Cardiac Myxoma Tumor Dynamics: A Monte Carlo Simulation As a Basis For a Tumor Vaccine

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INTRODUCTION

- Mathematical models analyzing tumor-immune interactions provide a framework that can be used to better understand tumors and specifically target tumor antigens, which can potentially be used for a cure for multiple malignancies.
- An important aspect of tumor-immune surveillance to consider is elimination of tumor cells.
- We created a mathematical model using synthetic antigens which are tumor epitopes expressed by cardiac myxomas to both test:

→ **the strength of a model human immune system**

→ **and evaluate the immune system's response.**

- Utilizing multi-organ mapping and the lack of division by heart cells, the antigens of the heart and the tumor antigens of cardiac myxomas can be studied together to better understand tumor-immune dynamics.
- Currently the overexpression of the **ANXA3, ACOX2, MIA, PLA2GA2, PRKAR1, NKX2-5, MEF2, and GATA4** genes has been linked to the development of cardiac myxomas.

METHODOLOGY

- We constructed a model based on the immune system model by de Pillis, one that we previously used to examine lung cancer[1].
- MATLAB was utilized to numerically simulate and all equations describing **tumor-immune growth, antigen presentation, host immune response, and interaction rates.**
- The immune system is modeled through thirteen coupled differential equations in which each equation exhibits **the rate of change of a cell population in terms of growth, death, cell-cell kill, cell recruitment, and cell inactivation.**
- This model has been modified further to introduce the addition of cardiac myxoma "vaccines" using Monte-Carlo processes to simulate an antigen stimulation response to a variety of HLA epitopes.
- The strength of binding depended on the generated values of two variables from the Monte-Carlo process.
- A simulator was utilized to vary the response of an individual's immune system when exposed to a tumor vaccine and model the immune system once a cardiac tumor is detected.
- The resultant model is composed of cardiac myxoma epitopes of different fragment sizes (41-452 amino acids long).

FIGURES

$$\frac{dc}{dt} = R_c C \log C - k_1 T_e C - k_3 MC \quad (1)$$

$$\frac{dN}{dt} = B_n - D_n N + \frac{R_n NC}{M_n + C} - L_n Nc \quad (2)$$

$$\frac{dTn}{dt} = b_t - d_t T_n - \frac{m_n T_n A_p}{mt + A_p} \quad (3)$$

$$\frac{dTe}{dt} = \frac{m_n T_n A_p}{mt + A_p} - D_t T_e + r_T I_2 T_e - i_H R_e T_e \quad (4)$$

$$\frac{dH_n}{dt} = b_h - d_h H_n - \frac{m_n H_n A_p}{mt + A_p} \quad (5)$$

$$\frac{dH_e}{dt} = \frac{m_n H_n A_p}{mt + A_p} - D_h H_e + r_T I_2 H_e - i_H R_e H_e \quad (6)$$

$$\frac{dI_2}{dt} = C_t I_2 - d_t I_2 - i_H I_2 T_e - i_H I_2 H_e - r_T I_2 R_e \quad (7)$$

$$\frac{dA_p}{dt} = r_a C - d_a A_p \quad (8)$$

$$\frac{dR_n}{dt} = b_r - d_r R_n - \frac{m_n R_n A_p}{mt + A_p} \quad (9)$$

$$\frac{dR_e}{dt} = \frac{m_n R_n A_p}{mt + A_p} - D_h R_e + r_T I_2 R_e \quad (10)$$

$$\frac{dM}{dt} = r_a C - d_n M - l_n MC \quad (11)$$

$$\frac{dr_r}{dt} = 0 \quad (12)$$

$$\frac{dm_{ax}}{dt} = 0 \quad (13)$$

- Cardiac myxoma tumor antigens of random sizes were obtained from various databases and processed via an MHC class I pathway.
- A simulator (random number generator for both R_c and M_a) was utilized to vary the response of an individual's immune system when exposed to a tumor vaccine as seen above.
- The above model was then subjected to MATLAB, an open source math modeling program, was utilized to simulate the model, estimate parameter values, as well as determine scenarios in which tumor vaccines produce varying immune responses.
- Below is a table of all parameters and estimated values:

Parameter and units	Parameter description	Parameter value	Reference or Estimation
R_c (1/day)	Cancer Propagation	$1 \times 10^{-10} < x < 1 \times 10^{-4}$	Estimation
K_1, K_2, K_3, L_n (Cell/day × nL)	Interaction between cancer, NK, CD8, and Macrophages	3.50×10^{-12}	de Pillis et al. in 2005
		4.60×10^{-7}	
		7.50×10^{-12}	
		1.00×10^{-13}	
B_n (cell/day × nL)	Birth (fixed) and death rates of NK cells/Macrophages	1.30×10^{-2}	de Pillis et al. in 2005
D_n (1/day)		4.12×10^{-8}	
R_n (1/day)	Recruitment of circulating NK cells	2.50×10^{-8}	de Pillis et al. in 2005
M_n (cell²/nL)		20.2	
M_a (1/day)	Antigen Presentation	$1 \times 10^{-7} < x < 1 \times 10^{-3}$	Estimation
B_t (cell/nL × day)	Birth and death rates of naïve CD4 cells	8.55	Kim et al. in 2007
D_t (1/day)		3.00×10^{-8}	
D_t (1/day)	Death rates of CD4, CD8, and CD4 regulatory cells	2.00×10^{-8}	Kim et al. in 2007
D_h (1/day)		4.00×10^{-8}	
D_r (1/day)		1.00×10^{-9}	
R_t (cell/nL × day)	Recruitment rates of CD4, CD8, and CD4 regulatory cells	$3.75 \times \times 10^{-8}$	de Pillis et al. 200
R_H (cell/nL × day)		1.88×10^{-9}	
R_r (cell/nL × day)		3.75×10^{-8}	
I_t (1/day)	Inhibition of CD4/ CD8 Activity by CD4 Regulatory cells.	5.00×10^{-7}	de Pillis et al. 2005
I_h (1/day)			
B_h (cell/nL × day)	Birth and death rates of naïve CD8 cells	6	Kim et al. in 2007
D_{th} (1/day)		3.00×10^{-8}	
B_r (cell/nL × day)	Birth and death rates of naïve CD4 regulatory cells	4.50×10^{-5}	Kim et al. in 2007
D_r (1/day)		3.00×10^{-8}	
C_t (1/nL × day)	Production and degradation of IL-2	1.00×10^{3}	Kim et al. in 2007
D_i (1/day)		1.00×10^{-7}	
R_a (1/day)	Antigen production and death of APCs	1.00×10^{-4}	Kim et al. in 2007
D_a (1/day)		3.00×10^{-8}	
A list of parameters used for the model. Parameter values are indicated to be utilized from another paper or estimated from computer simulations.			

Table 1: Parameter descriptions and values.

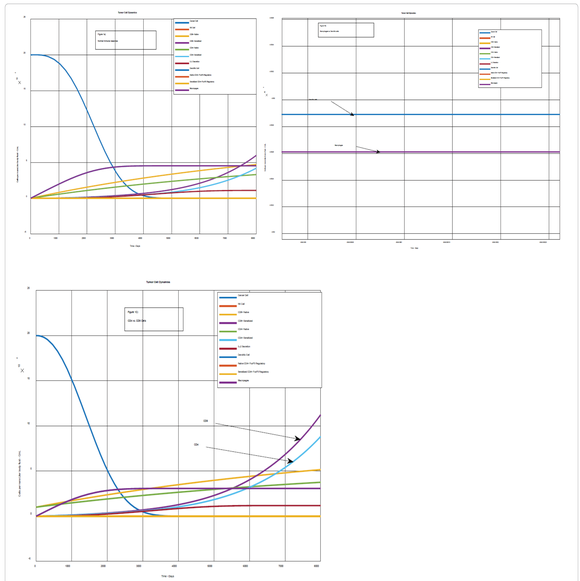

Figure 1A-1C: Time plots of cell populations with the utilization of the initial model. Figure 1A depicts a normal immune response to cancer (C=200,000). Figure 1B depicts antigen presenting cells during the innate immune response with dendritic cells (C=200,000, M=DC=1,000). Figure 1C depicts a normal immune response with modified naïve CD4 and CD8 cells (Naïve CD8=Naïve CD4=1,000). CD8 cells are predominant during the adaptive immune response.

RESULTS AND DISCUSSION

- Cardiac myxomas are encountered three times more often in women[2]. It is more common in the fourth to seventh decades of life, mostly diagnosed in adults.
- 60 to 80% arise in the left atrium typically in the fossa ovalis, 15-28% in the right atrium, 12% in ventricles or valves[2].
- About 755 of cardiac myxomas are in the left atrium and 25% in the right atrium[2].
- We used a total of 12 different tumor antigen epitopes from cardiac myxomas to test the immune system response:

→ **5 from the ANXA3 gene, 1 from ACOX2, 1 from MIA, 1 from PLA2GA2, 1 from PRKAR1, 1 from NKX2-5, 1 from MEF2, and 1 from GATA4.**

- Our mathematical model and Monte Carlo simulation showed that a **robust immune response can be generated if the immune system recognizes epitopes that are between 41 to 452 amino acids long.**
- The model can be utilized to simulate the strength of a host's immune response after a host is inoculated with a cardiac myxoma vaccine.
- Results from the model are *in silico*, meaning that results from this model can be applied to a clinical setting.

CONCLUSION

- Our model for vaccines against specific cardiac myxoma tumor antigens can be used as a basis for both better understanding cardiac malignancies and to hopefully develop a cure that does not involve surgical resection.
- Here, we showed and can infer that if a synthetic epitope is not between 41-452 amino acids long, a host will produce an immune response.

REFERENCES

1, 2: Available Upon Request

DISCLOSURES: NONE