Mathematical Model of Tumor-Immune Surveillance

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1 Brief Introduction of the Project
   • Biological Background

2 Aim and Objectives

3 Methodology: Mathematical Model

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Cancer is a major cause of death worldwide, resulting from the uncontrolled growth of abnormal cells in the body.
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There were 12.7 million new cases of cancer in 2008, and the global cancer burden is expected to double to 21.4 million cases with the corresponding deaths of 13.5 million by 2030 [1].

Tumor escape from host’s immune surveillance is recently considered as one of the emerging hallmarks of cancer.
Immune System

Definition
The immune system consists of a sophisticated network of specialised cells and organs working together to protect the body against attack of “foreign” invaders like viruses and bacteria or transformed cells in the body such as cancer cells.

- Immune cells are known as immunocompetent cells because they can distinguish “self” from “non-self” and “foreign” cells.
- The immune system has two major components: innate immune system and adaptive immune system
Figure: Overview of immune cells [2].
understand how tumour cells escape the immune surveillance and suggest ways that can be used to reduce tumour escape using mathematical models.
Specific Objectives

We propose to answer the following questions:
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- How do tumour cells escape from the host immune surveillance?
- It is known that the immune response can be enhanced by immunotherapy by stimulating anti-tumor immunity. What are the main mechanisms by which the immunotherapy enhance the anti-tumour immune response and how can we model them?
Figure: A schematic view of the binding and detachment of a tumor cell to a natural killer (NK) cell.
### Table: Model Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
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<tbody>
<tr>
<td>L</td>
<td>Activated CD8&lt;sup&gt;+&lt;/sup&gt; cytotoxic T lymphocytes (CTLs)</td>
</tr>
<tr>
<td>N</td>
<td>Natural killer (NK) cells</td>
</tr>
<tr>
<td>T&lt;sup&gt;0&lt;/sup&gt;</td>
<td>Naive tumor cells</td>
</tr>
<tr>
<td>T&lt;sup&gt;1&lt;/sup&gt;&lt;sub&gt;N&lt;/sub&gt;</td>
<td>Wild-type tumor cells that escaped from NK cells</td>
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<tr>
<td>T&lt;sup&gt;1&lt;/sup&gt;&lt;sub&gt;L&lt;/sub&gt;</td>
<td>Wild-type tumor cells that escaped from activated CD8&lt;sup&gt;+&lt;/sup&gt; CTLs</td>
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<tr>
<td>T&lt;sup&gt;1&lt;/sup&gt;&lt;sub&gt;NL&lt;/sub&gt;</td>
<td>Wild-type tumor cells that escaped from both NK cells and activated CD8&lt;sup&gt;+&lt;/sup&gt; CTLs</td>
</tr>
<tr>
<td>C&lt;sub&gt;N&lt;/sub&gt;</td>
<td>Complex formed by NK cell and naive tumor cell</td>
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<tr>
<td>C&lt;sub&gt;L&lt;/sub&gt;</td>
<td>Complex formed by CTL and naive tumor cell</td>
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<td>C&lt;sub&gt;N&lt;/sub&gt;&lt;sup&gt;N&lt;/sup&gt;</td>
<td>Complex formed by NK cell and wild-type tumor cell that escaped from activated CD8&lt;sup&gt;+&lt;/sup&gt; CTLs</td>
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<td>C&lt;sub&gt;NL&lt;/sub&gt;&lt;sup&gt;L&lt;/sup&gt;</td>
<td>Complex formed by CTL and wild-type tumor cell that escaped from NK cells</td>
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Figure: Tumor cells, natural killer cells and CD8+ CTLs interactions.
Model Equations

\[
\frac{dN}{dt} = s - \mu_1 N - (1 - p_N) \alpha_N^+ N T^0 - (1 - \pi_N) \alpha_L^+ N T_N^1 \quad (1)
\]

\[
\frac{dL}{dt} = \frac{r_1 \beta_L^+ L T^0}{\beta_L^-(g + T^0)} + \frac{r_2 \beta_N^+ L T_N^1}{\beta_N^-(g + T_N^1)} - \mu_2 L - (1 - q_L) \beta_L^+ L T^0 - (1 - \zeta_L) \beta_N^+ L T_N^1 \quad (2)
\]

\[
\frac{dT^0}{dt} = a T^0 (1 - b T^0) - \alpha_N^+ N T^0 - \beta_L^+ L T^0 \quad (3)
\]

\[
\frac{dT_N^1}{dt} = a T_N^1 (1 - b T_N^1) + p_T \alpha_N^+ N T^0 - \beta_N^+ L T_N^1 \quad (4)
\]

\[
\frac{dT_L^1}{dt} = a T_L^1 (1 - b T_L^1) + q_T \beta_L^+ L T^0 - \alpha_L^+ N T_L^1 \quad (5)
\]

\[
\frac{dT_{NL}^1}{dt} = a T_{NL}^1 (1 - b T_{NL}^1) + \zeta_T \beta_N^+ L T_N^1 + \pi_T \alpha_L^+ N T_L^1 \quad (6)
\]
Initial Conditions

Followings are the positive initial conditions of the system:

\[ N(0) = N_0, \quad L(0) = L_0, \quad T^0(0) = T_0, \]
\[ T^1_N(0) = T^1_L(0) = T^1_{NL}(0) = 0, \quad s(0) = s_0. \]
Effects of the weak immune system on tumor evasion

Figure: Plots indicating the growth of the tumor cell populations and immune cells over time in the instance where there is low influx of natural killer (NK) cells, $s = 3.2 \times 10^3 \text{ day}^{-1} \text{ cells}$ and low recruitment of activated CD8$^+$ cytotoxic T lymphocytes (CTLs), $r_1 = 0.2988 \times 10^{-8} \text{ day}^{-1} \text{ cells}$ and $r_2 = 0.2755 \times 10^{-8} \text{ day}^{-1} \text{ cells}$. 
Effects of the strong immune system on tumor evasion

**Figure**: Plots indicating the growth of the tumor cell populations and immune cells over time in case where there is high influx of natural killer (NK) cells, $s = 3.2 \times 10^4 \text{ day}^{-1} \text{ cells}$. The plot indicates that immune system is capable of eliminating some “wild-type” tumor cells, particularly $T^1_L$, or reducing growth of other “wild-type” tumor cells, $T^1_N$ and $T^1_{NL}$.
Global Sensitive Analysis (GSA)

Figure: PRCC results with naive tumor cell population chosen as a baseline PRCC analysis variable.
Figure: PRCC scatter plots for parameters $s, \mu_1$, and $\alpha_L^+$. 
Local Sensitivity Analysis (LSA): Model implications for Immunotherapy

Figure: Increasing the source of NK cells leads increased cell density of NK cells for certain period of time.
Figure: The evolution of the “wild-type” tumor cells, $T^1_L$, indicating the effect of varying the source term of NK cells.
Conclusions

- An influx of external source of NK cells might play a crucial role in enhancing NK-cell immune surveillance;
- Immune system alone is not fully effective against progression of tumor cells;
- The development of immunoresistance by tumor cells is inevitable in tumor immune surveillance.

Future Research Focus

Use oncolytic virus to further subvert tumor-immune evasion.
Thank you for listening!
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