Modeling the Effect of Melanoma Tumor Cells When in the Presence of Natural Killer Cells
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INTRODUCTION

Cancer is the 2nd leading cause of death in the United States. Current treatments primarily consist of chemotherapy and radiation, which have significant side effects, such as tissue damage, bleeding, and secondary carcinogenesis. There is an increasing need to provide treatments, which are more specific and less traumatic. The aim of this project was to model a relatively new adoptive immunotherapy to investigate the immune response against cancer. To achieve this goal, experimental and mathematical modeling were used to predict how natural killer (NK) cells interact with and kill melanoma cells.

RESEARCH OBJECTIVES

Experimentation using NK cells and melanoma cells has been outlined to create the following objectives:
- Predict interaction between NK cells and tumor cell populations in combined in vitro cultures
- Create a mathematical model that can be used to develop and improve immunotherapies for cancer patients
- Use MATLAB, to develop continuous partial differential equations based on data from published literature
- Experiments are expected to validate the model and allow for further modifications
- Perform experiments to validate model
- Experiments performed at the University of Tennessee involved a migration assay that allows the cells to be injected individually and observed over time
- Parameters will be validated through examining cell directional movement and velocity

METHODS

Variables Definitions
NK  natural killer cells
NKR  natural killer cells with NKG2D receptors
TMICA  Tumor microenvironmental cell adhesion proteins
MMP-TMICA  matrix metalloproteinases bound to TMICA
CT  cytokines secreted by tumor
ECM  extracellular matrix

A. Mathematical Model

The mathematical model was developed using MATLAB, and the following partial differential equations were used to represent the system:

\[
\frac{\partial N}{\partial t} = D_N \nabla^2 N - k_1 N K - k_2 N \text{ECM}
\]

\[
\frac{\partial K}{\partial t} = k_1 N K - k_2 N \text{ECM}
\]

\[
\frac{\partial \text{ECM}}{\partial t} = \frac{k_2 N \text{ECM}}{1 + k_3 (NKR)} - \lambda \text{ECM}
\]

B. Simulation Results

Figure 3: Graphs depicting the effects of MMPs released by NK cells on tumor growth when in the presence of an extracellular matrix. A) Low MMP levels. B) Normal MMP levels. C) High MMP levels.

C. Biological Model

- Blood separation performed to remove mononuclear cell layer
- Mononuclear cell layer separated into specific immune cell types through a Pecoll™ gradient
- Immune cell fractions tested using flow cytometry to analyze for purity of NK cells
- NK and A375 cells were placed in two separate wells in Delta T dish
- Images of Delta T dish were taken using an automated stage microscope
- Quantitative analysis performed using image software
- Information received from quantitative analysis utilized to validate mathematical model

D. Conclusions

- Developed assay to provide data for mathematical model
- Biological models can be developed to provide quantitative data for a mathematical model
- Multiple biological experiments are needed to provide data for all parameters in biological model

E. Future Work

- Simulate mathematical model that takes receptor density into account
- Perform time-lapse imaging with biological experiments
- Begin validating mathematical model with experimental data

REFERENCES
