A mathematical model of tumor cell evolution and its immune escape

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Abstract

We constructed a mathematical model of the evolution of tumor cells through interactions with immune cells in the context of tumorigenesis in human body. This model considers the killing of tumor cells mediated by NK cells and activated CD8+ T cells and provides the interaction between two immune cells and immature tumor cells in vivo with their three evolutionary forms in the form of ordinary differential equations. Through this model, we depicted the changes of tumor cells and immune cells of the body over time under different immune conditions. In addition, we also analyzed the influence of various parameters on the model deduction results and gave corresponding biological explanations. To a certain extent, this model has made a mathematical explanation and prediction for the immune escape and evolution of tumor cells, which enables us to better understand the mechanism of this process.

Keywords: T cells, NK cells, tumor cells, immune escape, mathematical model

1 Introduction

Cancer is one of the most threatening diseases that human beings have not been able to completely overcome, and its occurrence and evolution in the body is a problem that people have been paying close attention to. However, the immune system could clear cancer cells before they cause harm to the body, with a function known as immune surveillance. Immune surveillance can inhibit tumor development, but some tumors can still develop under normal immune surveillance. It means that some tumor cells could escape during the interaction with immune cells and rapidly evolve to be immune to the attack by immune cells for a long time. Many studies have shown that tumor immune escape mechanism is the main obstacle affecting tumor treatment. (Yasumoto et al., 2009,Méndez et al., 2007 , Raval et al., 2014)

In the body, NK cells and CD8+ T cells can directly kill tumor cells. As an innate immune cell, NK cells can kill tumor cells by expressing Fas ligand (FasL), TNF-related apoptosis-inducing ligand (TRAIL), and secreting perforin. NK cells can also lyse tumor cells through antibody-dependent cytotoxicity (ADCC), which includes antibody binding to the FcγRIIIa receptor (CD16) on NK cells (Seidel et al., 2013, DiLillo and Ravetch, 2015). Activated CD8+ T cells (CTL) can kill tumor cells by means of interacting with death cell ligands or secreting perforin and granzyme. Considering the crucial functions of NK cells and CTL cells in tumor immune surveillance, we mainly focused on the functions of NK cells and CTL cells in the process of build this model.

According to relevant studies, tumor cells that survive the interaction with immune cells will undergo certain changes, such as down-regulation of pro-apoptotic receptors and up-regulation of anti-apoptotic receptors (Igney and Krammer, 2002, Classen et al. , 2012), and the evolution of cells occurs in this process. The evolutionary outcome depends on the type of immune cells that interact with the tumor cells. If the tumor cell can survive after interacting with both NK cells and CTL cells, it will acquire complete or maximal resistance to such immune cells (Al-Tameemi et al., 2012). Therefore, tumor cells will change dynamically with the interaction with immune cells.

Here we use differential equations to demonstrate the fluctuation of the tumor cells and immune cells in the body. We first summarized the previous view about the evolution of the tumor cells and build a model on these hypotheses. The model suggests that

2 Proposition of the initial model

There has been some work using modeling approaches to study the interaction of tumor cells with immune cells (Adam, 1993, de Pillis et al., 2005, Kolev, 2003, Mallet and de Pillis, 2006, Banerjee and Sarkar, 2008, Kirschner and Panetta, 1998). We briefly summarize the specific assumptions, content and analysis of the models involved in these literatures, as follows.

2.1 Model assumptions

a. All tumors are immunogenic to trigger an immune response and grow logistically in the absence of an immune response. (de Pillis and Radunskaya, 2003)

b. Tumor cells' resistance to NK-mediated killing increases after brief exposure to NK cells if the tumor has escaped NK cell surveillance, which also applies to CTL immune surveillance.(Classen et al., 2012, Bubenik, 2005, Bubenik, 2004, Haworth et al., 2015, Siddle et al., 2013, Teicher, 2007)

c. "Wild-type" tumor cells that have escaped NK-mediated killing have little or no probability of being identified and then complexed with NK cells (implicit intercalation parameters). The same applies to "wild-type" tumor cells that have escaped CTL-mediated killing. (Al-Tameemi et al., 2012)

d. NK cells are always present in the host immune system as part of the natural immune system, but cytotoxic T lymphocytes are only present in the presence of tumors.(de Pillis et al., 2006, de Pillis and Radunskaya, 2003, de Pillis and Radunskaya, 2003)

e. The killing effect of NK cells and CTLs is significantly weakened after their first encounter with tumor cells but failure to kill (de Pillis and Radunskaya, 2003, Kuznetsov, 1997)

f. Both NK cells and CTLs can kill tumor cells alone.

In fact, the existing view holds that if immune cells fail to kill the first time they meet with tumor cells, the immune cells will have a weaker killing effect and more likely to undergo apoptosis. The main reason is that the immune cells are activated to increase in the expression of FasL, the expression of Fas also increased, and after the tumor cells escaped successfully, the expression of FasL was down-regulated but the

expression of Fas was increased. Therefore, in the event that immune cells fail to kill tumor cells, it cannot be ignored that immune cells are subject to Fas/FasL binding to mediate apoptosis (T.J. Stewart, 2008, F.H.Igney, 2002, M.Ahmad,2004, L.G.de Pillis , 2006). Therefore, it can be considered that when immune cells fail to kill tumor cells, immune cells will enter an inactive state or undergo apoptosis.

2.2 Building the model

The Fas/FasL binding-mediated tumor killing model illustrates the mechanism by which NK cells and T cells play a role in immune surveillance. FasL is a 37-40kDa type II membrane protein. When FasL on immune cells recognizes and binds to Fas on tumor cells, the complex formed will transmit apoptosis signals to tumor cells, thereby triggering apoptosis. (Fig 1.A)

This complex-mediated killing is widespread in immune cell-mediated immune surveillance. Therefore, in this model, we believe that immune cells mediate tumor cell killing by complex formation. In addition, during the treatment, the fraction of immune cells and tumor cells that formed the complex was removed from the total number of both, indicating that the complex was formed. As an intermediate state that is not stable enough, the complex will disintegrate after a brief period of time. The disintegration of the complex here may bring the following two results.

One is the apoptosis of tumor cells, and the immune cells that successfully kill the immune cells detach from the complex and re-enter the total number of immune

cells ready to function again; the other is that the tumor cells escape and evolve, and the immune cells that fail to kill enter a state of being inhibited. This will cause the immune cells used to form the complex to be unable to return to the total number of immune cells with killing activity. On the contrary, the tumor cell will be immune to this immune cell and evolve.

We believe that tumors evolve in three stages, cells that are naïve, cells that are resistant to one type of immune cell, and cells that are resistant to both types of immune cells (NK and CD8+ T cell). The specific evolution process is as follows: First, naïve tumor cells are naturally generated. When the tumor cells interact with T cells in the immune system and escape an immune surveillance, they will acquire resistance to T cells. Tumor T cells interact with NK cells and escape immune surveillance, and the tumor cells will again acquire resistance to NK. The same is true for tumors that interact with NK cells first and then T cells.

According to the previous discussion, the process of action of tumor cells and immune cells has two consequences: immune cells kill tumor cells or tumor cells escape immune surveillance, acquire a response to such immune cells and cause the inactivation of immune cells. Therefore, the interaction can be simplified as the process of forming a complex (denoted as C) and then dissociating from the complex with a certain probability to generate immune cells or "evolved" tumor cells.

Then we suggest the following differential equations to demonstrate the model (T

represents tumor cells, N represents NK cells, L represents killer T cells CTL, T represents four types of tumor cells, C represents tumor cells and immune cells form a complex body)

$$\frac{dN}{dt} = \underbrace{s}_{\text{supply}} - \underbrace{\mu_1 N}_{\text{natural death}} - \underbrace{\alpha_N^+ NT^0 + p_N \alpha_N^- C_N}_{\text{local kinetics}} - \underbrace{\alpha_L^+ NT_L^1 + \pi_N \alpha_L^- C_{NL}^N}_{\text{local kinetics}} \quad (1)$$

$$\frac{dL}{dt} = \underbrace{f(C,T)}_{\text{recruitment}} - \underbrace{\mu_2 L}_{\text{natural death}} - \underbrace{\beta_L^+ LT^0 + q_L \beta_L^- C_L}_{\text{local kinetics}} - \underbrace{\beta_N^+ LT_N^1 + \epsilon_L \beta_N^- C_{NL}^L}_{\text{local kinetics}} \quad (2)$$

$$\frac{dT^0}{dt} = \underbrace{aT^0(1 - bT_{total})}_{\text{logistic growth}} - \underbrace{\alpha_N^+ NT^0}_{\text{local kinetics,with N}} - \underbrace{\beta_L^+ LT^0}_{\text{local kinetics,with L}} \quad (3)$$

$$\frac{dT_N^1}{dt} = \underbrace{aT_N^1(1 - bT_{total})}_{\text{logistic growth}} + \underbrace{jp_T \alpha_N^- C_N}_{\text{escaped,from N}} - \underbrace{\beta_N^+ LT_N^1}_{\text{local kinetics,with L}} \quad (4)$$

$$\frac{dT_L^1}{dt} = \underbrace{aT_L^1(1 - bT_{total})}_{\text{logistic growth}} + \underbrace{jq_T \beta_L^- C_L}_{\text{escaped,from L}} - \underbrace{\alpha_L^+ NT_L^1}_{\text{local kinetics,with N}} \quad (5)$$

$$\frac{dT_{NL}^2}{dt} = \underbrace{aT_{NL}^2(1 - bT_{total})}_{\text{logistic growth}} + \underbrace{j\epsilon_T \beta_N^- C_{NL}^L}_{\text{escaped,from L}} + \underbrace{j\pi_T \alpha_L^- C_{NL}^N}_{\text{escaped,from N}} \quad (6)$$

$$f(C,T) = \underbrace{\frac{r_1 C_L}{g + T_0}}_{\text{Proliferation of CTLs in response to the naive tumors}} + \underbrace{\frac{r_2 C_{NL}^L}{g + T_N^1}}_{\text{Proliferation of CTLs in response to the wild-type tumors}} \quad (7)$$

The differential equations corresponding to several complexes are as follows:

$$\frac{dC_N}{dt} = \underbrace{\alpha_N^+ NT^0}_{\substack{\text{Complex formation} \\ \text{between N \& T0}}} - \underbrace{\alpha_N^- C_N}_{\substack{\text{Complex detachment} \\ \text{between N \&T0}}} \quad (8)$$

$$\frac{dC_L}{dt} = \underbrace{\beta_L^+ LT^0}_{\substack{\text{Complex formation} \\ \text{between L \& T0}}} - \underbrace{\beta_L^- C_L}_{\substack{\text{Complex detachment} \\ \text{between L \& T0}}} \quad (9)$$

$$\frac{dC_{NL}^N}{dt} = \underbrace{\alpha_L^+ NT_L^1}_{\substack{\text{Complex formation} \\ \text{between N and T^1\_L}}} - \underbrace{\alpha_L^- C_{NL}^N}_{\substack{\text{Complex detachment} \\ \text{between N \& T^1\_L}}} \quad (10)$$

$$\frac{dC_{NL}^L}{dt} = \underbrace{\beta_N^+ LT_N^1}_{\substack{\text{Complex formation} \\ \text{between L \& T^1\_N}}} - \underbrace{\beta_N^- C_{NL}^L}_{\substack{\text{Complex detachment} \\ \text{between N \& T^1\_N}}} \quad (11)$$

Items have been briefly explained in the above formulas, and only some items with

more complex biological meanings are further explained here. First, for the two terms of (1) and (2) interacting with tumor cells, according to the previously described Fas/FasL complex-mediated tumor cell apoptosis mechanism, the two types of NK cells and CTL cells Immune cells need to form complexes to kill target cells. Therefore, the treatment method adopted here is to remove the part of immune cells that form complexes from the total immune cells, and then according to the two types of complex-induced killing. The results set two flow directions of the complex: one is to kill the successful immune cells from the complex and re-enter the total number of immune cells ready to play again; the other is to kill the failed immune cells into a suppressed state, which will lead to this part. The immune cells used to form the complex cannot return to the equation (1),(2), and the differential equation shows that it cannot return to the original differential equation. In addition, for tumor cells, it is believed that they grow in a logistical pattern undisturbed, while the part of the tumor that interacts with immune cells is either killed or evolved. For both possibilities, the tumor cells that interact to form a complex will no longer return to the original collection of tumor cells, so the differential equation can be expressed as (3), (4), (5), (6).

In addition, although NK cells influx at a constant rate during tumor immunity, CTL cells (activated T cells) need to be recruited, and the recruitment equation adopted here is (7).

The above system of differential equations can be represented by an interaction network as Fig. 1 B.

2.3 Model Analysis

We reproduced the interaction network and obtained the fitting analysis results of the interaction network as shown in Fig. 1 C, Fig. 1 D.

As far as the fitting results are concerned, there are many unreasonable points. For example, the four types of tumor cells almost reach their own environmental capacity at a speed that is not affected by any influence, and the role of the immune system can hardly be reflected in this balance process, and the interaction between tumor cells cannot be reflected. This model has a poor ability to reflect the dynamic action network. Therefore, we try to improve and optimize this model from the perspective of biological principles.

3 Model optimization and improvement

First, we believe that although tumor cells evolve correspondingly after each exposure to immune cells, we do not believe that tumor cells can completely escape from immune cells after a single victory in the fight against immune cells. Therefore, we consider the introduction of multiple evolutions of tumor cells, that is, we think that after surviving once, the tumor may not necessarily acquire a complete escape ability, and it will re-enter the tumor cell set recognized by such immune cells with the probability of evolution factor j Waiting for the next recognition.

Second, we believe that interactions between multiple tumor cells cannot be ignored. The growth environment of most tumor cells is intersecting, and although tumor cells can release substances such as vascular endothelial growth factor to promote the delivery of nutrients to the tumor cell range, competition between these tumor cells cannot be avoided. Therefore, we consider that the environmental capacity corresponding to the logistic growth models of the four tumor cells is shared, that is, there is a competitive relationship among tumor cells at all evolution stages.

Then, we analyzed the influx of NK cells. Equation (1) did not reflect the changes in the interaction between NK cells and tumor cells in the process. As a result of continuous influx of NK cells and the subsequent inhibition by tumor cells, inactivated immune cells will accumulate in the peripheral area of the tumor, which, to a certain extent, assists the formation of the privileged zone around the tumor. In the mathematical modeling of this point, we assumed that the effect of this effect is like the shielding effect of the accumulation of inactivated NK cells on the recruitment and influx of immune cells, so the strength of this effect is obviously related to the number of inactivated immune cells. In terms of the choice of the mathematical relationship between the effect strength and the number of inactivated cells, we have selected a variety of possible shielding effect mathematical models to try. On the premise of combining biological significance, we found that the use of shielding factors using exponential decay model can well reflect the relationship between the influx rate of NK cells and the number of

inactivated tumor cells.

Finally, we believe that it is unreasonable to simulate the activation and recruitment of CTL cells by the Mie equation. On the contrary, we believe that both NK cells and CTL cells can contribute to the CTL cell recruitment when they are interacting with tumor cells. Moreover, considering that the recruitment rate should be positively correlated with the number of immune cells involved in the immune response and tumor cells, we modified the recruitment process in the form of a secondary response.

The modified differential equation system is as follows:

$$\frac{dN}{dt} = \underbrace{se^{-gI}}_{\text{supply}} - \underbrace{\mu_1 N}_{\text{natural death}} - \underbrace{\alpha_N^+ NT^0 + p_N \alpha_N^- C_N}_{\text{local kinetics}} - \underbrace{\alpha_L^+ NT_L^1 + \pi_N \alpha_L^- C_{NL}^N}_{\text{local kinetics}} \tag{1}$$

$$\frac{dL}{dt} = \underbrace{f(C,T)}_{\text{recruitment}} - \underbrace{\mu_2 L}_{\text{natural death}} - \underbrace{\beta_L^+ LT^0 + q_L \beta_L^- C_L}_{\text{local kinetics}} - \underbrace{\beta_N^+ LT_N^1 + \epsilon_L \beta_N^- C_{NL}^L}_{\text{local kinetics}} \tag{2}$$

$$\frac{dT^0}{dt} = \underbrace{aT^0(1 - bT_{total})}_{\text{logistic growth}} - \underbrace{\alpha_N^+ NT^0}_{\text{local kinetics,with N}} - \underbrace{\beta_L^+ LT^0}_{\text{local kinetics,with L}} + (1-j)p_T \alpha_N^- C_N + (1-j)q_T \beta_L^- C_L \tag{3}$$

$$\frac{dT_N^1}{dt} = \underbrace{aT_N^1(1 - bT_{total})}_{\text{logistic growth}} + \underbrace{jp_T \alpha_N^- C_N}_{\text{escaped,from N}} - \underbrace{\beta_N^+ LT_N^1}_{\text{local kinetics,with L}} + (1-j)\epsilon_T \beta_N^- C_{NL}^L \tag{4}$$

$$\frac{dT_L^1}{dt} = \underbrace{aT_L^1(1 - bT_{total})}_{\text{logistic growth}} + \underbrace{jq_T \beta_L^- C_L}_{\text{escaped,from L}} - \underbrace{\alpha_L^+ NT_L^1}_{\text{local kinetics,with N}} + (1-j)\pi_T \alpha_L^- C_{NL}^N \tag{5}$$

$$\frac{dT_{NL}^2}{dt} = \underbrace{aT_{NL}^2(1 - bT_{total})}_{\text{logistic growth}} + \underbrace{j\epsilon_T \beta_N^- C_{NL}^L}_{\text{escaped,from L}} + \underbrace{j\pi_T \alpha_L^- C_{NL}^N}_{\text{escaped,from N}} \tag{6}$$

$$f(C,T) = \underbrace{r_1 \beta_L^+ LT^0 + r_3 NT^0}_{\substack{\text{Proliferation of CTLs in response to} \\ \text{the naive tumors}}} + \underbrace{r_2 \beta_L T_N^1 + r_4 NT_L^1}_{\substack{\text{Proliferation of CTLs in response to} \\ \text{the wild-type tumors}}} \tag{7}$$

$$\frac{dC_N}{dt} = \underbrace{\alpha_N^+ NT^0}_{\substack{\text{Complex formation} \\ \text{between N \& T0}}} - \underbrace{\alpha_N^- C_N}_{\substack{\text{Complex detachment} \\ \text{between N \&T0}}} \tag{8}$$

$$\frac{dC_L}{dt} = \underbrace{\beta_L^+ LT^0}_{\substack{\text{Complex formation} \\ \text{between L \& T\^0}}} - \underbrace{\beta_L^- C_L}_{\substack{\text{Complex detachment} \\ \text{between L \& T\^0}}} \tag{9}$$

$$\frac{dC_{NL}^{N}}{dt} = \underbrace{\alpha_L^+ NT_L^1}_{\substack{\text{Complex formation} \\ \text{between N \& T^1\_L}}} - \underbrace{\alpha_L^- C_{NL}^N}_{\substack{\text{Complex detachment} \\ \text{between N \& T^1\_L}}} \tag{10}$$

$$\frac{dC_{NL}^{L}}{dt} = \underbrace{\beta_N^+ LT_N^1}_{\substack{\text{Complex formation} \\ \text{between L \& T^1\_N}}} - \underbrace{\beta_N^- C_{NL}^L}_{\substack{\text{Complex detachment} \\ \text{between N \& T^1\_N}}} \tag{11}$$

$$\frac{dI}{dt} = (1-p_N)\alpha_N^- C_N + (1-\pi_N)\alpha_L^- C_{NL}^N + (1-q_L)\beta_L^- C_L + (1-\epsilon_L)\beta_N^- C_{NL}^L \tag{12}$$

We demonstrate the modified tumor cell-immune system interaction network as Fig. 2 A.

3.2 Prediction results

The size of the parameters involved in the above action network is shown in Table 1 below:

Table 1. The origin and value of parameters

Parameters	Value	Reference	Parameters	Value	Reference
α_N^+	1e-7	6,23	π_N	0.80	Estimate
α_N^-	24	6	π_T	0.18	Estimate
α_L^+	1.2e-7	6,23	ϵ_L	0.85	Estimate
α_L^-	24	6	ϵ_T	0.13	Estimate
β_N^+	1.3e-7	6,23	s	32000	24
β_N^-	24	6	μ_1	4.12e-2	2
β_L^+	1.3e-7	6,23	μ_2	2.0e-2	2
β_L^-	24	6,23	a	0.5822	14
p_N	0.94	Estimate	b	2.33e-6	14
p_T	0.05	Estimate	r_1	0.2988e-8	6,23
q_L	0.94	Estimate	r_2	0.2755e-8	6,23
q_T	0.05	Estimate	r_3	4.9077e-10	23
k_{self}	1.3e-14	23	r_4	5.8467e-11	23
j	0.85~1	Estimate	g	1.43e-5	Esitimate

Further, by giving the initial value and then performing numerical integration, we

can obtain the following prediction results (Fig. 2 B-C)

From the above results, we can see that T_N and T_{NL} tumor cells account for most tumor cells in the later stage of evolution, and NK cells account for a very high proportion of immune cells in the population. We believe that this situation is reasonable, and it can be said that T cell exhaustion in the later stage of tumor immunity is almost inevitable. Although the number of NK cells is high, tumor cell proliferation cannot be inhibited because the composition of tumor cells is mostly T_N and T_{NL}, which have a strong escape ability to kill NK cells. We believe that to a certain extent, this explains the fact that although immune cells still exist, they cannot effectively kill some kinds of tumors.

4 Parameter analysis

One of the methods to demonstrate the effects of parameters in the model is sensitivity analysis. Sensitivity analysis refers to judging the sensitivity of the objective function to the parameters by analyzing the variation range of the objective function when a limited number of parameters change. (Fig 3)

From the results of the sensitivity analysis above, the degree of influence of various parameters on diverse types of cells is not consistent. But among them, the more representative ones are the parameter b, μ_1 and the parameter p_N. Therefore, to draw further conclusions, we first analyzed the changes in the number of NK cells over time when the two parameters of b and p_N were changed at the same time

and plotted them into a three-dimensional dynamic graph (see appendix). It can be seen from this dynamic graph that the number of NK cells increases with the increase of the b value in the late stage of tumor growth. This reflects the inhibitory effect of tumor cells on NK cell activity. The inhibitory ability of NK cells is strong, and the number of active NK cells is small. Secondly, we will also use the time when various cells reach equilibrium from the initial value as an index reflecting the influence of the parameters to draw the equilibrium time p_N and μ_1 changes and also draw a dynamic graph (see appendix), here we compare by comparing The time when different tumor cells start to metastasize, it is believed that this equilibrium time is related to the time when local tumor cells metastasize to a certain extent, and it can be found from the moving image that this time has a very close relationship with these two parameters. It can be used as a marker of starting point of cancer metastasis.

5 Discussion

We mainly discuss the mathematical model of the dynamic interaction network between tumor cells and the immune system and give the corresponding prediction results and analysis. In this process, starting from the existing research results, we first summed up the previous assumptions and proposed an initial model. After finding that the prediction results were not ideal, we made bold improvements to the model combined with the biological background. During the process, we proposed Many pioneering improvements have been made.

As for the future development of the model, we can try to build a multi-stable model. From the perspective of the cancer occurrence process of the organism, given the same initial conditions, it is possible to achieve two steady states of tumor occurrence and non-occurrence. The situation will be more realistic to some extent. In addition, the recruitment equation, the shielding equation of NK cell influx by inactivated immune cells, and the values of each parameter can be made more accurate.

Despite there are many aspects not so satisfying with this model, the reference significance of the prediction results of this model is still meaningful. First, this model gives possible reasons why CAR-NK therapy is less effective than CAR-T in some types of tumors. Secondly, this model illustrates that NK cells may play a significant role beyond expectations in the process of tumor immunity, providing a major research direction for further tumor immunotherapy. Finally, we also derived possible major factors that influence tumor metastasis. A major factor that threatens the life of tumor patients is the metastasis of tumor cells. How to delay the metastasis of tumor cells is of great significance to prolong the life of tumor patients. Moreover, the model suggests a time point that can be used as a direction.

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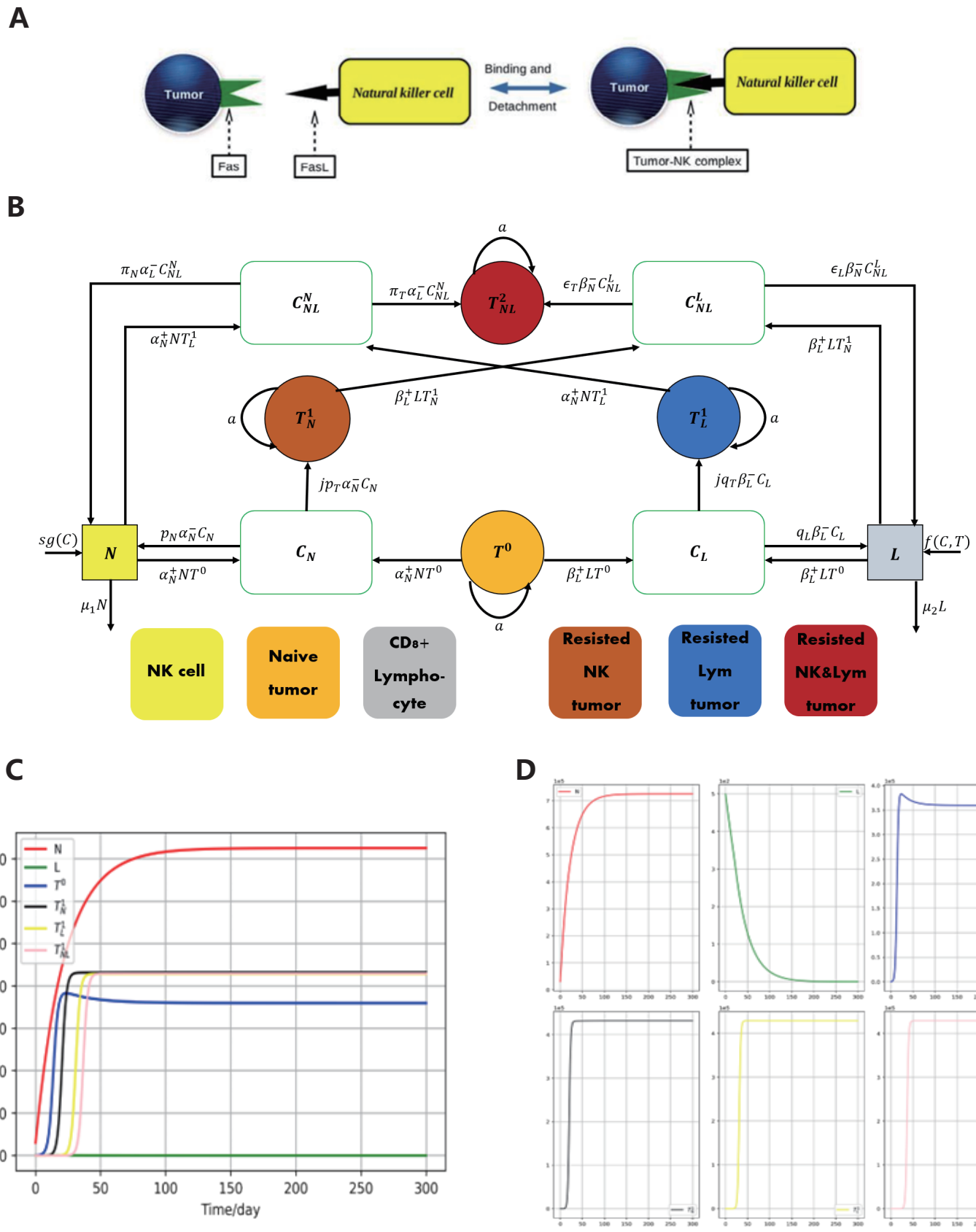

Figure 1. The creation and prediction of the orginal model

(A) The Fas-FasL interaction between tumor and immune cell.
(B) Original model of tumor evolution based on previous research.
(C) Prediction of immune and tumor cell number using the original model.
(D) The predicted number of immune and tumor cell number. Plotted separately.

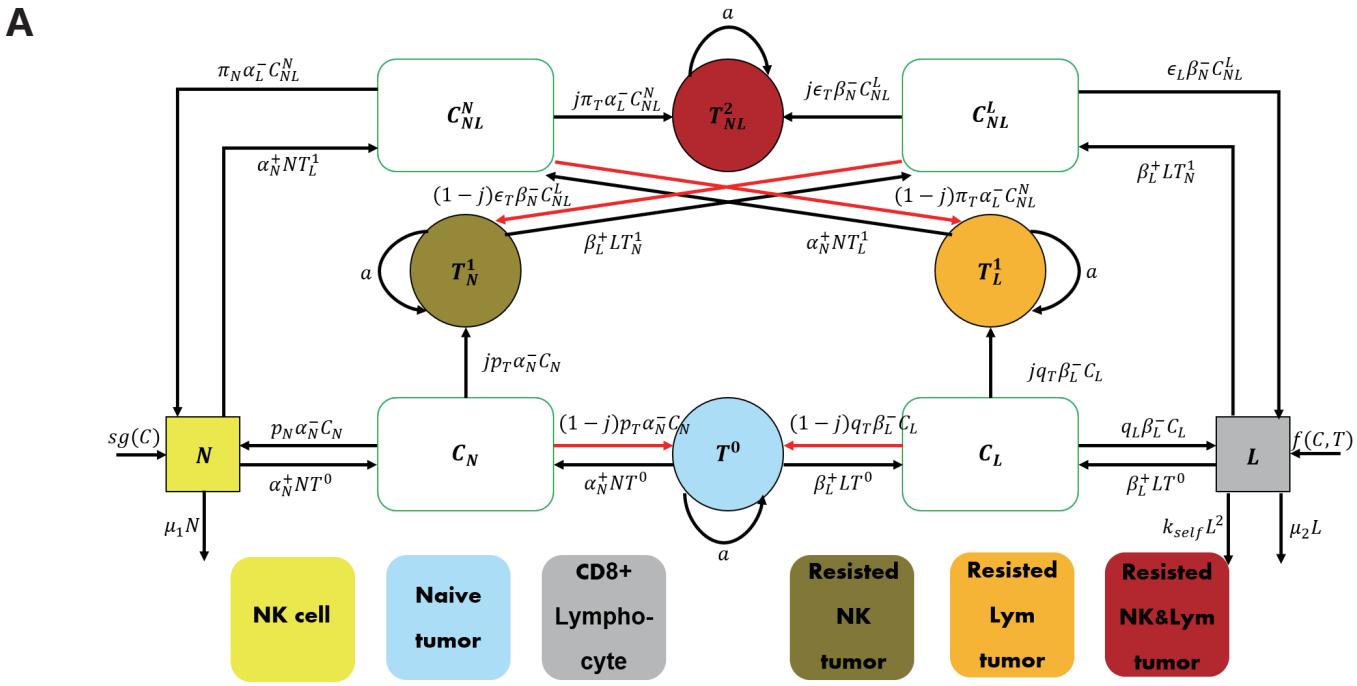

Figure 2. The creation and prediction result of the refined model

(A) Refined model of tumor evolution.

(C) Prediction of immune and tumor cell number using the refined model.

(D) The predicted number of immune and tumor cell number. Plotted separately.

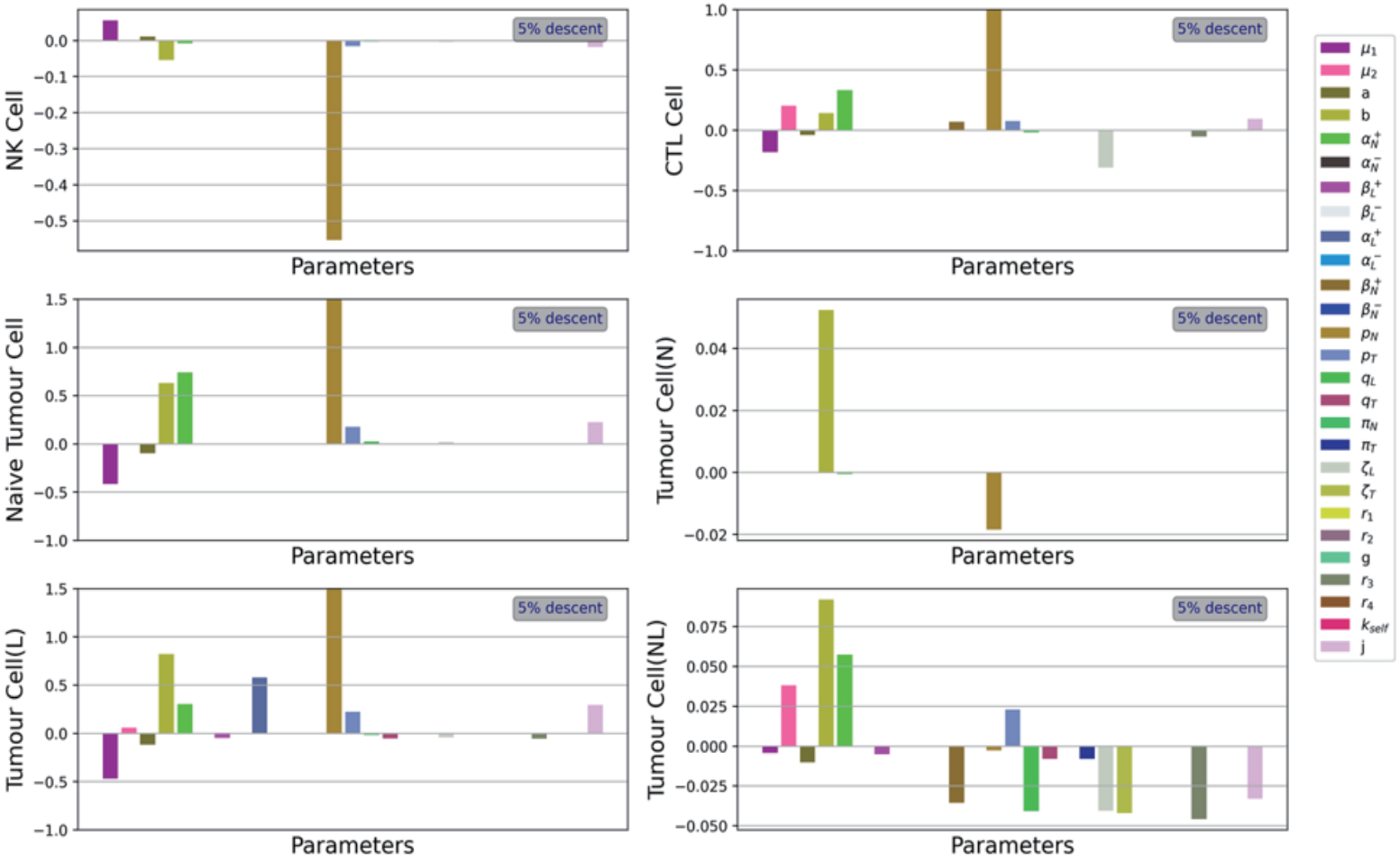

Figure 3. Global sensitivity analysis by partial rank correlation coefficient (PRCC)

(A) PRCC result for NK cell.
(B) PRCC result for naive tumor cell.
(C) PRCC result for tumor cell with resistant to CD8+ T cell.