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A MODEL OF PROLIFERATION CONTROL IN IMMUNE RESPONSE

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A considerable proliferation of participating cells is a characteristic feature of the immune response. Some new experimental findings suggest that this proliferation is controlled by a lymphocyte factor called interleukin 2. Assumptions on the course of the immune response under such control are formulated, and a new model of the immune response is constructed; it consists of a system of differential equations and some functions describing transition probabilities.

1. INTRODUCTION

Immune response is the result of a complex interplay and mutual relationship of many components of the immune system. It is this complexity which makes experiments involving non-homogeneous cell populations insufficient for studying the dynamics of immune response. To avoid this problem isolated clones of different lymphocyte subsets and their behaviour *in vitro* are studied. Another approach is using simulations of immune response in mathematical models.

Concerning the studies of individual components participating in immune response, lymphocyte factors involved in the control of immune response have been recently studied in detail. Particular attention has been paid to the distinct class of molecules having growth supporting abilities, called interleukin 2 (IL 2). Besides its function [20] biochemical properties of IL 2 have been studied [4].

Studies dealing with long term cultures of lymphocytes *in vitro* where the presence of IL 2 is essential [5], [16], [18], [6], [23], [19], [22] have contributed to the elucidation of IL 2 function. Smith et al. [21] have suggested a participation of IL 1 and IL 2 in T lymphocyte proliferation. On the basis of these findings we have prepared a model for the mechanism of the effect of IL 2, in which the clonal expansion of cells involved in the response to a given antigen is controlled.

It is known that substances isolated as IL 2 and assayed functionally also have the ability to enhance antibody formation by B cells [24], [7], [17]. Therefore

we started with the assumption originally formulated for T cells — that the proliferation of cells in immune response is controlled by IL 2. This extends the previous models in which participation of B cells and antigen only were assumed [8], [9], [10], [11], for further subsets of cells and a cooperation mediated by their products — IL 1, IL 2.

2. MODEL ARRANGEMENT

This model involves three populations of cells, an antigen and two-factors — IL 1, IL 2 — produced by the cells after initial antigenic stimulus.

The model is based on the following assumptions:

1) Cells (differentiation and proliferation indicated by solid lines in Fig. 1):

Macrophages ($M\phi$) — remain constant, produce IL 1 after an antigenic stimulation.

T helpers — enter the system as hX precursors, after antigenic stimulus they change into hX' sensitive to the second signal. IL 2 effects a change of hX' into the proliferating hY , while IL 1 effects a direct change of hX' into hZ ; hY after repeated antigenic signal change into hZ producing IL 2.

B cells — enter the system as precursors X ; after an antigenic stimulus they become X' sensitive to the second stimulus (IL 2), thus becoming proliferating Y , which after repeated antigenic signal change into antibody (Ab) producing Z cells. Without meeting the antigen again, and in absence of sufficient amount of IL 2, Y -cells become memory cells Y_m .

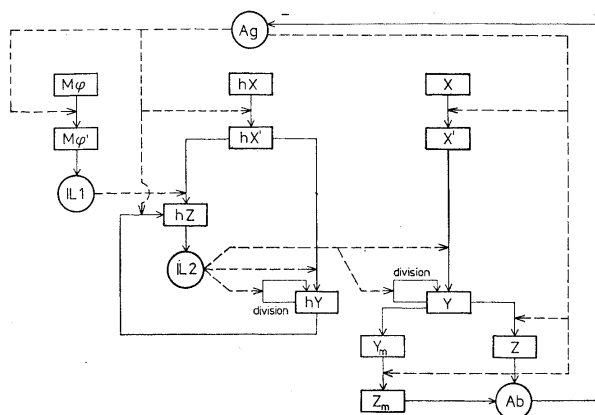


Fig. 1. Block diagram of interactions during the immune response (\rightarrow transition of cells, \dashrightarrow signals).

2) Signals (indicated by dashed lines in Fig. 1):

Antigen (Ag) – I. external information labelling the cells which take part in the immune response; II. signal to the final differentiation (after proliferation and decrease in IL 2 concentration).

IL 1 – initiates the lymphocyte response via a stimulation of hX' to become hZ and to produce IL 2.

IL 2 – a signal for hY and Y to proliferate.

3. NOTATION

t	time (in hours)
a	amount of antigen
v	amount of IL 1
w	amount of IL 2
	} (in arbitrary units)
h_x	number of non-activated precursors of helper cells (hX-cells)
h_a	number of precursors of helper cells activated by antigen (hX'-cells)
h_y	number of proliferating precursors of helper cells (hY-cells)
h_z	number of helper cells producing IL 2 (hZ-cells)
x	number of non-activated precursors of effector cells (immunologically competent cells, X-cells)
y	number of precursors of effector cells activated by antigen and proliferating (X'- and Y-cells)
y_m	number of memory cells (Y _m -cells)
z	number of effector cells (antibody producing cells, Z-cells), progeny of Y-cells
z_m	number of effector cells (Z _m -cells), progeny of Y _m -cells
s	total number of effector cells, $s = z + z_m$
m	number of macrophages (Mφ)
r_m	number of specific receptors on the surface of a Y _m -cell ($r_m = \eta_y r_x, \eta_y \geq 1$)
$\eta_y r_x$	number of specific receptors on the surface of a Y _m -cell
r	total number of specific receptors, $r = r_x(x + y + h_x + h_a + h_y + \eta_y y_m)$
λ_x	transition rate from stem cells into X- and hX-cells
λ_y	proliferation rate of Y-, Y _m - and hY-cells
λ_v	rate of production of IL 1 by a macrophage
λ_w	rate of production of IL 2 by a hZ-cell
μ_z	death rate of Z-, Z _m - and hZ-cells
μ_y	death rate of Y- and hY-cells
μ_{y_m}	death rate of Y _m -cells
μ_v	binding rate of IL 1 to hX'-cells
μ_w	binding rate of IL 2 to hX'-, hY-, X'-, Y- and Y _m -cells
μ_{vw}	decay rate of IL 1 or IL 2
a_0	amount of antigen at $t = 0$

Table 1. Transition functions (probabilities) $P(Q) = Q^v/(1 + Q^v)$

Q	$P(Q)$ (notation)	$P(Q)$ is probability	$1 - P(Q)$ is probability
$a/(q_x r)$	φ_x	of the transition $X \rightarrow Y$ or $hX \rightarrow hX'$, respectively	of the surviving of X or hX , respectively
$a/(q_y r)$	φ_y	of the transition $Y \rightarrow Z$ or $hY \rightarrow hZ$, respectively	of the surviving of Y or hY , respectively
$a/(q_{ym} r)$	φ_{ym}	of the transition $Y_m \rightarrow Z_m$	of the surviving of Y_m
$w/(q\theta v)$	θ	of the transition $hX' \rightarrow hY$ under condition that transition $hX' \rightarrow hY$ or hZ will be realized	of the transition $hX' \rightarrow hZ$
$(v + w)/[q_\theta h_a + q_w(h_a + h_y + y + y_m)]$	χ	of the transition $hX' \rightarrow hY$ or hZ	of the surviving of hX'
$a/(q_m r)$	ζ	that macrophage produces IL 1	that macrophage does not produce IL 1
$h_z/[q_\psi(h_y + y + y_m)]$	ψ_1	$\psi = \psi_1 \psi_2$ is probability that the cell will be stimulated to proliferation	$1 - \psi$ is probability that the cell will not be stimulated to proliferation
$w/(q_a a)$	ψ_2		

h_0 amount of hX-cells at $t = 0$

x_0 amount of X-cells at $t = 0$

m_0 amount of macrophages at $t = 0$

Notation of transition functions is given in Table 1.

4. MODEL

Regulation of the immune response depends on absolute amounts of elements engaged in it (i.e., cells, antigen, interleukins) as well as on relations between them. As the first approximation to these relations, we suppose to use transition functions given in Table 1 in the standard form

$$(1) \quad P(Q) = Q^v/(1 + Q^v)$$

with $Q = A/(qB)$, where A and B are concentrations or amounts of appropriate substances or cells, respectively, q is value, for which $P(Q) = \frac{1}{2}$, and the constant v determinates curvature of the function $P(Q)$. (Similar functions are often used as threshold functions – see, e.g., [11], [14]; $P(Q(t)) dt$ is the probability that appropriate event occurs during the interval $(t, t + dt)$).

The proposed model describing the course of the immune response is given by the following system of 11 ordinary differential equations:

Let us suppose that non-activated precursors of helper cells hX arise from stem cells with constant rate, and that they do not proliferate; their birth and death rates are identical.

Contact of these cells with antigen causes their change into activated cells hX'; probability of this change depends on the ratio of the amount of free antigen and of the number of cells capable to bind it (or of the number of specific receptors on the surface of these cells, respectively). Hence,

$$(2) \quad \dot{h}_x = \lambda_x - h_x(\varphi_x + \lambda_x/h_0).$$

Activated precursors of helper cells (hX') arise from non-activated precursors (see above), and IL 1 or IL 2 may cause their further change into hY- or hZ-cells, respectively, with transition probability depending on the relative amount of IL 1 and/or IL 2 with respect to the number of cells which may be stimulated by interleukins. Hence

$$(3) \quad \dot{h}_a = h_x \varphi_x - h_a \chi.$$

Cells hX' influenced by IL 2 change into proliferating precursors of helper cells hY; hY-cells proliferate if sufficient amount of IL 2 is available (probability of this proliferation depends on the relative amount of IL 2 with respect to the number of appropriate cells as well as on the ratio of the amount of IL 2 and antigen). In the case of dominance of antigen, they change into helper cells hZ.

$$(4) \quad \dot{h}_y = h_a \chi \theta + h_y [(\lambda_y \psi - \mu_y) - \varphi_y (1 - \psi)].$$

Helper cells hZ producing IL 2 arise from hX'-cells (especially at the beginning of the immune response) and from hY-cells:

$$(5) \quad \dot{h}_z = h_a \chi (1 - \theta) + h_y \varphi_y (1 - \psi) - \mu_z h_z.$$

Fate of non-activated precursors of effector cells (X) is similar to that of non-activated precursors of helper cells:

$$(6) \quad \dot{x} = \lambda_x - x(\varphi_x + \lambda_x/x_0).$$

Only one differential equation is constructed for cells activated by antigen (X') and for proliferating cells (Y) (this simplification is negligible as the amount of X'-cells is usually very small). This equation describes their rise from X-cells, their proliferation caused by IL 2 (similarly as proliferation of hY-cells), their natural decrease as well as their transition (after decrease of the relative amount of IL 2) into memory cells or antibody forming cells. Hence,

$$(7) \quad \dot{y} = x \varphi_x + y [(\lambda_y \psi - \mu_y) - (1 - \psi)].$$

When Y-cell ceases its proliferation, and if sufficient amount of antigen is present,

then Y-cell changes into non-proliferating antibody forming cell Z:

$$(8) \quad \dot{z} = y \varphi_y (1 - \psi) - \mu_z z .$$

When Y-cell ceases its proliferation, but does not contact sufficient amount of antigen, it changes into a memory cell Y_m surviving for a long time (this is expressed by its death rate μ_{ym} , usually very small). This cell is capable of proliferating (under an eventual further stimulus by IL 2) or of changing into antibody forming cell Z_m (under the eventual further stimulus by antigen), respectively,

$$(9) \quad \dot{y}_m = y(1 - \varphi_y)(1 - \psi) + y_m[(\lambda_y - \mu_{ym}) - \varphi_y(1 - \psi)] .$$

Z_m -cells have similar fate as Z-cells,

$$(10) \quad \dot{z}_m = y_m \varphi_y (1 - \psi) - \mu_z z_m .$$

Total amount of antibody forming cells is

$$(11) \quad s = z + z_m .$$

Macrophages form IL 1 with intensity rate λ_v , and with probability depending on the relative amount of free antigen with respect to the number of cells sensitive to the antigen. IL 1 is run out by hX'-cells (rate μ_t); its natural decay rate is μ_{vw} . Hence

$$(12) \quad \dot{v} = \lambda_v m \zeta - (\mu_v h_a + \mu_{vw}) v .$$

IL 2 is produced by hZ-cells (with rate λ_w) and is run out by hX'-, hY-, X'-, Y- and Y_m -cells (rate μ_w); its natural decay rate is μ_{vw} . Hence,

$$(13) \quad \dot{w} = \lambda_w h_z - [\mu_w (h_a + h_y + y + y_m) + \mu_{vw}] w .$$

The amount of macrophages is supposed to be constant, $m = m_0$.

The basic regulatory factor of the immune response is the antigen. Its fate is a rather complicated process controlled by many factors (number of specific cells, amount of antibodies, etc.). As an substitute of this process the following description of the amount of antigen is used:

$$(14) \quad a(t) = a_0 \exp \{ -\mu t \} , \quad t > 0 ,$$

where $\mu (>0)$ is a suitable constant (intensity of the decrease of the amount of antigen).

5. EXAMPLE

Course of the primary immune response (after a dose of non-proliferating antigen given at $t = 0$) was simulated by the numerical integration of the system of differential equations (2)–(10), (12), (13).

Results of the integration for one set of parameter values are given in Fig. 2–4,

time course of transition functions given in Table 1 can be found in Fig. 5-6; the appropriate parameter values were chosen on the basis of experimental findings from the literature as well as of extensive comparison study of simulation results

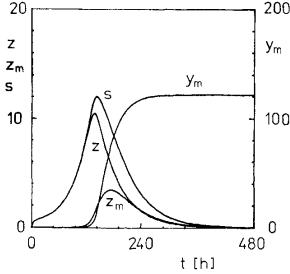


Fig. 2. Time course of the mean number of antibody forming cells (z, z_m, s) and memory cells (y_m) during primary immune response.

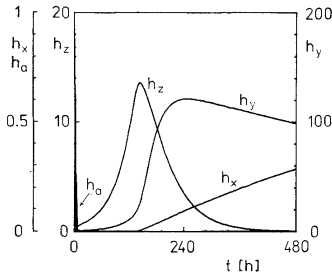


Fig. 3. Time course of the mean number of helper cells and their precursors (h_x, h_a, h_y, h_z) during primary immune response.

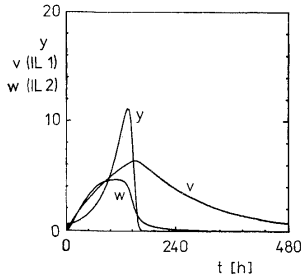


Fig. 4. Time course of the mean number of Y cells (y) and of the mean amount of IL 1 and IL 2 (v, w) during primary immune response.

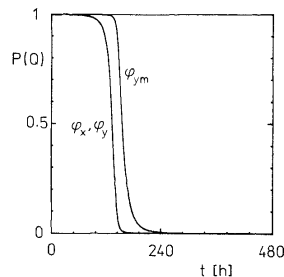


Fig. 5. Time course of transition rates φ_x (from precursors X or hX into activated cells), φ_y (from proliferating into producing cells), φ_{ym} (from memory Y_m into antibody producing Z_m).

for different sets of parameter values. In this example, following parameter values were used:

$$\begin{aligned} \mu &= 0.02, \lambda_x = 0.001, \lambda_y = 0.07, \mu_y = 0.001, \mu_{ym} = 0.00002, \mu_z = 0.02, r_x = 10^4, \\ \eta_y &= 10, \lambda_a = \mu_v = 0.07, \lambda_w = 0.15, \mu_w = 0.015, \mu_{vw} = 0.007, q_x = q_y = 10, \\ q_{ym} &= q_m = 1, q_a = 10^{-10}, q_\theta = q_\psi = q_v = q_w = 0.1, v = 2; \text{ initial values: } a_0 = \\ &= 10^8, h_x = h_0 = 1, x = x_0 = 1, m = m_0 = 1, h_a = h_y = y = y_m = z = z_m = \\ &= s = v = w = 0. \end{aligned}$$

All rate constants are related to the used time scale and have dimension h^{-1} .

Results of the simulation agree with the known course of the immune response: for many antigens experimentally used, the primary response increases quickly until its maximum is reached (about 6th day), then decreases more slowly; there is clear preparation to the secondary response (number of memory cells increases).

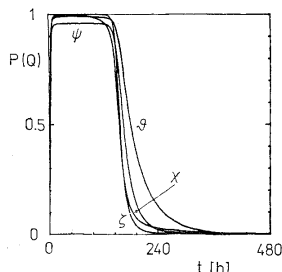


Fig. 6. Time course of transition rates θ (from activated hX' into proliferating hY cells), χ (from hX' into hY or hZ cells), ζ (of $M\phi$ to produce IL 1), ψ (of a cell to be stimulated to proliferation).

6. DISCUSSION

This model is based upon previous models of antibody formation in immune response ([10], [8], [9], [11]) but instead of assuming a constant maximum number of Y cells generations we consider a regulatory mechanism the existence of which can be supposed on the basis of recent experimental results. Although there are several mathematical models for cell cooperation during immune response ([12], [15], [1], [3], [13]) in which the stimulatory and inhibitory effects of T cells on the antibody production by B cells are modelled, no one has yet attempted to model immune response where the influence of T cell growth factor would be involved. On the other hand, some authors assume that the proliferation signal is given by an antigen, while a second signal – for differentiation into plasma cells – is given by a monovalent specific substance produced by T cells [2].

As already mentioned above, the results of our modelling of the course of the antibody response are in good qualitative agreement with experimental results. The model exhibits also a number of other properties known from experimental data: the maximum of the antibody response increases with increasing dose of given antigen but after exceeding a particular value of the antigen dose, the maximum of the response decreases with increasing dose of antigen, and extremely large doses entirely suppress the immune response.

The numerical integration of our system of differential equations for various sets

of parameter values has shown that even minute changes of the values of some parameters have influenced behaviour of the system dramatically (e.g. λ_i) whereas great changes of values of some other parameters have influenced the system slightly (e.g. x_0 , h_0 , m_0 , q_x , q_m , q_{ym}). Also, simultaneous great changes of some parameters when their ratio remained constant have influenced the behaviour of the system less than a slight change of one parameter value which has changed the parameters ratio (e.g. parameters bearing upon IL 1 and IL 2). These findings necessitated possibilities of simplification of proposed system of equations, and, further, the possibility of searching for optimal arrangement of experiments *in vitro*.

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