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A Mathematical Investigation on Tumor-Immune Dynamics: The Impact of Vaccines on the Immune Response

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INTRODUCTION

- An effective way to cure disease is to prevent the development of it all together.
- One modality to combat disease is cancer vaccines that would "program" an individual's immune system to recognize foreign antigens by stimulating cytotoxic T lymphocytes (CTL) to attack cancer cells expressing a certain tumor antigen [1-5].
- Current vaccine strategies to combat cancer include vaccines consisting of lymphocytes, which include: helper T lymphocytes (Th), dendritic cells (DC), macrophages, or reprogrammed oncolytic viruses [1,2].
- We developed a mathematical model of tumor dynamics in response to a vaccine injection composed of lung cancer epitopes (Survivin, Kita-Kyushu lung cancer antigen 1 (KKLC1), and epidermal growth factor receptor (EGFR)) of different fragment sizes (8-12 amino acids (aa) long) with the goal of determining which epitopes produce a strong immune response.

METHODOLOGY

- The dynamics of the mathematical model, as well as parameter values, are borrowed from assertions, prior mathematical models, as well as through parameter estimation through numerical simulations.
- Our model is based on a previous model published by de Pillis et al. [9], but expanded to include simplified T cell development and more cell populations to better depict the immune response to cancer.
- No patient data was integrated into this model yet as this model is in its infancy; a literature review shows no prior model with an integrated MonteCarlo simulator.
- Generated data now is theoretical but has applicability to the clinical setting. The basis for the model is listed below.

METHODS

- The dynamics of the mathematical model, as well as parameter values, are borrowed from assertions, prior mathematical models, as well as through parameter estimation through numerical simulations.
- Our model is based on a previous model published by de Pillis et al. [9], but expanded to include simplified T cell development and more cell populations to better depict the immune response to cancer.
- No patient data was integrated into this model yet as this model is in its infancy; a literature review shows no prior model with an integrated MonteCarlo simulator.
- This model has been modified further to introduce the addition of lung cancer "vaccines" using Monte-Carlo processes to simulate an antigen stimulation response to different HLA epitopes [9,13,19]. The model is as follows:

FIGURES

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

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

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

$$\frac{dTe}{dt} = \frac{m_a T_n A_p}{mt + A_p} - D_t T_e + r_T I_2 T_e - i_H \mathrm{R}_e T_e \quad (4)$$

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

$$\frac{dH_e}{dt} = \frac{m_a H_n A_p}{mt + A_p} - D_h H_e + r_T I_2 H_e - i_H \mathrm{R}_e H_e \quad (6)$$

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

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

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

$$\frac{dR_e}{dt} = \frac{m_a R_n A_p}{mt + A_p} - D_h \mathrm{R}_e + r_T I_2 \mathrm{R}_e \quad (10)$$

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

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

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

- **Equation #1** describes the change in population of a cancerous pathology in which the state variable is C. Cancer populations propagate (r_c) at a fixed rate and die off due to cell-to-cell interactions between NK cells (k_1), CTL's (k_2), and macrophages (k_3).
- **Equation #2** describes the change of NK cell populations in which the state variable of this equation is (N). NK cells are born at a fixed rate (B_n) and die off (D_n) in proportion to population levels. In addition, NK cells are recruited in response to cancer antigen presentation at a fixed rate (Rn and Mn) as well as die off due to cell-cell interactions with cancer (L_n).
- **Equation #3** describes the change of naive CD8 populations in which the state variable of this equation is (T_n). Naive CD8 populations are born at a fixed rate (B_t) and die off (D_t) in proportion to population levels. Such cells then transition from the naive to primed states due to cancer antigen acquisition (M_a) by antigen presenting cells at a fixed rate (M_t), which then present the processed cancer antigen to naive populations.
- **Equation #4** describes the change of primed CD8 populations in which the state variable of this equation is (T_e). Naive CD8 populations are primed with cancer antigen transition from their naive to primed states to combat cancer (first term) and die off (D_e) in proportion to population levels. Primed CTL populations are then influenced due to memory cell recruitment by interlukin-2 (R_t) and are inhibited (I_h) by T regulatory cells.
- **Equation #5** describes the change of naive CD4 populations in which the state variable of this equation is (R_n). Naive CD4 regulatory populations are born at a fixed rate (B_r) and die off (D_r) in proportion to population levels. Such cells then transition from the naive to primed states due to cancer antigen acquisition (M_a) by antigen presenting cells at a fixed rate (M_t), which then present the processed cancer antigen to naive populations.
- **Equation #6** describes the change of primed CD4 populations in which the state variable of this equation is (R_e). Naive CD8 populations are primed with cancer antigen transition from their naive to primed states to combat cancer (first term) and die off (D_r) in proportion to population levels. Primed CTL populations are then influenced due to memory cell recruitment by interlukin-2 (R_t) and are inhibited (I_h) by T regulatory cells.
- **Equation #7** describes the change of interleukin-2 concentration in which the state variable of this equation is (I_2). IL-2 is produced at a constant rate (C_i) by primed immune cells, mainly of HTL lineage, and is consumed in varying proportions (R_h ,R_t, and R_r) to recruit circulating memory cells to combat cancer populations. In addition, IL-2 denatures (D_i) in proportion to population levels.
- **Equation #8** describes the change of antigen presenting cells in which the state variable of this equation is (A_p). APC populations are primed (R_n) in direct proportion to cancer antigen and die off (d_A) in proportion to population levels.
- **Equation #9** describes the change of naive CD4 regulatory populations in which the state variable of this equation is (R_n). Naive CD4 regulatory populations are born at a fixed rate (B_r) and die off (D_r) in proportion to population levels. Such cells then transition from the naive to primed states due to cancer antigen acquisition (M_a) by antigen presenting cells at a fixed rate (M_t), which then present the processed cancer antigen to naive populations.
- **Equation #10** describes the change of primed CD4 regulatory populations in which the state variable of this equation is (R_e). Naive CD4 regulatory populations are primed with cancer antigen transition from their naive to primed states to combat cancer (first term) and die off (D_r) in proportion to population levels. Primed CTL populations are then influenced due to memory cell recruitment by interlukin-2 (R_t).
- **Equation #11** describes the change of macrophage populations in which the state variable of this equation is (M). NK cells are primed at a rate (R_a) in proportion to cancer antigen and die off (D_n) in proportion to population levels as well as interactions with cancer cells (L_n) .
- **Equations #12 and #13** act as placeholder equations for two variables (R_c and M_a)-that act as the Monte-Carlo Simulator via a pseudo-number generator that affects the output of the other eleven equations

RESULTS AND DISCUSSION

- MHC class I molecules are designed to recognize peptide fragments of about eight to ten aa along with the maximum being 11.
- With the involvement of intracellular antigens for cancer, the selection of the right HLA gene complex depends on the sequence involved to activate the system.
- Our results illustrate that amino acid epitopes between 8-11 aa long will produce a robust immune response, while anything not in this estimated range will produce a non-robust immune response.
- This model, although useful in predicting the long-term status of a patient, cannot effectively predict which antigen epitopes and HLA combinations will produce a strong immune response due to the current nature of the model.

CONCLUSION

- In our model, three antigens Survivin, KKLC1, and EGFR [24] were utilized from the TANTIGEN database to predict an immune response once cancer was detected within an individual following utilization of a synthetic vaccine.
- We applied mathematical modeling as a tool to depict the strength of a host's immune response after it has been subjected to a lung tumor vaccine.
- Here, we showed and can infer that if a synthetic epitope is not between 8-11 aa long, a host will produce an immune response, but that is not ideal to the elimination of cancer [26,27].

References

- Available Upon Request
- All references found: Quinonez J, Dasu N, Qureshi M (2017) A Mathematical Investigation on Tumor-Immune Dynamics: The Impact of Vaccines on the Immune Response. J Cancer Sci Ther 9: 675-682. doi:10.4172/1948-5956.1000491 – Open Access