Dynamics of tumor immune escape via adaptive change

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Abstract: Despite of several complementary mechanisms that are inherently equipped with the immune system to eliminate tumor cells, some adaptive change of tumor cells such as down-regulating expression level of Major HistoCompatibility (MHC) class I to evade killing from T cells can be beneficial. Description of complex interactions among tumor and immune cells is useful to understand how some of adaptive change are effective for tumor cells to escape from immunosurveillance. In this paper, we formulate a mathematical model representing tumor killing by two different immune subsets to investigate under what conditions down-regulation of MHC class I expression can be favorable for tumor cells. Mathematical analysis and numerical computation results suggest that tumor cells prefer down-regulation of MHC class I if the killing of tumor cells by T cells is more potent than NK cells. This implication may support empirical observations that tumor escape via down-regulation of MHC class I expression can commonly occur.

Key Words: mathematical modeling, tumor immunoescape

1. Introduction
The immune system plays an important role in eliminating invading pathogens and foreign proteins [4]. The immune system is also capable of recognizing endogenous factors such as tumor derived antigen. Recent accumulating clinical and basic studies revealed that the immune system has been making significant contributions to eliminate tumor cells. Despite of its potential role of tumor killing, persistence of tumor cells is a major clinical issue. One of important mechanisms that support tumor persistence is escape of immunosurveillance: evasion of immune-mediated detection and killing of

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tumor cells [3].

Tumor cells use numerous strategies to evade killing from immune cells. Down-regulation of MHC class I expression is a common strategy to evade immune response [1]. This mechanism utilizes an inherent equipped mechanism of T cell mediated killing. The population of CD8 positive T cells is the subset of the immune system which eliminates antigen in an antigen-specific manner [4]. CD8 positive T cells usually recognize their corresponding specific antigen via interaction with antigen-bearing MHC class I molecules displayed on the surface of a target cell. Some of tumor cells can develop to down-regulate MHC class I expression [2]. Then CD8 positive T cells become to fail in recognizing tumor cells, leading to escape from T cell mediated killing. While down-regulation of MHC class I expression can be favorable for tumor cells, a complementary mechanism to prevent the escape has been inherently equipped with the immune system. The population of Natural Killer (NK) cells are one of immune subsets which specifically detect tumor cells with low MHC class I expression [9]. In fact, recent studies have identified the molecular mechanisms to support the killing of tumor cells with low MHC class I expression by NK cells.

It is a straightforward question why tumor cells can grow via down-regulating MHC class I expression despite the pressure of NK cell mediated killing. Complex interactions among tumor, T and NK cells would determine the outcome whether down-regulation of MHC class I expression is a beneficial behavior for tumor cells. To obtain a basic insight, mathematical analysis and simulation are useful to obtain simple but clear understandings to under what conditions down-regulation of MHC class I expression is really beneficial for tumor growth. In this paper, we formulate a mathematical model and perform mathematical analyses and numerical computation to investigate the outcome of adaptive change of tumor cells via modulating MHC class I expression.

The organization of this paper is as follows. In the next section, we formulate a mathematical model. More precisely, we consider population dynamics of two different types of tumor cells in terms of the expression level of MHC class I and two immune subsets which differ in the ability of tumor killing. In section 3, existence and stability conditions for equilibria of the main system are derived. Numerical simulations are carried out to investigate probable outcomes of tumor-immune interactions. In section 4, we investigate the possibility of tumor-immune escape by modulating the expression level of MHC class I. Biological implications are proposed and discussed in section 5, based on the results of mathematical analyses and numerical computations. In Appendix A, subsystems of the main system are analyzed in details.

2. Model formulation

We previously considered a mathematical model in which interactions among dendritic cells (DCs) and T cells are explicitly incorporated. In this paper, we start by considering the following system of differential equations:

\[
\begin{align*}
\frac{d}{dt}C_H(t) &= r_H C_H(t) \left(1 - \frac{C_H(t)}{K}\right) - \gamma_H C_H(t) N_T(t) \\
\frac{d}{dt}N_{DC}(t) &= a N_T(t) C_H(t) - \delta_{DC} N_{DC}(t) \\
\frac{d}{dt}N_T(t) &= b_T N_{DC}(t) C_H(t) h_{DC} + N_{DC}(t) - \delta_T N_T(t),
\end{align*}
\]  

(1)

where \(N_{DC}, N_T\) and \(C_H\) represent the population densities of DCs, T cells and tumor cells with high expression of MHC class I, respectively. Definition of all parameters will be introduced in the end of this section.

Hereafter we assume that de-activation rate of DCs is high, that is, \(\delta_{DC} \gg 1\). This assumption leads to apply the quasi-steady state approximation (QSSA) to the original model. QSSA is a convenient approximation which is widely used to reduce the dimension of a dynamical system when a variable representing fast dynamics is included. QSSA has been mathematically justified (see for example, [8]) and is useful to consider a dynamical system composed of both fast and slow dynamics. By QSSA, variables representing fast dynamics can be ignored from the main system. In our case, if \(\delta_{DC} \gg 1\),
then \( \varepsilon := 1/\delta_{DC} \ll 1 \). The second equation of (1) is rewritten as

\[
\varepsilon \frac{d}{dt}N_{DC}(t) = \frac{a}{\delta_{DC}}N_T(t)C_H(t) - N_{DC}(t) \simeq 0.
\]

We have implicitly assumed that \( a/\delta_{DC} \) is not small. The second equation of (1) is now replaced with

\[
N_{DC}(t) \simeq \frac{a}{\delta_{DC}}N_T(t)C_H(t).
\] (2)

By substituting (2) into the third equation of (1), we obtain that

\[
\frac{d}{dt}N_T(t) = \frac{b_T C_H(t) N_T(t)}{h_t + C_H(t) N_T(t)} N_T(t) - \delta_T N_T(t).
\] (3)

Let \( C_L \) and \( N_K \) denote the population densities of tumor cells with low expression of MHC class I and NK cells, respectively. Furthermore, let \( h_T = \frac{h_T}{\delta_{DC}} \) be a new notation. To incorporate interaction between T and NK cells via cytokine production, we introduce variable \( I_T \) representing the concentration of interferon-\( \gamma \) (IFN-\( \gamma \)) produced by T and NK cells. Furthermore, change of MHC class I expression is incorporated as a transition between types of tumor cells \( C_H \) and \( C_L \). Although CD8 T cells may eliminate tumor cells with low expression of MHC class I, for simplicity we assume that T cells kill only tumor cells with high MHC class I expression, whereas NK cells eliminate only tumor cells with low expression of MHC class I. Then the main system of tumor-immune interactions is given by

\[
\begin{align*}
\frac{d}{dt} C_H(t) &= r_H C_H(t) \left(1 - \frac{C_H(t)}{K_H}\right) - \gamma_H C_H(t) N_T(t) + m_L C_L(t) - m_H C_H(t) \\
\frac{d}{dt} N_T(t) &= \frac{b_T C_H(t) N_T(t)}{h_T + C_H(t) N_T(t)} N_T(t) - \delta_T N_T(t) + \frac{m_T I_T(t)}{a_T + I_T(t)} \\
\frac{d}{dt} C_L(t) &= r_L C_L(t) \left(1 - \frac{C_L(t)}{K_L}\right) - \gamma_L C_L(t) N_K(t) + m_H C_H(t) - m_L C_L(t) \\
\frac{d}{dt} N_K(t) &= \frac{b_K C_L(t)}{h_K + C_L(t)} N_K(t) - \delta_K N_K(t) + \frac{m_K I_T(t)}{a_K + I_T(t)} \\
I_T(t) &= p_T N_T(t) + p_K N_K(t).
\end{align*}
\] (4)

where all the associated parameters are \( r_H, r_L, K_H, K_L, \gamma_H, \gamma_L, m_H, m_L, b_T, b_K, h_T, h_K, \delta_T, \delta_K, m_T, m_K, a_T, a_K, p_T \) and \( p_K \).

Subscripts \( H \) and \( L \) represent tumor cells with “high” and “low” MHC class I expression, while \( T \) and \( K \) are used for describing T and NK cells, respectively. Assume that population growth of tumor cells (\( \circ \) for \( H \) or \( L \)) follows the logistic law with replication rate \( r_\circ \) and carrying capacity \( K_\circ \). Tumor cells are eliminated by the corresponding immune subset (either T cells or NK cells) with rate parameter \( \gamma_\circ \). The rate of transition between high and low expression of MHC class I are given by \( m_H \) and \( m_L \), respectively. The maximum activation rate of immune subset (\( \bullet \) for \( T \) or \( K \)) is given by \( b_\bullet \) while de-activation rate is \( \delta_\bullet \). Activation of immune cells mediated by antigenic stimulation is formulated by the Holling type II (or Michaelis-Menten) functional response with half saturation constant \( h_\bullet \). In the same manner, activation mediated by cytokine communication which does not depend on antigenic stimulation is formulated by the Holling type II functional response with maximum rate \( m_\bullet \) and half saturation constant \( a_\bullet \). Let \( p_\bullet \) denote the production rate of IFN-\( \gamma \) by immune subset \( \bullet \). Initial condition is given by

\[
C_H(0) \geq 0, \quad N_T(0) \geq 0, \quad C_L(0) \geq 0, \quad N_K(0) \geq 0.
\] (5)

3. Mathematical analysis and numerical computations

3.1 Cytokine mediated co-activation model

By ignoring the transition between tumor cells with high and low expressions of MHC class I (\( m_H = m_L = 0.0 \)), system (4) becomes
always exist. Equation (7) has a unique positive root if and only if

In summary,

However, from (10), we have

Existence of $E_1^1$ is determined by the following quadratic equation with respect to $I_γ$:

Equation (7) has a unique positive root if and only if

On the other hand, hereafter we will show that (7) never has two positive roots. In fact, if equation (7) has two positive roots, then the following conditions (9) and (10) should hold:

and

However, from (10), we have

In summary, $E_1^1$ exists if and only if (8) holds.

Note that $N_T^* = \frac{m_T}{h_T}(1 - \frac{C_H}{K_H})$ and $N_K = \frac{m_K}{h_K}(1 - \frac{C_L}{K_L})$. We have $C_H^* < K_H$ and $C_L^* < K_L$. Existence of equilibrium $E_1^1$ is determined by the following equations with respect to $C_H$ and $C_L$:

In summary, $E_1^1$ exists if and only if $C_H^* < K_H$, $C_L^* < K_L$ and (11) has at least one positive root. We skip for writing mathematical conditions for the local stability of equilibria.

3.2 Transition mediated switch model

In this subsection, we neglect co-activation between T and NK cells via cytokine mediated interaction ($m_T = m_K = 0$). Then we obtain the following subsystem:

$$
\begin{align*}
\frac{d}{dt}C_H(t) &= r_HC_H\left(1 - \frac{C_H(t)}{K_H}\right) - r_HC_H(t)N_T(t) + m_CL(t) - m_HC_H(t) \\
\frac{d}{dt}N_T(t) &= \frac{b_TC_H(t)N_T(t) - \delta_T N_T(t)}{h_T + C_H(t)N_T(t)} - \frac{m_T I_γ(t)}{\alpha_T + I_γ(t)} \\
\frac{d}{dt}C_L(t) &= r_LC_L\left(1 - \frac{C_L(t)}{K_L}\right) - r_LC_L(t)N_K(t) \\
\frac{d}{dt}N_K(t) &= \frac{b_KC_L(t)N_K(t) - \delta_K N_K(t) + m_K I_γ(t)}{\alpha_K + I_γ(t)} \\
I_γ(t) &= p_T N_T(t) + p_K N_K(t)
\end{align*}
$$

Equilibria of system (6) are given by $E_0^1 = (0, 0, 0, 0)$, $E_1^1 = (K_H, 0, 0, 0)$, $E_2^1 = (0, 0, K_L, 0)$, $E_3^1 = (K_H, 0, K_L, 0)$, $E_4^1 = (0, N_T^0, 0, N_K^0)$, and $E_5^1 = (C_H^*, N_T^*, C_L^*, N_K^*)$. Equilibria $E_0^1$, $E_1^1$, $E_2^1$ and $E_3^1$ always exist. Equilibrium $E_4^1$ indicates that no tumor cells are found, whereas $E_5^1$ represents tumor persistence under T and NK cell mediated immune responses. In the following, we focus on deriving existence conditions for the equilibria of system (6).

Existence of $E_1^1$ is determined by the following logistic equation with respect to $I_γ$:

$$
I_γ^2 + \left(a_K + a_T - \frac{p_T m_T}{\delta_T} - \frac{p_K m_K}{\delta_K}\right) I_γ + \left(a_K a_T - \frac{a_K p_T m_T}{\delta_T} - \frac{a_T p_K m_K}{\delta_K}\right) = 0.
$$

(7)

In summary, $E_1^1$ exists if and only if (8) holds.

$$
1 < \frac{p_T m_T}{\delta_T} + \frac{p_K m_K}{\delta_K a_K}.
$$

(8)

However, from (10), we have

Note that $N_T^* = \frac{m_T}{h_T}(1 - \frac{C_H}{K_H})$ and $N_K = \frac{m_K}{h_K}(1 - \frac{C_L}{K_L})$. We have $C_H^* < K_H$ and $C_L^* < K_L$. Existence of equilibrium $E_1^1$ is determined by the following equations with respect to $C_H$ and $C_L$:

$$
\begin{align*}
\frac{b_TC_H\frac{r_H}{h_T}(1 - \frac{C_H}{K_H})}{h_T + C_H\frac{r_H}{h_T}(1 - \frac{C_H}{K_H})} + \frac{m_T p_T \frac{r_H}{h_T}(1 - \frac{C_H}{K_H})}{h_T + C_H\frac{r_H}{h_T}(1 - \frac{C_H}{K_H})} - \delta_T &= 0, \\
\frac{b_KC_L\frac{r_L}{h_L}(1 - \frac{C_L}{K_L})}{h_T + C_L\frac{r_L}{h_L}(1 - \frac{C_L}{K_L})} + \frac{m_K p_T \frac{r_H}{h_T}(1 - \frac{C_H}{K_H})}{h_T + C_L\frac{r_L}{h_L}(1 - \frac{C_L}{K_L})} - \delta_K &= 0.
\end{align*}
$$

(11)

In summary, $E_1^1$ exists if and only if $C_H^* < K_H$, $C_L^* < K_L$ and (11) has at least one positive root. We skip for writing mathematical conditions for the local stability of equilibria.
Equilibria of system (12) are given by $E^*_0=(0,0,0,0)$, $E^*_1=(C_H,0,C_L,0)$, and $E^*_2=(C_H^*,N_T^*,C_L^*,N_K^*)$. At $E^*_2$,

$$C_L = \frac{r_H - m_H}{m_L} C_H - \frac{r_H}{m_L K_H} (C_H)^2, \quad C_H = \frac{r_L - m_L}{m_H} C_L - \frac{r_L}{m_H K_L} (C_L)^2,$$

(13)

The system of equations (13) has at least one positive root. Hence equilibria $E^*_0$ and $E^*_1$ always exist. Existence of equilibrium $E^*_2$ is determined by the following quadratic equation with respect to $C_H$:

$$r_H C_H^* + K_H(m_H - r_H)C_H + K_H\left(\frac{\gamma_H \delta_T h_T}{b_T - \delta_T} - \frac{m_L \delta_K h_K}{b_K - \delta_K}\right) = 0.$$

Equation (14) has a unique positive root if and only if

$$\frac{\gamma_H \delta_T h_T}{b_T - \delta_T} < \frac{m_L \delta_K h_K}{b_K - \delta_K}.$$

Equation (14) has two positive roots if and only if

$$\frac{\gamma_H \delta_T h_T}{b_T - \delta_T} > \frac{m_L \delta_K h_K}{b_K - \delta_K}, \quad \Delta > 0,$$

where $C_H^* = \frac{-K_H(m_H - r_H)\pm\sqrt{\Delta}}{2 \gamma_L}, N_T^* = \frac{-K_H(m_H - r_H)\delta_T}{b_T - \delta_T}, C_L^* = \frac{\delta_K h_K}{b_K - \delta_K}, N_K^* = \frac{r_L}{\gamma_L} \left(1 - \frac{C_L^*}{K_L}\right) + \frac{m_H C_H^* - m_L C_L^*}{\gamma_L C_L^*}, \Delta = K_H^2(m_H - r_H)^2 - 4 r_H \left(\frac{K_H \gamma_H \delta_T h_T}{b_T - \delta_T} - \frac{K_H m_L \delta_K h_K}{b_K - \delta_K}\right).$ 

Hence the condition for the existence of one positive equilibrium is given by

$$\delta_T < b_T, \quad \delta_K < b_K, \quad \frac{\gamma_H \delta_T h_T}{b_T - \delta_T} < \frac{m_L \delta_K h_K}{b_K - \delta_K}.$$

(15)

(16)

On the other hand, the condition for the existence of two positive equilibria is given by

$$\delta_T < b_T, \quad \delta_K < b_K, \quad \frac{\gamma_H \delta_T h_T}{b_T - \delta_T} > \frac{m_L \delta_K h_K}{b_K - \delta_K}, \quad K_H > \frac{4 r_H}{(m_H - r_K)^2} \left(\frac{\gamma_H \delta_T h_T}{b_T - \delta_T} - \frac{m_L \delta_K h_K}{b_K - \delta_K}\right).$$

(17)

(18)

Although mathematical conditions for local stability of equilibria might be useful to understand dynamical behavior exhibited by system (4), we skip to write it in this paper.

4. Immune escape via down-regulation of MHC class I expression

4.1 Qualitative classification of dynamics

To investigate whether down-regulation of MHC class I can be advantageous for tumor cells to escape from immunosurveillance, extensive numerical simulations are performed. Note that parameters $m_H$ and $m_L$ represent transition rates between high and low MHC class I expression. Hence it is reasonable to vary these two parameters to observe whether tumor cells can escape from immunosurveillance. We implemented numerical computation by statistical software R [7]. The default parameter values are given by

$$r_H = r_L = 3.0, \quad K_H = K_L = 10.0, \quad \gamma_H = 2.0, \quad \gamma_L = 1.0, \quad m_H = 0.1, \quad m_L = 0.1, \quad b_T = b_K = 0.5, \quad h_T = h_K = 10.0, \quad \delta_T = \delta_K = 0.1, \quad m_T = m_K = 0.01, \quad a_T = a_K = 10.0, \quad \rho_T = \rho_K = 0.0, \quad \rho_K = 10.0, \quad C_H(0) = C_L(0) = 10.0, \quad N_T(0) = N_K(0) = 0.01.$$

(19)

Although numerical values in (19) are chosen arbitrarily, qualitative behaviors of dynamics exhibited by (4) are well captured with parameter (19) with a few changes (see Figs. 1–3). Note that the same numerical value is assigned to a pair of equivalent parameters such as $r_H$ and $r_L$ to impose that there is no significant effect of MHC class I expression in terms of growth and death of tumor cells.

The left panel of Fig. 1 shows the trajectories of system (4) with parameter (19). Both tumor cells with high and low MHC class I expression are moderately suppressed by T cells and NK cells.
Fig. 1. [Successful tumor suppression] Population dynamics of system (4) with parameter (19). Left: Moderate control of tumor cells. Right: Complete control of high MHC class I expression tumor cells ($\gamma_H = 0.2$). Purple solid line: $T$ cells, Green solid line: $NK$ cells, Red dashed line: MHC class I high expression tumor cells, Green dashed line: MHC class I low expression tumor cells.

Fig. 2. [Failure of immune activation] Population dynamics of system (4) with parameter (19). Left: Failure of NK and T cell activation ($r_H = r_L = 0.03$). Right: Failure of T cell activation ($m_H = 0.0$). The same colors and lines types to Fig. 1 are used.

Fig. 3. [Recovery of successful tumor suppression] Population dynamics of system (4) with parameter (19) with $m_L = 0.0$ (continued from Fig. 2). Recovery of sustained T cell response via increase of the activation rate (Left $b_T = 1.0$) or decrease of deactivation rate (Right $\delta_T = 0.05$).
right panel of Fig. 1 is an example of complete control of tumor cells with high MHC class I expression via sufficient activation of T cell responses. This type of dynamics appears when tumor elimination rate is slow \((\gamma_H = 0.2)\), implying that low killing rate of tumor cells may lead to supplying enough amount of antigenic stimuli which in turn induces sufficient activation of T cells.

Two panels of Fig. 2 show examples for failure of immune activation. This type of dynamics occurs when growth rate of tumor cells is slow \((r_L = r_H = 0.03)\), implying that slow recovery of the tumor population will lead to insufficient amount of antigenic stimuli for immune activation. The right panel of Fig. 2 shows the disappearance of tumor cells via down-regulation of MHC class I expression. To confirm this speculation, the right panel of Fig. 2 suggests that immuno-escape of tumor cells via down-regulation of MHC class I expression might be selected as an adaptive change of tumor cells. In conclusion, efficient T cell mediated killing under the support of IFN-\(\gamma\) production by NK cells shows disappearance of tumor cells, while efficient NK cell killing under the support of IFN-\(\gamma\) production by T cells shows moderate phenotypic change of tumor cells. In both cases, down-regulation of MHC class I expression is advantageous for tumor growth.

Finally, to investigate whether T cell response can be recovered from the situation depicted in the right panel of Figure (2) \((m_H = 0.0)\), activation rate \(b_T\) or deactivation rate \(\delta_T\) of tumor cells are varied from the original parameter value \((b_T = 0.5\) and \(\delta_T = 0.1\)). The left and right panels of Fig. 3 represent the increase of activation rate \((b_T = 1.0)\) or decrease of deactivation rate \((\delta_T = 0.05)\), respectively. In both cases, recovery of T cell response is observed. This implies that there exists a possibility that T cell responses are still activated to suppress tumor cells even though transition rate of MHC class I expression is biased toward decreasing its expression.

### 4.2 Adaptive change of MHC class I expression

The right panel of Fig. 2 suggests that immuno-escape of tumor cells via down-regulation of MHC class I expression might be selected as an adaptive change of tumor cells. To confirm this speculation, we perform simple stochastic computations to imitate adaptive change of tumor cells in terms of MHC class I expression. Two parameters \(m_H\) and \(m_L\) are therefore chosen as the control parameters. The total tumor density is used as a measure of phenotypic fitness. In other words, we assume that tumor cells are advantageous if the total density becomes higher after a walk on the \((m_H, m_L)\)-plane.

The simulation scheme of the adaptive change on the \((m_H, m_L)\)-plane consists of the following rules: Firstly, an initial point is placed at \((m_H, m_L) = (0.7, 0.7)\). Secondary, a neighbor grid of the initial point is randomly chosen, and the total tumor density at time \(t = 1000\) is calculated. Let \(C_1\) and \(C_2\) denote the total tumor density at the current grid 1 and candidate grid 2, respectively. If the candidate grid has a higher density, that is, \(C_2 > C_1\), then the walk to the candidate grid is accepted with probability 1. On the other hand, the walk is accepted with probability \(C_1/C_2\) if the candidate grid has a lower density than that of the current grid.

The left panel of Fig. 4 represents a stochastic sample path of phenotypic change with the heatmap of total tumor density \((40 \times 40\) grids\). The heatmap exhibits the existence of a boundary which segregates the entire space into two regions: high and low tumor density regions. On the boundary of two regions, sudden disappearance of T cell response occurs. Moreover, we observe that disappearance of T cell response is like to occur for higher \(m_H\) and lower \(m_L\) values. This implies that the tumor population would prefer to change its phenotype toward down-regulating MHC class I expression. Note that the resulting sample path drawn as a trajectory is not entirely random. Movement toward reducing \(m_L\) is preferred. This example suggests that down-regulation of MHC class I expression is advantageous for tumor cells.

We examine whether down-regulation of MHC class I is advantageous even though the killing rate of NK cells is more potent than that of T cells. The right panel of Fig. 4 is a stochastic sample path with the heatmap of the total tumor density generated by numerical simulation with parameter (19) with \(\gamma_H = 1.0\), \(\gamma_L = 2.0\), \(p_L = 1000\) and \(p_K = 0\). Although disappearance of T cell response is not observed, tumor cells prefer to down-regulate MHC class I expression. In conclusion, efficient T cell mediated killing under the support of IFN-\(\gamma\) production by NK cells shows disappearance of T cells, while efficient NK cell killing under the support of IFN-\(\gamma\) production by T cells shows moderate phenotypic change of tumor cells. In both cases, down-regulation of MHC class I expression is advantageous for tumor growth.
5. Conclusions

We constructed a mathematical model which describes interactions among tumor and immune cells. Two distinct types of tumor cells were considered in terms of expression level of MHC class I on the surface of tumor cells. For simplicity, we considered only two categories whether the expression level of MHC class I is high or low. Depending on the expression level, we assumed that either one of distinct immune subsets is capable of eliminating tumor cells. In this paper, we assumed that T cells and NK cells exclusively kill high and low MHC class I expressing tumor cells, respectively. Cytokine mediated interaction among these two immune subsets was incorporated. Moreover, transition between high and low MHC class I expressing tumor cells was considered to investigate how adaptive change of tumor cells can lead to escape from immunosurveillance.

In sections 3, we found that system (4) exhibits a variety of qualitative behaviors (Figs. 1–3). Note that bistability of T cell response whether it becomes anergic (no T cell response) or being activated can naturally occur (see existence of multiple positive equilibria in section 3). Under this property, T cells can diminish owing to insufficient level of activation signals. Interestingly, this property is exploited by tumor cells with high expression of MHC class I to escape from T cell mediated immune response by down-regulation of MHC class I expression (the right panel of Fig. 4). Among several possible interventions, in this paper, we showed that reducing the deactivation rate of T cells can restore sustained immune response even though tumor cells have escaped T cell mediated immunity by down-regulating the expression of MHC class I (the right panel of Fig. 3). Under the setting of our mathematical model, advantage of therapeutic intervention to block deactivation of T cells via apoptosis is effective. This intervention has demonstrated effective known as PD-L1 blockage.

We can also provide some biological imprecations derived from mathematical analysis and numerical computations. Since failure of the immune response is also implicated when replication rate of tumor cells is small (the left panel of Fig. 2), these therapeutic interventions might be effective only for actively proliferating tumor cells. Although careful consideration is required, a good strategy for tumor cells to escape from the immune response is a combination of slow replication with down-regulation of MHC class I expression. Further mathematical modeling and simulations could provide a useful guide to how to prevent tumor immune-escape.
MHC class I is given by

The subsystem of (6) consisting of NK cell mediated killing of tumor cells with low expression of A.2 NK cell mediated tumor killing model

In [5], we considered the following model:

We analyze a subsystem of the main model (4) which has already been studied in [5] (see also [6]).

A. Summary of previous results

Appendix

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A.1 T cell mediated tumor killing model

We analyze a subsystem of the main model (4) which has already been studied in [5] (see also [6]). In [5], we considered the following model:

Equilibria of system (A-1) are explicitly given by

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Mathematical conditions that support the existence of positive equilibrium \( E_2^2 \) is given by

Note that \( E_3^2 = (K_H, 0) \) is always locally asymptotically stable. To investigate the stability of \( E_2^2 \), we derive the characteristic equation which is defined for the linearized system of system (A-1) around positive equilibrium \( E_2^2 \). Mathematical condition for the local stability is given by

\[ \frac{K_H \delta_T (b_T - \delta_T)}{b_T r_H} < C_H^* < \frac{K_H}{2}. \]

A.2 NK cell mediated tumor killing model

The subsystem of (6) consisting of NK cell mediated killing of tumor cells with low expression of MHC class I is given by

Equilibria of system (A-4) are \( E_0^4 = (0, 0) \), \( E_1^4 = (K_L, 0) \), and \( E_2^4 = (C_L^*, N_K^*) \) = \( \left( \frac{\delta_L h_L}{K_L}, \frac{\gamma_L}{K_L}(1 - \frac{\delta_L h_L}{K_L}) \right) \). The mathematical condition that ensures the existence of positive equilibrium \( E_2^4 = (C_L^*, N_K^*) \) is explicitly given by

We can show that if (A-5) holds, then equilibrium \( E_1^4 \) is unstable while \( E_2^4 \) is locally stable.

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