

A mathematical model for the dynamic of cytotoxic T cells

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The role of the immune system is to preserve the organism integrity when challenged by external and internal agents named antigens.

There are three basic agents: cells, immunoglobulines, and cytokines.

This model focuses on the cells known as T lymphocytes, responsible for the antigen recognition and system response. Lymphocytes are leukocytes (white blood cells) agranulocytes (without granules). T cells, in particular, are nonantibody-producing lymphocytes and constitute the basis of the cell-mediated immunity. There are two main classes of T cells: helper T cells (CD4+) and cytotoxic (or killer) T Cells (CD8+). The helper T cells activate B cells that produce antibodies. Suppressor T cells slow down and stop the immune response of B and T cells, serving as an off switch for the immune system. Cytotoxic T cells mainly destroy body cells infected with a virus or bacteria. Memory T cells remain in the body awaiting the reintroduction of the antigen.

The codes (e.g. CD4+) characterize the surface molecular markers which are used to identify the different types of lymphocytes and it has to be noticed that there exist some problems of reliability for a marker to discriminate among different types of lymphocytes.

It has been stated that the CD95 is a reliable marker to discriminate between cells which have not yet met the antigen (ANE, i.e. Antigen Non-Experienced) and cell having already experienced the antigens (memory and /or activated cells AE, i.e. Antigen Experienced).

Due to primary antigenic stimulation we consider the conversion from ANE CD95- to AE CD95+ T cells occurring with a rate α .

The secondary antigenic stimulation is responsible for a further expansion of the AE pool with a rate β . This further expansion causes an additional reduction of the ANE pool due to the conservation of the overall T cell compartment.

The idea is to focus not only on the time evolution of the cells but also to consider their spatial distribution. The scope is to analyze in the context of the model the role of heterogeneity in the general dynamics. We then deal also with the gradient of the density distribution.

Denoting as ρ_v the density of antigen non-experienced T cells [ANE CD95-] and ρ_m the density of antigen experienced (AE) T cells [AE CD95+ CD8+] we have the accumulation of AE T cells, i.e. the conversion from the ANE to the memory T cells due to the primary antigenic stimulation. Due to secondary antigenic stimulation we have expansion of the AE T cells at constant rate β .

Then, the following balance equations for the density of ANE T cells ρ_v is obtained:

$$(0.1) \quad \frac{\partial \rho_v}{\partial t} + \nabla \cdot \mathbf{J}_{\rho_v} = -\alpha \rho_v - \beta \rho_m$$

where α and β are the conversion rate factors and $\alpha, \beta \geq 0$.

The Fick's law of diffusion is assumed for the density flux of ANE T cells:

$$(0.2) \quad \mathbf{J}_{\rho_v} = -\gamma \nabla \rho_v$$

where γ is a phenomenological coefficient depending on temperature.

The hypothesis of conservation of the overall T cell compartment is expressed by the law of conservation of mass for the total density of cells:

$$(0.3) \quad \frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = 0$$

where $\rho = \rho_v + \rho_m$ and \mathbf{v} is the velocity.

Regarding to the gradient of the ANE T cells, we suppose that during both antigenic stimulation (primary and secondary) the decrement in the concentration of virgin T cells, together with the flow in the direction of contact with the antigen surface (the place with the receptors are activated) cause an increment in the gradient of the virgin T cells. The following balance equation for the gradient is then introduced:

$$(0.4) \quad \frac{\partial(\nabla \rho_v)}{\partial t} + \nabla \cdot \mathbf{J}_{\nabla \rho_v} = \beta \rho + (\alpha - \beta) \rho_v$$

In the following the flux of the gradient will be neglected being of the third order in the derivatives of the space variables (in case of Fick's law for its flux vector).

The particular dynamic we are considering, i.e. conversion of ANE T cells into AE one, happens mainly in the lymphatic fluid. Lymph is an alkaline fluid that flows in the lymphatic vessels and bathes tissues and organs. The lymphatic vessels have one-way valves that prevent back flow. Along these vessels there are small bean-shaped lymph nodes that serves as filters of the lymphatic fluid. In the lymph nodes antigen is usually presented to the immune system. We have chosen to model it as an ideal viscous fluid. Then the usual rheological equation

$$(0.5) \quad \Phi = p\mathbf{I} - \mu \xi^D$$

is assumed, where Φ is the Cauchy stress tensor, p is the pressure, μ is the dynamical viscosity and ξ^D is the deviator of the rate of deformation. This phenomenological equation is used together with the equation of motion to obtain the classical Navier-Stokes equation.

Considering, at our stage, only one space dimension, we obtain a quasi-linear system of equations of first order for the following state variables:

$\rho, \rho_v, \nabla \rho_v, v$ where v is the velocity in one dimension. We also deal with the following phenomenological parameters: α, β (conversion rates), and γ (coefficient of Fick's law), and the phenomenological coefficients p and μ . The stability of the system is analysed and discussed.

REFERENCES

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