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Induction and application of an equation to analyze a local ignition of the immune system for a complete deletion of a cancer mass

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Abstract: A mathematical model which consists of Th cells (helper T cells), Tc cells (cytotoxic T cells) and IL2 (interleukin 2) was already shown to delete cancer cells. Here the purposes of the model and the equations are to analyze the local ignition and concerned states of a cancer mass and to make a practical model and application. For these purposes, the total model the center of which is the micro and common field model in the whole cancer mass is shown as a simple but efficient one with a practical modeling precision. The local control mechanism of the immune system in the micro part of the cancer mass is proposed mathematically. An example for the practical use and application of the field model to know the micro behaviors state of the cancer disease is also proposed.

1. Introduction

With contact frequency probability at {x} $\alpha(\{x\})$, affinity between lymphocytes and cancer cells at {x} $\beta(\{x\})$ and killing probability by lymphocytes at {x} $\gamma(\{x\})$, $\alpha(\{x\}) \cdot \beta(\{x\}) \cdot \gamma(\{x\})$ inhibits the proliferation of cancer cells at {x}. Then $\alpha(\{x\})$ has an equal effect to $\gamma(\{x\})$ to inhibit proliferation rate $\lambda_c(\{x\})$ of cancer cells mathematically. $\alpha(\{x\}) \cdot \beta(\{x\})$ can have a main effect for the beginning and the response intensity of the immune system.

The increase of λ_{im} which is the proliferation rate of activated cytotoxic T cells leads to the complete recovery of the disease and there will be a possibility to achieve the local ignition of the immune system in the cancer mass. So the quantitative level of λ_{im} and the distance to the local ignition can have importance for complete recovery.

I showed in [1] that the cancer and the immune system interaction model and its phenomena have two aspects. One comes from $\alpha(\{x\}) \cdot \beta(\{x\})$. This one has the physical and information processing aspects and has aspects similar to a neural network [6, 7]. The other one comes from $\beta(\{x\}) \cdot \gamma(\{x\})$. This one is determined by biological behaviors of each Tc and Th. The former one has the same effect with the latter one for the recovery from the disease mathematically. Moreover the recovery is thought to be almost completely determined from these two aspects determining λ_{im}.

Here I show in section 4.2 a special model the center of which is a model named here "a field model" micro and common in a cancer mass. This model should be simple, but must have an enough modeling precision. The field model has a completeness to analyze enough precisely with modeling the other body parts like lymph nodes. The purpose of the model is to express the states of the cancer mass and the immune system analytically and quantitatively to be able to get the information for treatment and the strategies.

Qualitative models are shown in [2, 3].

An example to use the model for treatments is shown in section 4.3.

There is a similarity between the basic phenomena and the calculation of a nuclear neutron distribution.

2. Basic situation of simulation model

2.1 the immune system for simulation

2.1.1. Elements considered of the immunity system

(1) Elements considered of the immunity system

- Th cell ・・・ helper T cell.
- Tc cell ・・・ cytotoxic T cell. This is activated by an antigen with simultaneous activation of Th cell.
- IL2 ・・・ interleukin 2
- It is assumed that there is only one cancer mass in a body.

There are actual examples where Tc cells work for the extinction of cancer cells as a main player [5].

(2) Elements not to be considered in the immunity system

- B cells supported by Th cells and the production of antibodies.
- The activation of Th cells and Tc cells by affinity with the special peptide of cancer cells in lymph nodes is not considered because it is assumed here that the peptide flows out of cancer cells is very little.
- Other interleukins and cytokines except IL2 are not considered.

(3) Summarized functions in the assumed conditions of the immune system

① The activation of lymphocytes through lymph nodes does scarcely occur with few cancer cell peptides flowing out from the cancer mass.

Then Th cells and Tc cells directly recognize the cancer masse not through lymph nodes.

If there are multiple cancer masses and the activation of the immune system is supported through lymph nodes, each cancer mass causes the attack by the immune system against all the cancer masses forming a network.

② Th cells and Tc cells have main roles.

③ Antibodies do not work.

④ Activated Tc and Th cells proliferate through IL2 which is produced by the activated Tc cells and activated Th cells.

⑤ A more precise affinity to a special cancer peptide is always being looked for through the support of Th cells. This causes also the beginning of the immune activation against the cancer mass.

2.1.2 The relationship of $\alpha(\{x\})$, $\beta(\{x\})$ and $\gamma(\{x\})$ in $\alpha(\{x\}) \cdot \beta(\{x\}) \cdot \gamma(\{x\})$

(1) Common notation

$\alpha(\{x\})$ ・・・ average contact frequency between activated Tc cells and cancer cells per unit volume at $\{x\}$. This depends on both $[C(\{x\})]$ and $[Tc(\{x\})]$.

$\beta(\{x\})$ ・・・ affinity of contact vectors between the activated Tc cells and the cancer cells at $\{x\}$ $0 \leqq \beta(\{x\}) \leqq 1$. This is mathematically the inner product of the two vectors.

$\gamma(\{x\})$ ・・・ probability for the Tc to kill the cancer cell $0 \leqq \gamma(\{x\}) \leqq 1$

$\{x\}$ ・・・ a position vector in the body especially in the cancer mass and around it.

$[C(\{x\})]$ ・・・ density of cancer cells at $\{x\}$ in the cancer mass

$[Th(\{x\})]$ ・・・ density of helper T cells at $\{x\}$ in the cancer mass

$[Tc(\{x\})]$ ・・・ density of cytotoxic T cells at $\{x\}$ in the cancer mass

$[IL2(\{x\})]$ ・・・ density of interleukin 2 at $\{x\}$ in the cancer mass and around the mass

(2) Functions of $\alpha(\{x\}) \cdot \beta(\{x\})$ in $\alpha(\{x\}) \cdot \beta(\{x\}) \cdot \gamma(\{x\})$
$\alpha(\{x\}) \cdot \beta(\{x\})$ causes the following events
① Beginning of the immune system activation by $\alpha(\{x\}) \cdot \beta(\{x\})$ which has the function to detect cancer cells.
② Refinement of the receptor affinity of Tc by both Th and Tc by $\alpha(\{x\}) \cdot \beta(\{x\})$. There $\beta(\{x\})$ increases
③ Memorization of a peptide of the cancer cell by memory Th and memory Tc through $\alpha(\{x\}) \cdot \beta(\{x\})$
Memorization strength degree is assumed to be determined by the number of memory T cells.
④ Secretion of IL2 by activated Th and Tc. Th and Tc are activated by $\alpha(\{x\}) \cdot \beta(\{x\})$. These cause the increases of the proliferation rate of Tc and Th cells, $[Tc(\{x\})]$ and $\alpha(\{x\})$.

3. A short estimate by a scalar expression from a matrix expression
Scalar expression can be obtained when the situation of an eigen value problem is considered in a cancer mass from a matrix expression like in section 4.1.

$[IL2] = c_1 \cdot N_{Tact}$
$[IL2] \cdot \cdot \cdot$ IL2 density
$N_{Tact} \cdot \cdot \cdot$ activated Tc cells c_1 is constant..

$\Delta N_{Tc} = c_2 \cdot N_{Tact} \cdot [IL2] = c_1 \cdot c_2 \cdot N_{Tact}^2$
$\Delta N_{Tc} \cdot \cdot \cdot$ additional activated Tc cells by proliferation c_2 is constant..

$N_{Tact2} = \Delta N_{Tc} + N_{Tact} - N_0$
$= (c_1 \cdot c_2 \cdot N_{Tact}^2 - N_0) + N_{Tact}$
$N_0 \cdot \cdot \cdot$ extinction of Tact cells

$\lambda_{im} = N_{Tact2} / N_{Tact}$
$= c_1 \cdot c_2 \cdot N_{Tact} - N_0 / N_{Tact} + 1$

Conditions for $\lambda_{im} > 1$
(1) Enough large initial N_{Tact}
The following conditions contribute to this condition.
(1.1) Enough large number of CD4 T cells and CD8 T cells with an enough high affinity entering into a cancer mass.
(1.2) Increase of permeability of CD4 T cells and CD8 T cells into the cancer mass by cytokines especially after some number of CD4 T cells and CD8 T cells are activated in the mass.
Through these two conditions, N_{Tact} and λ_{im} are increased.
This is consistent with the control mechanism of the immune system in section 4.2.

4. Field model and application to analysis for states of diseases and for treatment strategies
A model and a method to know the situation in and around a cancer mass analytically and quantitatively and to make strategies linking the situation and the data of a patient to analysis model are shown.

4.1 Field model

4.1.1 The meaning and the purpose of a field model
[What is the field model.]
Here a field model means a small micro part of a cancer mass between two adjacent parallel

capillaries as shown in Fig. 1.1 and Fig 1.2. Each field has a very similar condition in the whole cancer mass and can express a micro behaviors in the cancer mass.

The relationship of a field model with the whole cancer mass and a lymph node is shown in Fig. 1.1. The case of a very small and much localized cancer mass is shown in Fig. 1.2.

[The merits of the field model]

- To be able to know much localized but common behaviors of T cells and cancer cells in a micro and spatial area of an interstitial tissue between two adjacent capillaries.
- The distance to the local ignition of the immune system from the present state can be known. This has a possibility to be used to know a hidden situation precisely in actual cancer diseases as shown in the example of section 4.3.1.
- This can be used to seek strategies to cure.
- To be able to get an intuitive visual actual feeling about behaviors happening in a micro site using simulations like especially those by Monte Carlo method.

4.1.2 Basic equations

Here it is assumed that equations like diffusion are digitized by numerical methods including biological phenomena like activation and proliferation of T cells. So the phenomena are expressed by matrices recursively.

$$\begin{Bmatrix} \{Tact\} \\ \{T\} \\ \{Tm\} \end{Bmatrix}_{i+1} = \lambda_{im} \begin{bmatrix} A1 & B1 & Bm1 \\ B2 & A2 & [0] \\ Bm2 & [0] & A2 \end{bmatrix} \begin{Bmatrix} \{Tact\} \\ \{T\} \\ \{Tm\} \end{Bmatrix}_{i} \qquad (4.1)$$

λ_{im} ・・・Eigen value and increase rate of Tact cells, T cells and Tm cells

The matrix includes the effects of mfp, frq, [IL2].and the affinity., and λ_{im} is hightened by them.

mfp.・・・・・ mean free path of T cells

frq ・・・・・ probabilistic moving frequency in a unit time.

- Each element of the vectors like Ti of {T} means a density of the cells at a spatial point i.
- Here, only T cells with an enough high affinity to be able to be activated are considered in {T}.
- {Tact}、{Tm} and {T} include activated cells of both Th cells and Tc cells, memory cells of the both and a set of CD4 T cells and CD8 T cells respectively.
- An element Ti of [T] is Thi・Tci where Thi, Tci are the elements of {Th} and {Tc} respectively. This means the support by Th cells to activate Tc cells.
- A1, A2 and A3 means the diffusion of {Tact}、{Tm} and {T}. A1 also means the proliferation of {Tact}.
- B1 and Bm1 mean the increase of of {Tact} by {T} and {Tm}.
- Bm2 means the increase of {Tm} by {Tact}. HereTact cells differentiate to memory T cells and effector T cells in equation (4.2(1)).

It is necessary to consider a wider range of [IL2] distribution beyond the field model in the whole cancer mass to know the precise [IL2] distribution in the field model. But even in this case, if the whole mass is big, the boundary condition will be for the [IL2] to scarcely flow across the boundary. Like this, the precise distribution of [IL2] in the field model can be expressed to a certain extent by the boundary condition. λ_{im} is increased by [IL2], mfp and frq changing the submatrices.

$$\{ \{C\}_{i+1} \} = \begin{bmatrix} \lambda c \cdot F & D \end{bmatrix} \begin{Bmatrix} \{C\}_i \\ \{T_{ceff}\}_i \end{Bmatrix} \qquad (4.2(1))$$

$\{T_{ceff}\}$ ・・・effector Tc cells differentiated from activated Tc cells

・Here, Cancer cells are deleted by $\{T_{ceff}\}$ through the submatrix D.

・$\lambda c \cdot F$ means the proliferation of cancer cells without the restriction by T cells and at the same time the proliferated cancer cells extend spatially keeping the density of cancer cells less than the maximum density.

λc ・・・increase rate of cancer cells in the cancer mass

D is a submatrix which causes the deletion of cancer cells by effector Tc cells.

A case which consider memory T cells is shown in [4].

Equation (4.2(1)) can be approximately expressed like the following expression.

$$\{C\}_{i+1} = (\lambda c - \lambda_{imn0}^{-}) \{C\}i \qquad (4.2(2))$$

Following macroscopic data from blood are used as the parameters of this model

① [Tc] ② [Th] ③ [T_{act}] ④ mfp and frq ⑤ [IL2]

IL2 is produced by Tact cells, but in IL2 therapy [8] this is provided additionally.

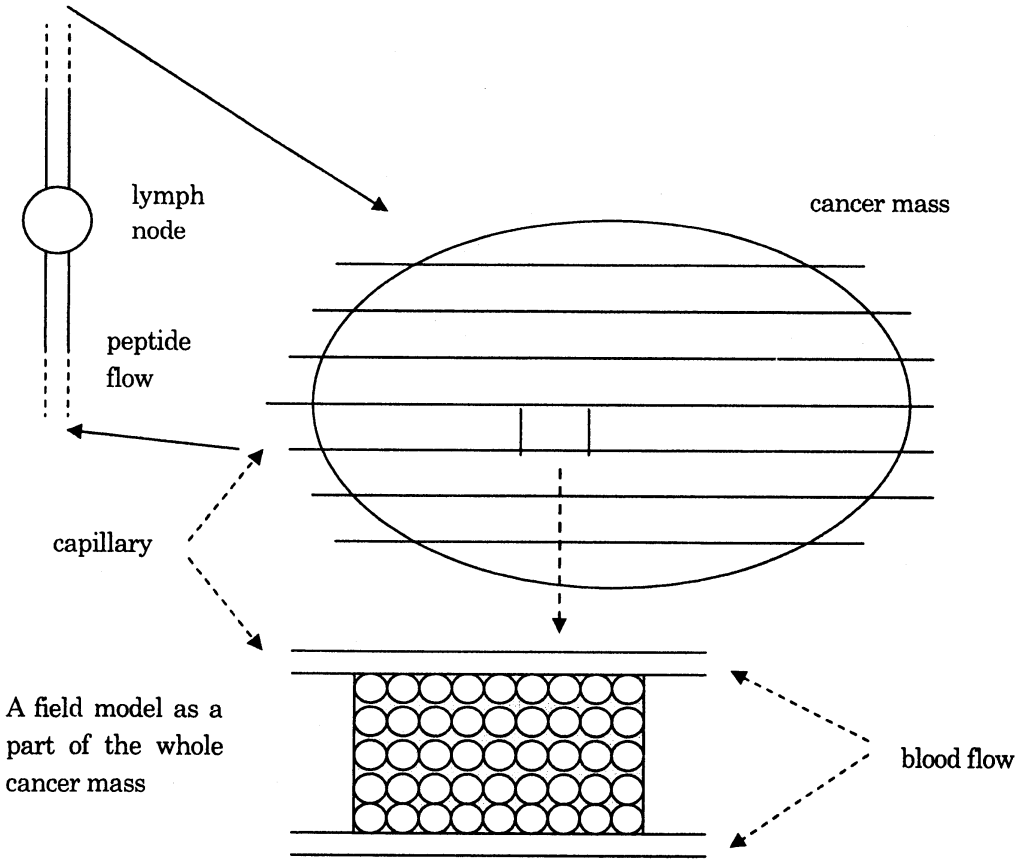

Fig. 1.1 A field model and its relationship with the whole cancer mass and a lymph node

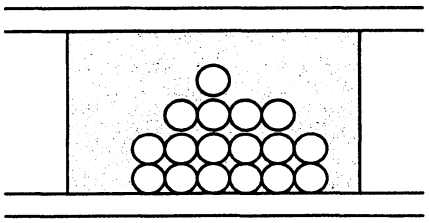

Fig. 1.2 A field model in the case with a much localized small cancer mass

4.2 Behaviors of basic equations and the way of control to delete the cancer cells in a field model by the immune system and its meaning

In Fig. 2, the relationships of λ_{im} v.s. x and T_{act} v.s. x are shown. Here x is total effect to increase λ_{im} including [Il2]. ε means the amount of CD4 T cells and CD8 T cells with a high affinity to the peptide of the cancer cells entering into the cancer mass by diffusion. So ε can be considered as live coals for firelighting the immune system. Although the ignition can not occur when $\lambda_{im} < 1$ and $\lambda_{im} \fallingdotseq 1$, and [Tact] is kept to be a value much greater than zero. Here a higher level of [Tact] a much part of which differentiates to effector Tc cells and the contacts of the effector Tc cells with cancer cells mean a higher degree of deleting cancer cells.

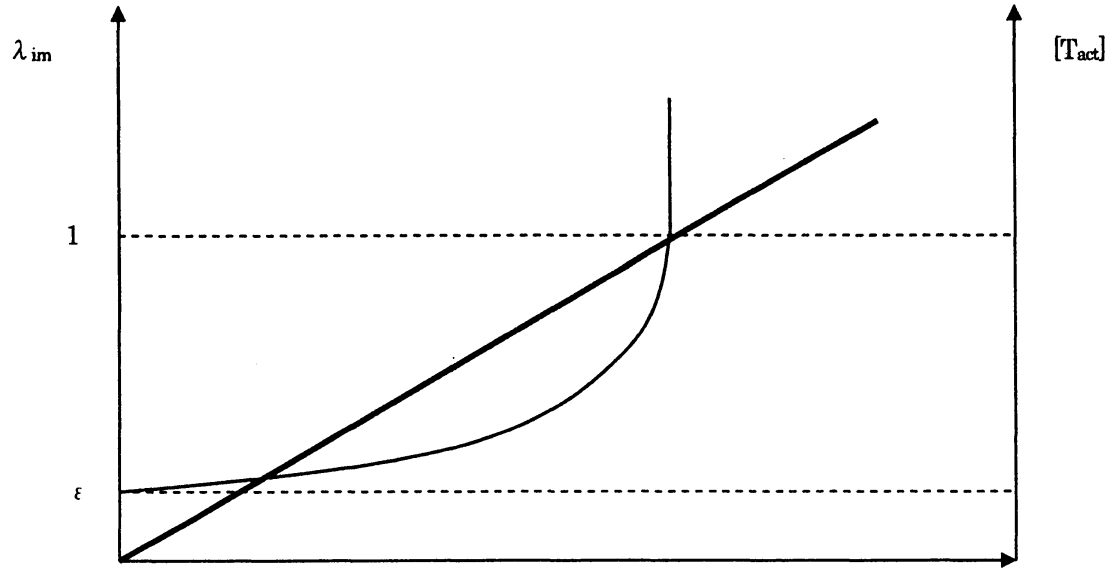

Fig. 2 λ_{im} v.s. x and T_{act} v.s. x graphs. Here x is total effect to increase λ_{im} like [Il2]

——— · · · λ_{im}

——— · · · [T_{act}]

x · · · Total effect to increase λ_{im} like [Il2]

ε · · · Entering Th cells and Tc cells with a high affinity into the field model constantly

The following behaviors are thought to occur theoretically.

These can be thought to be a controlling mechanism of the immune system. In other words, the control is done by the amount of CD4 T cells and CD8 T cells with the high affinity entering into the cancer mass to a large extent. This can be also controlled by the provision of the memory T cells with

a high affinity from lymph nodes and the permeability into the cancer mass by cytokines. Artificially this can be supplemented by vaccine therapy.

(1) Even if ε is a little large, [Tact] level can be kept high by the proliferation when $\lambda_{im} < 1$ and $\lambda_{im} \fallingdotseq 1$.

(2) Even if ε is enough large, [Tact] level can become high explosively when $\lambda_{im} > 1$.

(3) When ε becomes higher, [Tact] becomes higher, so [IL2] becomes higher. This means the increase of λ_{im}, so the local destructive activity against cancer cells can be controlled by the amount of CD4 T cells and CD8 T cells with a high affinity entering into the cancer mass.

This amount of CD4 T cells and CD8 T cells with the high affinity can be made higher with the provision of the memory cells from lymph nodes and the permeability into the cancer mass by cytokines.

The amount can be made higher by vaccine therapy, so this situation is much concerned with the therapy.

4.3 An application scheme example of the field model

4.3.1 The calculation of the quantitative effect of increases of [Tc]、[Th]、mfp and frq for the decrease of cancer mass as an application example of the field model

Here it is assumed that the input parameters [Tc]、[Th]、mfp and frq are obtained from the inspection of blood, etc..

$$\lambda_0 = (\lambda_c^+ - \lambda_{others}^-) - \lambda_{imn0}^- \quad (4.3)$$

$$\lambda_1 = (\lambda_c^+ - \lambda_{others}^-) - (1+\alpha)\cdot\lambda_{imn0}^- \quad (4.4)$$

Here $\lambda_c = \lambda_c^+ - \lambda_{others}^-$ where λ_c is in equation (4.2(1)) and (4.2(2)).

λ_{others}^- ・・・This is inhibitory effects to the cancer mass growth like the lack of angiogenesis ability other than the immune system.

λ_c^+ ・・・ Free growth of the cancer mass without any inhibition

λ_0 ・・・This is obtained from the growth of a cancer mass for a period before a therapy

λ_1 ・・・Result of the therapy at the time just after the therapy for the period

Δ[Tc]、Δ[Th]、Δmfp and Δfrq ・・・The result of the improvement of the immune system by the therapy

$\alpha \cdot \lambda_{imn0}$ is obtained from the following equation.

$$\Delta\lambda = \lambda_1 - \lambda_0 = \alpha \cdot \lambda_{imn0}^- \quad (4.5)$$

- α can be calculated by the analytical model as the increase rate of deletion ability by immunity effect of using Δ[Tc]、Δ[Th]、Δmfp and Δfrq
- So from equation (4.5) and α, λ_{imn0} is obtained.
- From equation (4.3) and $\alpha \cdot \lambda_{imn0}^-$, $(\lambda_c^+ - \lambda_{others}^-)$ is obtained.

If $\lambda_0 \fallingdotseq \lambda_1$ and $\Delta\lambda = \alpha \cdot \lambda_{imn0} \fallingdotseq 0$ in equation (4.3) and (4.4), it is inferred that the immune system has nearly zero effect on the cancer mass deletion. Especially it can be imagined that the affinity of T cells to the peptide of cancer cells is nearly zero. So the vaccine therapy is much concerned in this situation together with IL2 therapy and has the meaning to enhance the affinity..

4.3.2 The calculation of λ_{im} and the relationship between λ_{im} and λ_{imn0}^{-}

By λ_{im}, the distance to the ignition of T cells that is $\lambda_{im} > 1$ is known.

By the relationship between λ_{im} and λ_{imn0}^{-} calculated from equation (4.1) and (4.2(2)), the value of λ_{im} can be at the present time is known from λ_{imn0}^{-} obtained from (4.5).

5. Discussion

Here the followings have been especially shown.

(1) The total model the center of which is the micro and common field model in the whole cancer mass is shown.

(2) The local control mechanism in the micro part of the cancer mass has been proposed mathematically.

(3) An example for the practical use and application of the field model to know the micro state of the cancer disease has been proposed.

In application cases where the necessary and precise data can not be easily obtained, according to the precisions the application way seem to need to be modified.

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