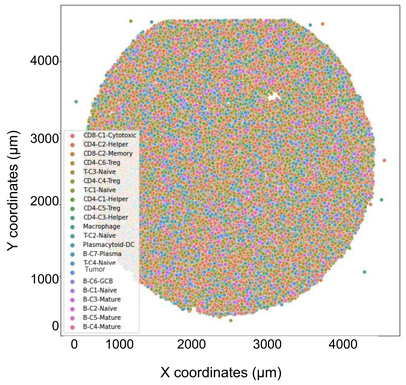
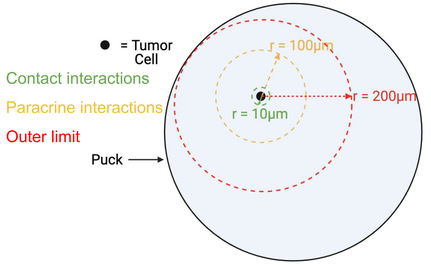


Figure 5: Model train accuracy: 0.983, test accuracy: 0.787

RESULTS - Tumor Proximity Analysis



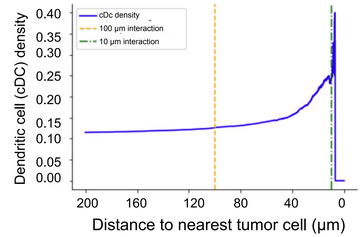


Figure 6, 7: Tumor proximity analysis approach overview; analysis results: Spearman's correlation (monotonic relationship): 0.99990, Spearman's p-value: 1.43e-121

CONCLUSION and FUTURE WORK

In conclusion, the Classical Hodgkin's Lymphoma tumor microenvironment is very complex, but with these methods we can learn more about the cellular and gene interactions within it. The neural network was correctly able to classify the cell types from the spatial transcriptomic data given gene expression inputs. This is important because it provides us with an efficient and cheaper method of determining cell locations in tissues. The next steps with the neural network include the ability to correctly classify multiple cell types that may be recorded in one data point (Figure 8). Current methods to address this include increasing the complexity of the model architecture to predict multiple cell type outputs for a given gene expression input. Another approach includes using latent space methods to conduct a simultaneous factorization of both the single-cell reference data and spatial data. Furthermore, we will next investigate how the properties of cells change in tumors using tensor decomposition methods to learn more about cellular interactions in tumors. The ultimate main goal of this project is to predict how cell-specific gene expressions may change in different regions of the tissue, which will allow us to develop more targeted cancer therapies.

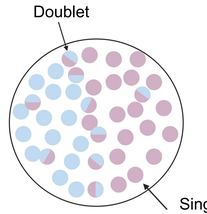


Figure 8: Representation of what spatial transcriptomic data actually looks like - some data points may contain more than one cell type

Bibliography: Trujillo et al. Cancer Research 32, 1057-1065, 1972; Eisinger et al. Nature 233, 104-18, 1971; Sykes et al. Cancer Research 22, 21-26, 1962; Von Kalle et al. Int. J. Cancer 1992