Heterogeneity in cell-mediated immune response

One of the hallmarks of human cancer, which is a challenge to the implementation of efficient targeted therapies, is heterogeneity. This includes interpatient heterogeneity (variations among tumors within different patients), intrapatient tumor heterogeneity (heterogeneity among the tumor cells of an individual tumor or patient) and immune cells heterogeneity (existence of many different immune cell subsets). Altogether these lead to heterogeneity in immune responses and also differences in treatment responses.

Mathematical models can be employed as a complementary approach to the current clinical and laboratory research to better understand the impact of heterogeneity on cancer therapy. Cancer and the immune response of the body are highly complex phenomena that involve several cell types, different molecules, and processes. Any mathematical model is just a simplification of this complexity and can only shed light on a small part of its driving mechanisms.

Model

Suppose that we have a very simple model of the immune response to the growth of a tumor with *ab initio* heterogeneity. Our system consists of two kinds of tumor cells, and two subtypes of effector cells:

$$\begin{aligned}
\frac{dT_1}{dt} &= g_1 T_1 - a_{11} E_1 T_1 - a_{12} E_2 T_1 \\
\frac{dT_2}{dt} &= g_2 T_2 - a_{21} E_1 T_2 \\
\frac{dE_1}{dt} &= p_1 - d_1 E_1 - e_1 (T_1 + T_2) E_1 + \frac{r_1 (T_1 + T_2)}{s_1 + T_1 + T_2} E_1 \\
\frac{dE_2}{dt} &= -d_2 E_2 - e_2 T_1 E_2 + \frac{r_2 T_1}{s_2 + T_1} E_2 + r_3 E_1 (T_1 + T_2)
\end{aligned}$$

where T_1 and T_2 are the two cancer cell types and E_1 and E_2 are the two effector subtypes. E_1 and E_2 are supposed to model, in a very simple way, two major types of cytotoxic cells representing the innate (NK) and adaptive ($CD8^+$) immune responses, respectively.

The innate immune responses are the first line of defense against invading pathogens by recognizing conserved features of pathogens that are not present in uninfected host. Natural killer (NK) cells are innate immune cells that show strong cytolytic function against physiologically stressed cells such as tumor cells and virus-infected cells.[1,2] Beside the important cytolytic

function, the innate immune response is required to initiate adaptive immune responses,[1,2] for example by secreting molecules and chemicals that initiates the clonal selection of lymphocytes and recruit the most effective cells to fight pathogens. These include for example $CD8^+$ T cells.

The adaptive immune system includes both humoral immunity components and cell-mediated immunity components and destroys invading pathogens. Unlike the innate immune system, which is pre-programmed to react to common broad categories of pathogen, the adaptive immune system is highly specific to each particular pathogen the body has encountered. The cells that carry out the adaptive immune response are white blood cells known as lymphocytes. B cells and T cells, two different types of lymphocytes, carry out the main activities: antibody responses, and cell-mediated immune responses. cytotoxic T cell (also known as $CD8^+$ T cell or killer T cell) is a T lymphocyte (a type of white blood cell) that kills cancer cells, cells that are infected by intracellular pathogens (such as viruses or bacteria), or cells that are damaged in other ways.

In our simple model we consider two types of cancer cells, a wild type and a mutant, and two types of effector cells, innate and adaptive cytotoxic cells. The model assumes an exponential growth for both tumor cells T_1 and T_2 in the absence of immune response, with intrinsic birth rates g_1 and g_2. The heterogeneity inside the tumor in this simple model is considered by having, first, different reproduction rates and, second, different interactions with effector cells. Impacts of the effector cells on tumor cells are modeled simply with prey-predator interactions. Innate effector cells E_1 are assumed to be present normally, even in the absence of tumor cells and are able to eliminate both kinds of tumor cells $T_{1,2}$, while the adaptive effector cells E_2 are unable to recognize or attack the tumor cell variant T_2. This could occur due to the inability of dendritic cells to process or deliver antigenic material from tumor cells T_2 to the adaptive immune system, possibly due to some mutation at the tumor T_2 antigen or epitope.[3] Both kinds of effector cells deplete their cytocidal capacities after some number of encounters. To consider this exhaustion of T cells in the model, we assume that both kinds of effector cells deplete their cytocidal capacities after some number of encounters with tumor cells, becoming inactive.[3] It is assumed that cytocidal activities of effector cells stimulate the recruitment of more effector cells of that type. For this recruiting term, we use Kuznetsov et al. (1994) assumption,[4] that leads us to a Michaelis–Menten dynamic. In the case of adaptive cells E_2, in addition to being recruited by interactions with T-cell processed tumor cells through a Michaelis–Menten dynamic, additional E_2 cells are stimulated by the interaction of E_1 cells with tumor cells.[5]

Tasks

1- Explain the ODEs: Simply explain how the above mentioned processes are formulated in our ODEs.

2- Improve the model:

> 2.1- Exponential growth might be a good approximation for the first stages of tumor growth but is not a realistic model, since it assumes access to infinite

amount of resources. To make the model more realistic, substitute the exponential growth term with a logistic growth which accounts for self-competition within each tumor cell population for resources like nutrients, space and others.

2.2- Also, consider interaction terms for mutual competitions between the two different kinds of tumors cells. Assign different interaction parameters since they may have different angiogenic factors, i.e., differences in the processes by which a tumor attracts blood vessels to nourish itself and sustain its existence.[3]

Hint: Appendix (Competitive Lotka–Volterra equations)

3- Explain the logic behind the Michaelis–Menten recruiting term.

Hint: Kuznetsov et al. (1994)

4- Build the improved model (task 2) with any desired software and run it with the parameters listed in the table and with the initial values of $T_1 = 8.0 \times 10^7$, $T_2 = 2.0 \times 10^7$, $E_1 = 1.10 \times 10^7$, $E_2 = 0$ cells.

parameter	unit	value*
g_1	day^{-1}	5.14×10^{-1}
g_2	day^{-1}	$l \times g_1$
K_1	cell	5.00×10^8
K_2	cell	$q \times K_1$
c_{12}	$cell^{-1}day^{-1}$	1.10×10^{-9}
c_{21}	$cell^{-1}day^{-1}$	$n \times c_{12}$
a_{11}	$cell^{-1}day^{-1}$	1.10×10^{-7}
a_{12}	$cell^{-1}day^{-1}$	1.10×10^{-10}
a_{21}	$cell^{-1}day^{-1}$	$m \times a_{11}$
p_1	$cell\,day^{-1}$	1.30×10^4
d_1	day^{-1}	4.12×10^{-2}
d_2	day^{-1}	2.00×10^{-2}
e_1	$cell^{-1}day^{-1}$	3.42×10^{-10}
e_2	$cell^{-1}day^{-1}$	3.42×10^{-10}
r_1	day^{-1}	1.24×10^{-1}
r_2	day^{-1}	1.24×10^{-3}
r_3	$cell^{-1}day^{-1}$	1.10×10^{-7}
s_1	cell	2.02×10^7
s_2	cell	2.02×10^7
l		0.35
m		1
n		1.5
q		1

* Some parameters are borrowed from [3, 4] and some are estimated.

4.1- An observed behavior that was mysterious to clinicians is called dormancy:

when the tumor stays very small for a relatively long period of time, and subsequently grows to be dangerously large.[3,5] Plot the tumor total volume (size) over time. Is our heterogeneous model able to generate such a behavior? To which parameter is this behavior sensitive?

4.2- Another interesting observation is that two simulated patients with almost identical characteristics can have drastically different fates: one can have a progressive disease (tumor grows to a large size) while the immune response of the other patient is able to keep the tumor relatively small.[3,5] Check if this model is sensitive (in the sense that described above) to the initial condition of E_1 effector cells. In the case of sensitivity, find the critical population of $E1$ effector cells. Plot the system trajectory in the phase space of "total tumor volume vs. number of E_1 cells," and also the tumor volume dynamics over time for two different initial value of E_1 below and above the critical value. One may expect intuitively that higher number of effector cells in the body improves the patient condition and decreases the tumor volume. Is your observation in agreement with this expectation?

4.3- Perform sensitivity analysis to discover which components of the model contribute most significantly to the final tumor volume.

Appendix: Competitive Lotka–Volterra equations

Given two populations, x_1 and x_2, with logistic dynamics, the Lotka–Volterra formulation adds an additional term to account for the species' interactions. Thus the competitive Lotka–Volterra equations are:

$$\frac{dx_1}{dt} = g_1 x_1 (1 - \frac{x_1}{K_1}) - c_{12} x_1 x_2$$
$$\frac{dx_2}{dt} = g_2 x_2 (1 - \frac{x_2}{K_2}) - c_{21} x_1 x_2$$

Here $x_{1,2}$ are the size of the populations at a given time, $g_{1,2}$ are inherent per-capita growth rates, and $K_{1,2}$ are the carrying capacities. c_{12} represents the effect species 2 has on the population of species 1 and c_{21} represents the effect species 1 has on the population of species 2. These values do not have to be equal. Because this is the competitive version of the model, all interactions must be harmful (competition) and therefore all c-values are positive. Also, note that each species can have its own growth rate and carrying capacity.

References

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