Cancer and immune system interaction model like a neural network model, analysis of cancer mass effect and meaning of vaccine

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Abstract. A numerical interaction model between a cancer mass and the immune system is shown based on a neural network part and diffusive recurrent parts. Using the numerical model as the basis of behavior analysis, how cancer mass effect weakens the efficacy of immunity, under what condition the immune system ignites and the meanings of vaccine therapy are explained especially from contact frequency between lymphocytes and cancer cells.

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 $\{x\}$ $\gamma(\{x\})$, $\alpha(\{x\}) \cdot \beta(\{x\}) \cdot \gamma(\{x\})$ inhibit the proliferation of cancer cells at $\{x\}$. Then $\alpha(\{x\})$ has an equal effect to $\gamma(\{x\})$ to inhibit proliferation rate $\lambda(\{x\})$ 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.

On the other hand, free cancer cells isolated from a cancer mass can hardly survive in a healthy body. Because if free cancer cells easily survived, cancer cells would continue to increase in not only blood but also in anywhere in body. This means a cancer mass may get an advantage especially to reduce the attack of the immune system. So it is inferred that $\alpha(\{x\})$ may give us physical behaviors to make such an advantage and let us know treatment methods breaking the advantage.

For the aim, the followings are shown here.

(1) To make the simulation model of cancer mass-immune system interaction to support the quantitative comprehension of the behaviors based on a neural network and a sink-source diffusion analysis (ref. 1, 2 and 3). Necessary densities of T cells for the complete recovery are thought to be caused by T cell proliferation rate >1 in the recurrent dynamical system.

(2) To get ignition condition for the immune system against a small cancer mass

(3) To know the effects and meanings of vaccine therapy from the analysis model in (1).

(4) Analysis of cancer mass effect which lowers the effect of the immune system.

・ The model shown here can be applied not only to cancer, but also infectious cases.

2. 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 (Ref.1).

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

・ B cells supported by Th cells and the production of antibodies which can cause ADCC (ref. 1).

- 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 hardly occurs.

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) Relationship with proliferation rate λ in the cancer mass

Here $\alpha(\{x\})$, $\beta(\{x\})$ and $\gamma(\{x\})$ affect equally to proliferation rate λ of cancer cells.

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

$\beta(\{x\})$ $\cdot$ $\cdot$ $\cdot$ 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.

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

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

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

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

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

$\lambda(\{x\})$ $\cdot$ $\cdot$ $\cdot$ proliferation rate of cancer cells at $\{x\}$. $\lambda(\{x\}) = \{ -\alpha(\{x\}) \cdot \beta(\{x\}) \cdot \gamma(\{x\}) + \lambda^+ \cdot [C(\{x\})] \}$ $/[C(\{x\})]$

λ^+ $\cdot$ $\cdot$ $\cdot$ proliferation rate of cancer cells without attack by the immune system

λv $\cdot$ $\cdot$ $\cdot$ averaged proliferation rate of cancer cells in V. $\lambda v = \int_V \lambda(\{x\}) dv/V$

When an activated Tc cell works to extinguish a cancer cell, following steps are necessary.

① (about α) The Tc cell encounter with the cancer cell.

② (about β) The affinity between the receptor of the Tc cell and the special peptide of the cancer cell is enough high to recognize the speciality of the cancer cell peptide.

③ (about γ) The Tc cell works to extinguish the cancer cell like by causing apoptosis.

The functions of $\beta(\{x\})$ and $\gamma(\{x\})$ are usually taken into account as the effect of Tc cells, but the effect α seems to be not usually considered in medical discussion. Effect of $\alpha(\{x\})$ has a meaning equal to $\beta(\{x\})$ or $\gamma(\{x\})$ in a mathematical equation and has a hidden efficacy to the extinction of cancer cells like $\alpha(\{x\})$.

(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 spatiotemporal strength or 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 $\alpha(\{x\})$.

2.2 Neural network model

$$y_j = f(^t\{w_j\} \cdot \{x_i\}) \qquad (2.1)$$

$$\Delta\{w_j\} = c \cdot y_j \cdot \{x_i\} \qquad (2.2) \qquad\qquad c \text{ is constant.}$$

$$\{w_j\}_t = \Delta\{w_j\} + \{w_j\}_{t-\Delta t} \qquad (2.3)$$

f() is the input-output monotonic linear function with saturation and a threshold.

$\{x_i\}$ · · · input vector i like a visual image. This corresponds to the vector given by a cancer peptide shown mainly with MHC1 of the cancer cell

[wj] · · · a vector formed by the electrical conductivities at all the synapses to neuron j. This corresponds to the vector given by a receptor of Tc or Th in this immune model.

yj · · · excitation and output level of neuron j caused by the input $\{x_i\}$. This corresponds to the activation level of the Th cell or the Tc cell.

Δ[wj] · · · change of [wj] by the input $\{x_i\}$. This means the memorization of vector $\{x_i\}$. This corresponds to the increment of the number and memorization strength of memory T cells to an antigen in this immune model.

The purposes of a neural network model are similar to those of the immune system.

(1) Recognition of input patterns by correlation. This corresponds to affinity in the immune system.

(2) Memorization of new input patterns. This corresponds to memory T cells in the immune system.

(3) Remembrance according to the importance of each input pattern
     This can be done by memory T cell in the immune system.

(4) Search of memorized patterns by the production of chaotic patterns related to an input pattern
     This can correspond to a certain extent to the production of random patterns of receptors of Th and Tc So to use a neural network model as the template to express the immune system has an advantage to express and comprehend the immune system.

$\alpha(\{x\})$ corresponds to the input process to a neuron in the neural network model

$\beta(\{x\})$ corresponds to correlation in the neural network model

$\gamma(\{x\})$ corresponds to the selection of an action for the body protection determined in neural networks.

2.2.1 Necessity of diffusion calculation to know {T] and {Tact] distributions.

To cause $^t\{w_j\} \cdot \{x_i\}$ in equation (2.1), the contact of a cancer cell and a T cell is necessary, so the calculation of [C($\{x\}$)] distribution and the distributions of [Th($\{x\}$)] and [Tc($\{x\}$)] including those of activated Tc and Th cells are necessary. These distribution equations of discrete expression are shown by (2.4), (2.5) and (2.6). These equations are shown by the recurrent form although the time steps are not shown.

$$\left\{ \begin{array}{c} \{Tact\} \\ \{T\} \end{array} \right\} = \left[\begin{array}{cc} A1 & B1 \\ B2 & A2 \end{array} \right] \left\{ \begin{array}{c} \{Tact\} \\ \{T\} \end{array} \right\} \qquad (2.4)$$

· {T} is the density vector of T cells whose element means Th cell or Tc cell density at $\{x\}$ and whose

affinity to a cancer peptide is very high. Here precisely speaking, {T} should be divided into {Th} and {Tc}, but the common expression is used. Generally each element of {T] at {x} has a distribution in the multidimensional continuous region according to various affinity between a cancer peptide and T cells.

· {Tact] is the density vector of activated T cells in space whose affinity to a cancer peptide is very high.

· A1 and A2 are the diffusion submatrices of {Tact} and {T} with the extinction of Tact cells and T cells.

· Submatrix B1 gives the additional production of Tact cells through the contact with cancer cells.

· Submatrix B2 gives the additional production of T cells with the same receptor vector and its high affinity through IL2 distribution produced by Tact cells. Here IL2 gives mutual excitatory proliferation stimulus like in a neural network with mutual connections.

$$\left\{ \begin{array}{c} \{Tact\} \\ \{Tm\} \end{array} \right\} = \left[\begin{array}{cc} A1 & Bm1 \\ Bm2 & A2 \end{array} \right] \left\{ \begin{array}{c} \{Tact\} \\ \{Tm\} \end{array} \right\} \qquad (2.5)$$

· {Tm] is the density vector of memory T cells in space.

· Equation (2.5) is similar to equation (2.4). {Tact], A1 and A2 are common with equation (2.4). But the element values of submatrix Bm1 are larger than B1, because memory T cells are more easily excited through the contact with cancer cells than T cells.

$${C} = [E] {C} \qquad (2.6)$$

· {C} is the existence vector of cancer cells in space.

· [E] matrix gives the growth and the extinction of cancer cells.

Equation (2.1)∼(2.6) give the total analysis equations of cancer-immune interaction model causing behaviors like in neural networks. These equations can be expressed like in Fig. 1.
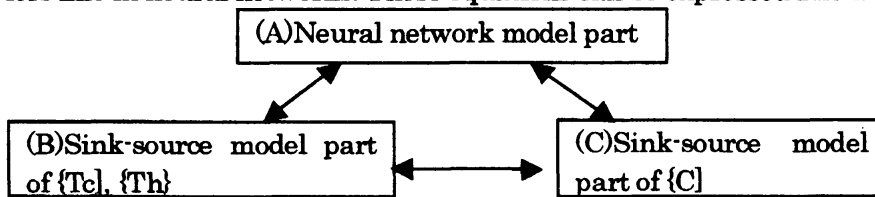

Fig. 1 (A),, (B) and (C) model parts affect each other simultaneously in the process of the stimulation.

Equation (2.4) and (2.6) and their behaviors are similar to those in nuclear analysis for neutron distribution.

2.3 The necessity of $\lambda_{Tc} > 1$ kept for a while for complete recovery from cancer disease and the conditions to ignite the immune system. λ_{Tc} is the proliferation rate of Tc cells in the part (B) of Fig.1.
(1) Activated T cells produce IL2, and IL2 makes activated T cells proliferate and produce T cells with the same high affinity receptors. So IL2 forms mutually excitatory network like neural networks with mutual connections. IL2 therapy exists (Ref. 4). But it seems to be not easy to keep IL2 density enough high for the ignition against diffusion especially when the cancer mass is small.
(2) The necessity of $\lambda_{Tc} > 1$ kept for a while for the complete recovery from cancer. And {Tact} and {T} with enough big norms are necessary to extinguish all the cancer mass completely. So $\lambda_{Tc} > 1$ is necessary.
(3) The condition for the ignition of the immune system and vaccine therapy

Vaccine therapy can contribute to the following ①, ②, $\lambda_{Tc} > 1$ and the increase of α ({x}) through the contact with cancer cells in lymph nodes and all the body especially when the cancer mass is small. These cause the ignition and $\lambda_{Tc} > 1$.

① Enough high density of IL2.

IL2 must be kept enough dense in and around the cancer mass. But IL2 is a molecule and diffuses,

so for the enough density to be kept, enough IL2 must be produced from activated T cells to compensate the loss.

② Necessity of enough high density of activated T cells in the cancer mass. Enough number of activated T cells produced by the vaccine in all the body and lymph nodes can be gathered to produce the state of ① into the cancer mass through adhesion molecules (Ref. 1).

2.4 Additional elements to the model

2.4.1 Possibility of $\sigma / n^{1/2}$ and increased protection for healthy cells against Tc cell attack.

As shown in section 2.3, IL2 causes mutual proliferation stimulation among activated T cells like neural networks with mutual connections.

(1) It is imagined that there can be mechanically variational matchings from mutual locational combinations of a cancer peptide and a T cell receptor. Then there can be statistical distribution around a maximum affinity which the T cell has with the cancer cell.

(2) Then $\sigma / n^{1/2}$ is the necessary standard deviation for n T cells to activate simultaneously by IL2 where σ is the standard deviation about the actual effect of affinity of each T cell receptor.

n is the number of activated T cells mutually stimulated by IL2. This means that for n T cells to be activated simultaneously, higher affinity is necessary.

2.4.2 Filter effect.
If cancer cells produce a lot of fiber proteins in the cancer mass, then the fiber proteins can work to lower diffusion coefficient of lymphocytes in the mass.

2.4.3
Th cells and Tc cells which respond to body cells are extinguished. At the same time, there must be Th cells and Tc cells whose receptor vectors distribute densely near the vectors which body cell peptides express, because then the cells can recognize mutated cells.

3. Cancer mass effect

3.1 The analysis of mass effect

Mass effect, its relationship with $\alpha(\{x\})$ and the level of mass effect

The situation of a cancer mass which causes the mass effect

[Assumption]

(1) It is assumed that the cancer mass is a sphere with radius r.

The unit of r is the scale of one cancer cell when cancer cells are dense in the mass.

(2) There is no blood vessels in the cancer mass. So the mass is small. If there are blood vessels in the mass, the mass effect tends to saturate according to the mass growth.

(3) There exist only one cancer mass.

[Two cases of the entrance processes of a Th cell or a Tc cell into the cancer mass]

(1) The case of a low affinity between the Tc cell and the peptide of the cancer cells

The case which is hardly expected to cause mass effect

① A Tc cell is attached to a point on the surface of a cancer mass by adhesion proteins.

② The Tc cell enters into the cancer mass.

③ The Tc cell diffuses with amoeboid movement into the center of the mass with a diffusion coefficient mechanically attaching to cancer cells without recognition.

(2) The case of a high affinity between the Tc cell and the peptide pattern of the cancer cells

The case which is expected to cause mass effect

① A Tc cell is attached to a point on the surface of a cancer mass by adhesion molecules.

② The Tc cell enters into the cancer mass.

③ The Tc is attached to a cancer cell by a mechanical conjunction with adhesion molecules.

④ The Tc cell recognizes it as a cancer cell with a high probability.

⑤ The Tc does a set of actions for the process to extinguish the cancer cell through like the injection of perforine and apoptosis. This process delays the diffusion. The diffusion coefficient is made smaller.

· This process can tend to protect inner cancer cells in comparison with cancer cells near the surface.
· The proliferation of inner cells in the mass also prevents the Tc cell from entering.

As shown in Fig. 2 it is assumed that Tc cells reach the surface of part A of the cancer mass after the beginning of Tc cell attack to the cancer mass surface.

[The case where diffusion coefficient is very small]

There can be few cancer cells left in part B. Then the cancer mass is cut from the surface, but it grows from the inner part A.

[The case where diffusion coefficient is large]

There can be cancer cells left sparcely in part B through rapid diffusion.

Then the mass also grows from the inner part B.

[Analysis of mass effect]

Fig. 2. A cancer mass attacked by Tc cells with a high affinity

Here to simplify the calculation, the case that the Tc cells cannot enter deep into the cancer mass by the mass effect is shown. α_0 is α which is determined as a uniform contact frequency by the surface and scattered Tc cells outside the mass surface with a uniform density [Tc].

Then α of total mass can be expressed by equation (3.1) when Tc cells are kept near the mass surface in the mass without entering deep. $\alpha = (S/V)\alpha_0$ · · · · (3.1)

S   · · · the area of the mass surface.   The unit is the space occupied by each cancer cell.

V   · · · the volume of the mass.   The unit is the space occupied by each cancer cell.

λ · · · cancer cell proliferation rate lowered by immunity.

$\lambda = [(S + c \cdot V) \cdot \lambda_0 + (1 - c) \cdot V \cdot \lambda^+]/(S + V)$ c · · · a constant with $0 \le c < 1$

c is expected to be almost zero. λ^+ · · · cancer cell proliferation rate without inhibition by immunity.

λ_0 · · · proliferation rate under a situation with a plate formed by cancer cells like cancer mass surface and Tc cell density [Tc] outside it. $\lambda_0 = \lambda_0([Tc], \beta, \lambda^+)$ β is the uniform value of $\beta(\{x\})$.

$\lambda = \lambda_0 \cdot S/V + \lambda^+ = \lambda_0 \cdot [(3/4)/r] + \lambda^+$ This means that when the mass becomes smaller, λ becomes smaller and the mass can be extinguished more easily.
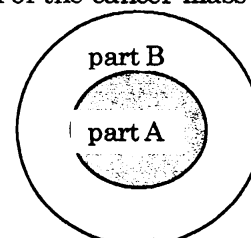

3.2 Mathematical meaning of mass effect

When the shape of $\{Tc\}$ with a constant norm is the same with that of $\{C\}$ with a constant norm, the inner product between the two vectors is maximized mathematically. This means the most effective state of the immune system. The cancer mass effect can be one of the elements which prevent the immune system from attacking cancer masses especially through $\alpha(\{x\})$ in $\alpha(\{x\}) \cdot \beta(\{x\}) \cdot \gamma(\{x\})$ by destroying the mathematical condition of inner product. Cytokine TNF-β is known to work to kill cancer cells. There can be possibly cytokines like TNF-β which work to kill cancer cells through increasing $\alpha(\{x\})$ and the parameters like a diffusion coefficient.

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