

Research Paper

A Mathematical Modelling of Initiation of Dendritic Cells-Induced T Cell Immune Response

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Abstract

Dendritic cells (DCs) are the most potent specialized antigen-presenting cells as now known, which play a crucial role in initiating and amplifying both the innate and adaptive immune responses. Immunologically, the motilities and T cell activation capabilities of DCs are closely related to the resulting immune responses. However, due to the complexity of the immune system, the dynamic changes in the number of cells during the peripheral tissue (e.g. skin and mucosa) immune response induced by DCs are still poorly understood. Therefore, this study simulated dynamic number changes of DCs and T cells in this process by constructing several ordinary differential equations and setting the initial conditions of the functions and parameters. The results showed that these equations could simulate dynamic numerical changes of DCs and T cells in peripheral tissue and lymph node, which was in accordance with the physiological conditions such as the duration of immune response, the proliferation rates and the motilities of DCs and T cells. This model provided a theoretical reference for studying the immunologic functions of DCs and practical guidance for the clinical DCs-based therapy against immune-related diseases.

Key words: dendritic cell, immune response, T cells, mathematical model, ordinary differential equations

Introduction

DCs are specialized antigen presenting cells, which have strong capabilities of antigen uptake and processing, can present antigens to naive T cells, and thus induce immune responses or tolerance. Functionally, DCs can be divided into immature DCs (imDCs) and mature DCs (mDCs) two differentiation stages. In the body, imDCs are located in peripheral tissues, whose main function is to uptake antigens through phagocytosis and pinocytosis [1-4]. After

obtaining the antigens, the imDCs gradually differentiate into mDCs and up-regulate the expression levels of cluster of differentiation (CD) molecules, including CD11c, CD40, CD80, CD86, CD83, major histocompatibility complex (MHC) and chemokine receptor 7 (CCR7), et al. Then, they migrate to secondary lymphoid tissues along the concentration gradient of CCL19 and CCL21 secreted by lymphatic endothelial cells. In the lymph nodes (LN), mDCs are dynamically

in physical interaction with the naïve T cells. The acquired antigens are presented to them by MHC I or II molecules on the surface of the cell membrane, stimulating the naïve T cell specific proliferation, thereby triggering adaptive immune responses or tolerance [2, 3].

The peripheral tissues (PT) including skin and mucosa not only serve as a mechanical barrier between the body and the external environment, but also the body's primary immune defense against potential external antigens [5, 6]. In skin tissue, there is a close signaling transduction among epithelial cells, immune cells, and stroma to ensure effective protection against external antigens and to maintain the homeostasis of the body's immune system [7, 8]. When infections or lesions occur in PT, DCs rapidly differentiate and perform their immunological functions [9, 10]. Naïve T cells within the LN are activated and proliferated by recognizing antigens presented by DCs. These DCs-induced antigen specific T cells emigrate from the LN to the diseased PT to eliminate antigens and maintain inflammation. Normally, the inflammation will gradually subside once the antigens are eliminated. In the healthy body (non-inflammatory state), there are still small amount DCs that migrate from the PT to LN in order to help the immune system maintain immune tolerance to autoantigens [3, 11].

In the initiation phase of the immune response, the abilities of DCs to migrate and stimulate the naïve T cell-specific proliferation play an important role in effective immune function. Moreover, the number of DCs that migrate to the LN after antigen acquisition at the site of the inflammatory PT and the subsequent number changes of effector T cells activated by DCs are closely related to the efficiency of the immune

function *in vivo*. However, due to the complexity of the immune system, there are few studies on the real-time monitoring of changes in the number of DCs and T cells during the initiation of inflammation. The initiation process of immune response caused by inflammation in the PT can be summarized four stages, as shown in Fig.1. Therefore, in order to more accurately investigate the number changes of DCs and effector T cells over time at the onset of inflammation, the present study simplified the migration of DCs and subsequent T cell-specific proliferation into several ordinary differential equations. By setting the relationship between parameters and functions, the number changes of DCs and T cells at different stages is reduced to a time-dependent equation to simulate these processes.

Methods

The initiation of a primary immune response requires contact between DCs and naïve T cells. First of all, the inflammatory site of PT is stimulated by antigens, and DCs moves through the blood vessels or lymphatic vessels to the inflammatory site. Secondly, DCs loaded antigens in the PT inflammatory region migrate to LN and interact with T cells. Subsequently, T cells are activated, proliferated and migrated to the inflammatory site to remove antigens [4, 6]. In this study, ordinary differential equation model was constructed to simulate the populations of DCs in PT and LN. In addition, changes in the number of effector T cells including CD4⁺ T cells and CD8⁺ T cells were given a prediction. The initial values of the functions and parameters involved in the model in terms of the related references are given in Table 1.

In this model, the DCs that mature at the initial PT site of the antigen stimulation were set to trace amounts. As the antigen concentration was increased to a threshold level (usually without definite limitations), it is sufficient to induce DCs to mature and leave the PT. On account of limited antigen-activated DCs that activate and migrate to LN-activated lymphocytes, and because of the different ability of the antigen to replicate under diverse conditions, we selected a limited number of antigens available in this mathematical model. It is important to point out that this model is more complicated in chronic inflammatory conditions and more than just one LN in the actual study. In short, we only focused on the dynamic model of one LN in the present study. The model was initially established on the PT of DCs as the first

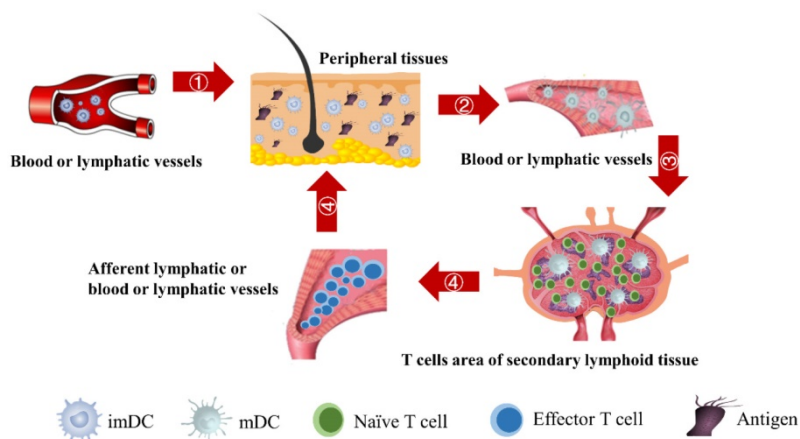


Figure 1. The schematic of DCs-induced inflammatory process. First, DCs migrate from PT to the inflammation site due to antigen stimulation. Secondly, antigen-loaded DCs migrate from inflammation site to the LN. Thirdly, the process of initial activation and specific proliferation of naïve T cells in the LN. Fourthly, the antigen specific effector T cells migrate to inflammatory PT and eliminate antigens.

step in developing this chronic inflammatory model. The model was only concerned with some simple factors, such as DCs antigen presentation, activation, migration, and the ability to stimulate the naive T cells.

Table 1. The initial value of variables and parameters

Variables/Parameters	Units	Initial Value
D_{PT}	DCs/mg PT	0
D_{LN}	DCs/mg LN	0
T	Primed T cells/mg LN	1
A	Ng of antigen/mg of tissue	0
t_{thresh}	h	4
A_{thresh}	Ng of antigen/mg tissue	4
D_{LNcrit}	DCs/mg LN	1×10^2
D_{LNmax}	DCs/mg LN	2×10^4
α_{DB}	DCs/mg of PT/h	$2 \leq \alpha_{DB} \leq 125$
D^*_{PT}	DCs/mg PT	$t_{thresh} \alpha_{DB}$
ρ	none	0
δ	1/h	1/72
$\alpha(D_{LN}, t)$	1/ (h T cells/mg LN)	0
m	T cells/DC	10
α_{max}	1/ (h T cells/mg LN)	0.1
K_0	1/h	2.08×10^{-7}
K_1	1/h	2.08×10^{-5}

The assumptions of the model

- The concentration of DCs in the blood was almost constant during the immune response of the model simulated PT inflammation.
- Linear accumulation of antigen on the surface of the PT until it reached its maximum.
- Without sufficient antigen stimulation, mature DCs migrated to LN was expected to be very small. When antigen concentration reached a certain amount, DCs migrated from peripheral blood to inflammatory sites and then emigrated from inflammatory sites to LN.
- DCs did not proliferate in the PT [12, 13].
- About 1% of the mature DCs loaded with antigen were able to leave the PT and went to the LN [3, 14-16], suggesting that DCs might be considerably lost during migration. In this study, we only focused on DCs that migrating from PT to LN and successfully activating immune response of T cells. So, it was hypothesized that DCs could reach the LN and activates T cells.
- It was assumed that when the concentration of DCs in the LN A reached a certain threshold A_{thresh} , T cells began to proliferate conforming to a logistic model. The activity of DCs began with the stimulation of the antigen in the PT. In this process, we assumed that the antigen concentration increased from the beginning of the stimulus to the critical value A_{thresh} . The time of arrival of this threshold was indicated as t_{thresh} .

For simplicity, it was assumed that the increase rate of the antigen per hour was 1 ng/mg of tissue until it reached to A_{thresh} . A minute amount of DCs continued to migrate from the blood to the PT before the critical value was reached. This continuous inflow was indicated by α_{DB} . Once the value of the antigen in the PT reached to A_{thresh} , DCs began to migrate from the blood to the PT at a high concentration. It was also supposed that this change occurred within a fairly short period of time, while α_{DB} was approximated as a discrete jump from a non-inflammatory to an inflammatory state in a short period of time.

Mathematical model

With the increase of the number of DCs in the PT, the migration rate of DCs from the PT to the LN was expressed by parameter $K = K(D_{PT}, D_{LN})$. Therefore; the rate of change of DCs in the PT (e.g. skin) could be described by the following equation:

$$\frac{dD_{PT}}{dt} = \alpha_{DB} - K(D_{PT}, D_{LN})D_{PT} \tag{1}$$

It is assumed that DCs reached the LN were only from the PT. In the model, the rate of DCs leaving the PT was the same as K at the rate of reaching the LN. The DCs in the LN were reduced by δ per hour. The DCs migrating from the PT to the LN had a loss rate represented by ρ per hour mortality. This DCs migration loss rate parameter we set is based on existing research observations. For example, under pathological conditions (such as tumors), the number of DCs does have a loss during the initiation of the immune response. For ease of calculation, we assume that the migration loss rate of DCs is a linear function. In this study we did not consider the loss of DCs during migration, so we set $\rho = 0$. The nonlinear expression, threshold range and influencing factors of the parameter ρ are our next research content. The change rate of DCs in the LN could be expressed as the following differential equation:

$$\frac{dD_{LN}}{dt} = (1-\rho) K(D_{PT}, D_{LN})D_{PT} - \delta D_{LN} \tag{2}$$

The parameter m that represents the carrying capacity of DCs is quite wide. In this study, we selected m value of 10, that is, each DC could stimulate 10 T cells to activate and proliferate [17-20]. It was noted that the change rate of T cell proliferation α was a function of DCs concentration D_L and time t . As noted in the assumption 6, T cell population grew logistically with a growth rate α /mg/h to a carrying capacity m times the size of the maximum number of

DCs in the LN. The time of arrival of D_{LNcrit} was expressed as t_{crit} , which was linearly increased at the rate of a until the maximum value of a_{max} . The equation describing the change of T cells is as follows:

$$\frac{dT}{dt} = \alpha T(mD_{LNmax} - T) / mD_{LNmax} \tag{3}$$

Model parameters and significance

In order to determine the parameter K , it was first identified as $0 < t < t_{thresh}$. At this point, $K = K_0$. Since the critical activation value was reached at the antigen level, only a few DCs loaded antigen migrated to the LN. If $t > t_{thresh}$, the migration rate can enhance about three times, when the DCs in PT increase approximately two times [4, 21, 22], so we set $K = K_1(3^{\log_2(D_S/D_S^*)})$. K_1 indicates the average rate of the activation of DCs from the PT to the LN. D_S^* indicates the number of DCs that reached the PT at the time of t_{thresh} . According to our experiment, the change of D_{PT}^* was consistent with the change of α_{DB} . The rate of DCs reaching noninflammatory PT tissue was 2 DCs/mg of PT/h, and the rate of DCs reaching inflammatory PT was 100 DCs/mg of PT/h [22-24]. Therefore, in the case of noninflammatory, $D_{PT}^* = t_{thresh}\alpha_{DB}$. The prerequisite for the establishment of the above equations is that there was sufficient space in the LN to allow new DCs entry, namely, $D_{LN} < D_{LNmax}$. Once the number of DCs in the LN reached a critical value of D_{LNmax} , DCs entered the LN from the PT at a constant rate. Thereafter, the number of DCs in LN remained homeostasis.

$$K(D_{PT}, D_{LN}) = \begin{cases} K_0, & \text{if } 0 \leq t \leq t_{thresh} \\ K_1(3^{\log_2(D_{PT}/D_{PT}^*)}), & \text{if } t > t_{thresh} \text{ \& } D_{LN} < D_{LNmax} \\ \min\{\delta D_{LN}/D_{PT}, K_1(3^{\log_2(D_{PT}/D_{PT}^*)})\}, & \text{if } t > t_{thresh} \text{ \& } D_{LN} < D_{LNmax} \end{cases} \tag{4}$$

The proliferation rate of T cells a was a function of time t and D_{LN} the number of T cells in the LN, and T cells proliferate only when DCs increased to the threshold value. T cells then showed a linear increase until the proliferation rate reached to their maximum value. In this study, the time of the linear proliferation t_a was 72 hours [25-30].

$$\alpha(D_{LN}, t) = \begin{cases} 0, & \text{if } D_{LN} < D_{LNcrit} \\ \min(\frac{\alpha_{max}(t - t_{crit})}{t_a}, \alpha_{max}), & \text{if } D_{LN} \geq D_{LNcrit} \end{cases} \tag{5}$$

The initial value of variables and parameters

- $D_{PT}(0) = 0$, indicates that the number of DCs at the PT tissue at the initial time is zero, that is, we set the PT to has no DCs before antigen stimulation or the number is negligible.

- $D_{LN}(0) = 0$, indicates that the number of activated DCs on the LN at the initial time was zero, that is, there was no activated DCs or LN before antigen stimulation.
- $T(0) = 1$, there were no activated T cells in the LN prior to antigen stimulation, and a non-zero initial value was needed for later growth in numbers.
- $m = 10$, indicates that one DC could activate 10 T cells after the number of DCs in the LN exceeded the critical value [13, 17, 19], so the maximum carrying capacity of DCs in a single LN is mD_{LNmax} .
- $t_{thresh} = 4$, indicates the time when the antigen concentration reached the threshold A_{thresh} . Other studies have shown that it takes 2 to 4 hours for DCs to process antigens at the inflammation after antigen stimulation [25-30], so we set t_{thresh} to 4 hours.
- $A_{thresh} = 4$, we hypothesized the rate of increased antigen level was 1 ng/mg of tissue/h, which was an estimated value, and the rate changed in different organ. In this model, we estimated that A_{thresh} was about 4 ng/mg of tissue/h. When reached this threshold, DCs could be stimulated to uptake antigen and then migrated from blood to the PT and then to LN. Once the concentration of DCs reached D_{LNcrit} (cells/mg of LN), T cells could be activated.
- $D_{LNcrit} = 100$, indicates that about 100 DCs in each LN could cause T cell immune response (LN around 10mg) [25-30]. In this model, we hypothesized that the number of DCs firstly reached D_{LNcrit} for t_{crit} .
- $D_{LNmax} = 2 \times 10^4$, indicates that the upper limit of the number of DCs per milligram of LN tissue was about 2×10^4 [25-30].
- Under noninflammatory conditions, $2 \leq \alpha_{DB} \leq 125$, under the inflammatory state, $100 \leq \alpha_{DB} \leq 6250$. α_{DB} was the rate at which DCs migrated from the blood to 1 mg of PT inflammation per hour, with the upper limit being the rate at which DCs entered the inflammatory tissue upon arrival of the antigen cutoff, and the lower limit was the rate at which DCs entered the inflamed tissue before the antigen threshold arrived [25-30].
- $D_{PT}^* = t_{thresh}\alpha_{DB}$, represents the number of activated T cells on the LN when the time of the accumulation of antigen concentration reached the critical time t_{thresh} .
- $\delta = 1/72$, mortality of DCs in the LN [12, 26, 27].

- $\alpha_{max} = 0.1 (0 \leq \alpha(D_{LN}, t \leq \alpha_{max})$, indicates the maximum proliferation rate of T cells in the LN. The selection of $\alpha_{max} = 0.1$ was an estimated value, which made the proliferation rate of T cells within a reasonable biological range.
- $K_0 = 2.08 \times 10^{-7}/h$, $K_1 = 2.08 \times 10^{-5}/h$, indicates the rate of migration of mDCs from the PT to the LN when the antigen concentration increased to the critical value. Studies have shown that when 1×10^5 DCs were injected into the skin, the migration rate of DCs after 48h was 0.01 [7, 20, 27], and the average migration rate was about $2.08 \times 10^{-5}/h$. Therefore, we predicted that the antigen concentration did not reach the critical level in the initial stage of inflammation, and the migration rate of DCs from the PT to the LN was lower, so that $K_0 = 2.08 \times 10^{-7}/h$.

Results

We investigated the effect of the parameter α_{DB} on the outcome of the model in an inflamed state. It was assumed that α_{DB} may range from around 100 up to 6250 under the inflammatory state. As shown in Fig.2, the growth rate of concentration of DCs in the PT decreased accompany with time changes, and the value of D_{PT} increased rapidly within 25 hours, and then increased at a very slow rate. As the value of α_{DB} increasing, the value of D_{PT} was also increased. The value of D_{PT} was always greater than that of DCs in the LN concentration D_{LN} , on account of the model assumption that the DCs in the LN originated from

the PT. As the value of α_{DB} increasing, the time required for the concentration of DCs in the PT and LN to reach the maximum value was shorter (Fig. 3). When α_{DB} was 6250, about 50 hours were required for D_{LN} reaching the maximum, while approximately 175 hours were need for T cells reaching the maximum value. When the value of α_{DB} was 100, more than 250 hours were required for both D_{LN} and T cells reaching the maximum value. The time for T cells reaching the maximum was always lagged behind D_{LN} . The greater value of the α_{DB} , the shorter time required for the specific proliferation of T cells and the higher efficiency of the immune response.

The numerical results in Fig. 4 showed that the value of α_{DB} affected the time required for the K value to reach the peak value. When $\alpha_{DB} = 1000$ and 2000, the value of K increased and then decreased. When α_{DB} was set to 100 or 500, the value of K didn't reach the peak value during the simulation time. When $\alpha_{DB} = 6250$, the time required for reaching the peak value of DCs migration rate K was less than 100 hours (Table 2). We also discovered that the time cost for migration rate K reaching its peak is a power function of α_{DB} . It also could found in Table 3, when α_{DB} was 6250, it cost about 22 hours for T cell response to proliferate. When α_{DB} was set to 100, the time was up to 68 hours for T cells started to proliferate. As showed in Fig. 5, there was a power function relationship between the time cause T cells to proliferate and the parameter α_{DB} .

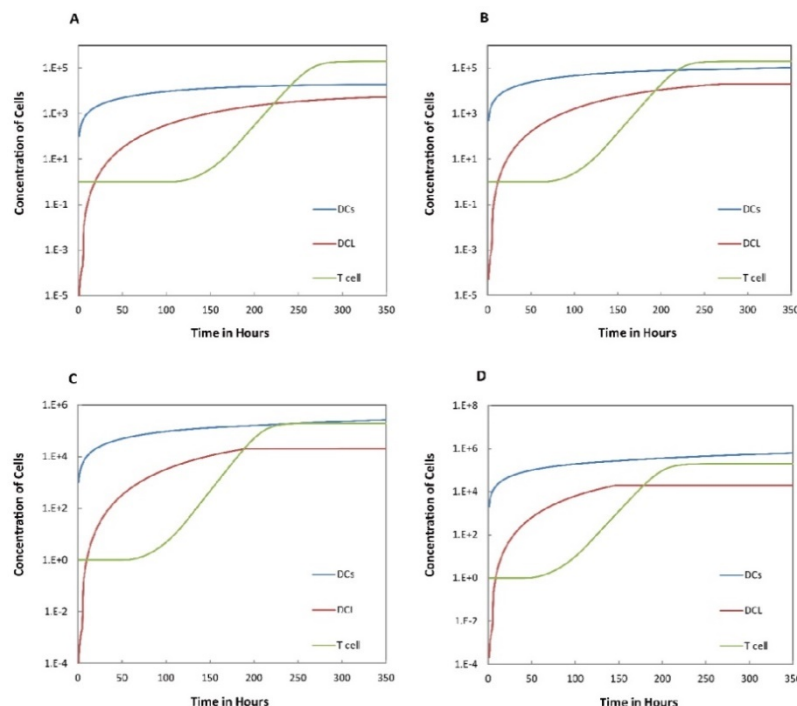


Figure 2. Numerical simulation of DCs in PT (D_{PT}) and DCs in LN (D_{LN}) and T cells in LN. A. $\alpha_{DB} = 100$, B. $\alpha_{DB} = 500$, C. $\alpha_{DB} = 1000$, D. $\alpha_{DB} = 2000$.

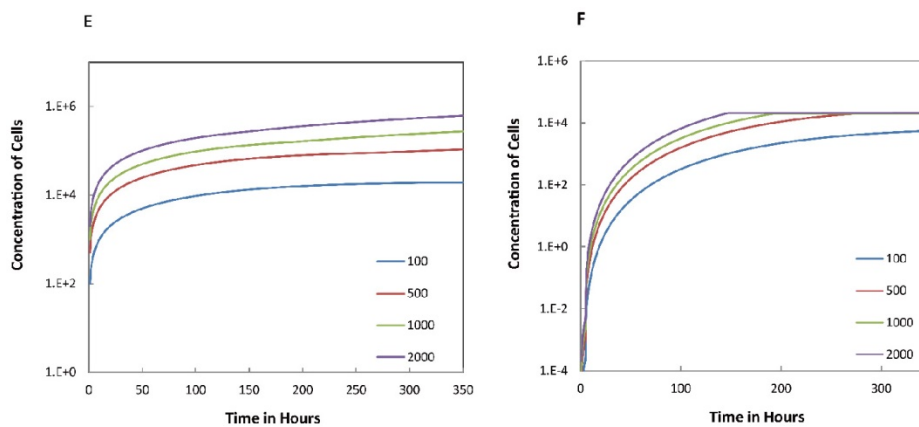


Figure 3. Trend curves of DC concentrations in PT and LN ($\alpha_{DB}=100, 500, 1000, 2000$). E. DC concentrations in PT, F. DC concentration in LN.

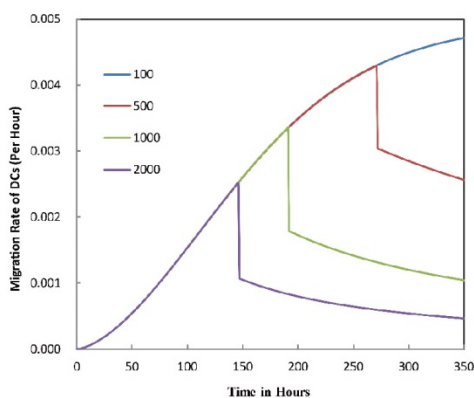


Figure 4. Trend curves of migration rate of DCs from PT to LN ($\alpha_{DB}=100, 500, 1000, 2000, 6250$)

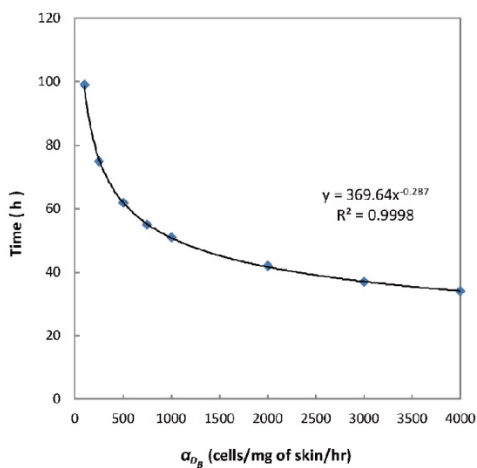


Figure 5. Numerical simulation of the times required for T cells to initiate proliferation.

Discussion

DCs, as the most potent specific antigen presenting cell in the body, plays a vital role in the initiation and regulation of immune response. When inflammation occurs, imDCs migrate from the

peripheral blood to the inflammatory site and acquire antigens, then gradually differentiate into mDCs and migrate to the LN to stimulate naive T cells to proliferate [1-4]. In this process, DCs undergo a long migration until reaching LN. Moreover, DCs-based vaccinations against tumors and autoimmune diseases have been achieved great clinical success. Anti-tumor immunotherapy based on DCs is even considered to be one of the possible methods to overcome cancer. However, the clinical efficacy of these therapies is unsatisfactory. Presently, there are still many problems to be solved, in which the relationship between the number of DCs that are adoptively reinfused and the number of naive T cell proliferation is difficult to predict. This requires further studying the immunological function of DCs from a multidisciplinary perspective, especially system biology.

Table 2. The time requirement for reaching the peak value of DCs migration rate K corresponding to different values of α_{DB} .

α_{DB}	100	500	1000	2000	6250
Migration rate K to peak time (h)	Not observed during numerical simulation	Not observed during numerical simulation	191	146	99

Table 3. The time of T cell activation in LN corresponding to different value of α_{DB} .

α_{DB}	100	500	1000	2000	6250
T cell proliferation time (h)	99	62	51	42	22

In the present study, by constructing ordinary differential equations, we simulate the dynamic changes of DCs during the entire migration process and the subsequent dynamic relationship between the number and time of T cells in LN. When the antigen concentration is low, DCs migrate from the blood to the PT in a low level. When the antigens concentration reaches the critical value A_{thresh} , DCs migrate from the blood to the PT inflammation site at high

concentration. In the first 25 hours, the value of D_{PT} increased with the fastest speed, which showed that DCs accumulated firstly in the inflammatory PT and then migrated to the LN. Therefore, the value of D_{PT} was always greater than the concentration of DCs in the LN D_{LN} . when the value of D_{PT} was above 6000, T cells require at least 22 hours to be activated as effector T cells. If the value of D_{PT} was less than 500, T cells were activated after at least 50 hours. Since the delay in T cell proliferation is mainly due to the fact that DCs contact T cells and stimulate T cells for at least 24 hours [10], the time delay of specific proliferation of T lymphocytes in LN stimulated by DCs is in line with the reality of T cell proliferation characteristics. Moreover, the value of α_{DB} has a power function correlation with the time of DCs initiation effect and T cell proliferation, inferring that it can predict the time required for activation of T cells through α_{DB} value, and the efficiency of the immune response.

The mathematical model constructed by Amy H. Lin Erickson et al. [23] is not accurate for the initial value of the PT-to-LN migration rate parameter K for DCs, resulting in the number of DCs migrating to the LN does not achieve a critical value. According to the relevant research [25-30], DCs could induce the proliferation of naive T cells only the number of DCs reaches that critical value. In their study also constructed a T cells change rate equation in LN. In our manuscript the model of T cell proliferation in equation (3) is optimized, which could better characterize the number of T cells in logistic growth and that was more realistic. More importantly, our study confirmed from the model point of view that the time required for T cells to initiate immune proliferation in the early stage of immunization could be inferred from the concentration of DCs in the blood. Bocharov G, et al. also modelled the localized population dynamics of DCs-cytotoxic T lymphocyte (CTL) interaction in the spleen, but they ignored the DCs recirculation between the spleen and blood. Our model considered more about the migration of DCs in blood and LN during the early stage of chronic inflammation [31]. Therefore, the model constructed in this study was more in line with the physiological behavior of DCs and the number of T cells during the inflammation initiation, which can predict the number of DCs and T cells at different time, as well as provides a theoretical reference for studying the immunological function of DCs.

Conclusion

The present model can simulate the migration of DCs and the specific proliferation of naïve T cells in DCs-induced immune response, which accords with

experimentally confirmed time needed for the migration and proliferation of DCs and T cell activation. This study laid the foundation for the construction of a mathematical model to simulate the physiological behavior of DCs under pathological conditions (such as tumor and rheumatoid). In DCs-based immunotherapy against diseases, the effects of the number of DCs injected and the migration rate of DCs on the initiation time of immune response induced by DCs have not been well quantified. The significance of this study is to predict the time of immune response induced by DCs according to the migration rate of DC in peripheral tissues, so as to guide clinical immunotherapy. Since the model is only a preliminary mathematical model, many immune processes are simplified, In future; we will continue to build more complex models based on this preliminary model to provide validation, prediction and hypothesis testing for clinical problems. We will collect clinical data from the perspective of pathophysiology to apply this mathematical model to the prediction of clinical efficacy of diseases such as tumors and autoimmune diseases.

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Author Contributions

Zhu Zeng, Jinhua Long, Wenzhu Huang and Wenhui Hu conceived and designed the experiments; Wenzhu Huang and Wenhui Hu, Jin Chen, Yun Wang, Zuquan Hu, Jing Zhou, Lina Liu, Fuzhou Tang, Shichao Zhang, Yan Ouyang, JinHua Long, Yun Wang, Yi Jia, Wei Qiu and Yuannong Ye performed the experiments and analyzed the data; Zhu Zeng, Jinhua Long, Wenzhu Huang and Wenhui Hu wrote the paper.

Competing Interests

The authors have declared that no competing interest exists.

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