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Mechanisms of Ageing and Development 124 (2003) 433–443

mechanisms of ageing and development

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Age related changes in population of peripheral T cells: towards a model of immunosenescence

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Received 16 June 2002; received in revised form 15 September 2002; accepted 20 December 2002

Abstract

In this paper, we presented the results of analysis of experimental evidence for the decline of the human immune system functioning with age using mathematical model of immunosenescence. The most prominent changes in this system are related to the decline in the T-cellular immunity. These include the decline in the naïve T cells generation rate, shrinkage of the volume of the peripheral lymphoid tissue, decline of absolute and relative concentrations of naïve T cells in the blood, shortening of the average telomere length of T cells. These alterations in the immune system are responsible for sharp increase of morbidity and mortality caused by infectious agents at old ages. Analysis shows that concentrations of memory and naïve T cells in peripheral lymphoid tissue are the key variables in this process. Simulation experiments with our model show that the average life span of memory T cells must grow with age, and that decreasing of antigenic load led to considerable increase in organism's resistance in middle ages, but only to slight increase in old ages. Restriction in the rate of thymus involution resulted in an increase of organism's resistance to infections in old ages. However, this growth is accompanied by the decline of concentration of memory T cells and shortening of their life span. The proposed model describes the trade-off between concentrations of naïve and memory T cells and their potential to proliferate in human organism.

Keywords: Immunosenescence; Mathematical model; T cells

1. Introduction

The efficiency of the immune system functioning declines with age. This statement is based on empirical data on substantial increase of frequency and lethality of infectious diseases at old ages (e.g. Aspinall, 2000). The decline of immunity is also accompanied by an increase in the frequency of cancer and autoimmune diseases (Wick et al., 2000). Several reviews summarize findings in this area (Fahey et al., 2000; Miller, 1996; Solana and Pawelec, 1998; Wick and Grubeck-Loebenstein, 1997). It turned out, however, that age related changes in the immune system do not look as just decline in major immunological indices. In particular, it was shown that although the number and functional activity of T cells declines with age the population of B cells does not experience significant changes. The components of the system of non-specific defense become even more active at old than at young ages. This means that age related changes in the immune system deal rather with the adjustment, adaptation and remodeling than with just the simple decline in functioning (Franceschi et al., 1999). Recent data suggest the possible role of replicative senescence of lymphocytes (Effros, 1998) and the reduction of the repertoire of the pool of the peripheral lymphocytes (Posnett et al., 1994) in such adaptation.

Centenarians studies brought new paradoxes in the complicate picture of immunosenescence: a number of immune parameters by centenarians are similar to those 50–60-years-old (Franceschi et al., 1995). These findings indicate that the weakening of immunity in old ages is not an inevitable process. They point on possibility to identify factors controlling aging of immune system and develop approaches for slowing down this process.

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0047-6374/03/$ - see front matter
doi:10.1016/S0047-6374(03)00019-8

The immune defense is a result of complex dynamic reactions, which include processes developing at the molecular, cellular, and tissue levels as well as at the level of the entire organism. The mathematical modeling of this phenomenon would be extremely helpful for testing the hypothesis about the regularity of these processes.

Up to date only one mathematical model of T cell dynamics in human aging was published (Luciani et al., 2001; Mariani et al., 2002). The purpose of this work is testing the hypothesis that the depletion of virgin $CD8^+$ T lymphocyte is a reliable measure of the death risk. This idea received interesting application to demographic data. The purpose of our work is to develop integrated dynamical model capable to reflect general patterns of T lymphocyte immunosenescence. We hope that this model will be useful for those who want to estimate the sensitivity of age related changes in immune system to real and hypothetical interventions.

In this paper we describe several processes which accompany immunosenescence and suggest the model of age related changes in the pool of peripheral T lymphocytes which take place in the human organism after 18 years. We investigate several regimes of functioning of the immune system. They include the consequences of 50% reduction of the pathogen load, the results of the 50% reduction of the rate of thymus involution, as well as slowing down of several other component processes in the immune system.

2. The immune defense mechanisms

The human immune system is composed of different species of cells. The most numerous of them are lymphocytes. In an organism of an 18–20-years-old individual about $(3–8 \times 10^{12})$ such cells are dispersed. The total weight of them is estimated between 800 and 1500 g. 95–98% of lymphocytes are located in lymphatic nodes and in the spleen. The rest are located in the blood (1%), lymph (1%), thymus and bone marrow. Lymphocytes located in the lymph nodes, spleen, lymph and blood comprise the pool of peripheral lymphocytes, which perform the immune defense of an organism. The defense mechanisms are based on the lymphocyte capability to recognize certain antigen or in other words, a unique molecular structure specific for a certain pathogen. The recognition of a pathogen results in lymphocyte proliferation and the generated effector cells population performs suppression and elimination of a pathogen.

The processes of antigen recognition and lymphocytes proliferation are performed in the lymphoid tissue, consisting for 98% of lymphocytes. Antigens are brought to the regional lymph nodes by the lymph from tissues and organs, and new-formed lymphocytes are delivered into the blood by the outflow lymph.

Three main species of lymphocytes are important to distinguish: B cells, cytotoxic T lymphocytes (CTLs) and T helpers. T helpers help in proliferation of both B cells and CTLs. The result of proliferation of B lymphocytes is plasma cells, which produce antibodies. CTLs are capable to recognize and destroy cells infected by virus. Coordinated response of populations of all three kinds of cells are necessary for suppression of the pathogen. Important features of the anti-infectious immune response are that lymphocyte proliferation starts only when the concentration of the pathogen is high enough, and that the first 10–12 lymphocytes' doublings are not accompanied by the production of the CTLs. During this period population of pathogens increases and the organism's damage increases as well. Substantial damage may even suppress the immune system and threaten the life of an organism. The time required for the production of the required number of lymphocytes of a given specificity depends on their initial concentration and the proliferation rate. Thus, the severity and the outcome of the disease depend on how many lymphocytes of a given specificity are available in the lymph nodes draining infected tissue and on their proliferative capacity. Both these parameters decline with age. Since acute infections are relatively rare events, the majority of lymphocytes in the nodes do not receive a signal for proliferation. In this case after about 10 days the lymphocyte leave the node, go into the blood and settle in some other node to wait for its antigen. Such a behavior, called the recirculation of lymphocytes, maintains the integrity of the immune system. It is believed that after several such voyages the lymphocyte dies. The rate of death depends on the lymphocyte's origin.

Part of the recirculating lymphocytes is produced by the stem cells with subsequent differentiation. Additional differentiation is associated with the synthesis and quality testing of the antigen receptors. T cells get such specialization in thymus. B cells become educated in the bone marrow. After such procedure these cells go into blood and recirculate. Such cells, which did not participate in the immune response, are called naïve lymphocytes.

The rest part of the pool of the recirculating lymphocytes consists of memory cells. They are created after completion of the immune response to the antigen. In the process of immune response lymphocytes perform 15–20 or more divisions. As a result the number of cells of a given specificity increases 10^5–10^6-fold. After elimination of a pathogen most of these cells die during about 10 days (Lanzavecchia and Sallusto, 2000). The concentration of the survived (memory) cells is about 100 times higher than that of initial naïve cells. This guaranties in future the rapid and powerful immune response. The estimates of the life span of both naïve

and memory T cells varies from 10 days to 10 years and depends on the state of the immune system and conditions of the experiment (McCune et al., 2000; Parijs and Abbas, 1998; Tough and Sprent, 1994).

The life span of lymphocyte is determined by homeostatic properties of the immune system. By homeostasis we mean the regulation of the lymphocytes' pool in an organism. It is assumed that the number of lymphocytes is determined by the capacity of the peripheral immune system. If the increment of these cells exceeds the 'free space' in the lymph nodes their death rate accelerates. In case of deficiency the lymphocytes (firstly memory, but naïve possibly too) proliferate until 'free space' in the nodes will be filled (Berzins et al., 1998; Koetz et al., 2000; Tanchot et al., 1997). Some authors assumed that immune space may be split into functionally spaces for the naïve and memory T and B cells (Tanchot et al., 1997).

Note that the interpretation of the experimental evidence concerning factors determining lymphocyte life spans depend in particular on experiment duration. The conclusion that concentration of some species of lymphocytes did not influence concentration and life span of the other during several weeks (as in case of typical experiments with mice) does not mean that such independence will continue for years. It is well known that for humans the relative and absolute concentration of naïve T cells declines, and that of memory T cells increases with age. This may indicate the presence of coordinated regulation of the pool of these cells at the longer time intervals (see Fig. 1).

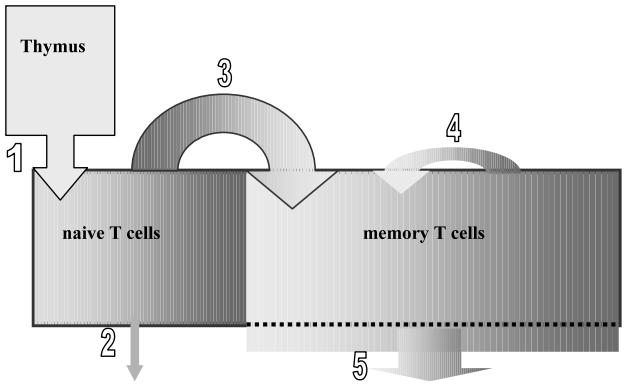

Fig. 1. A scheme of proposed mechanism controlling long-term homeostasis of peripheral T cell. The naïve and memory T cells share common space in lymphoid tissue. However, their concentrations are regulated by different rules. The naïve T cells have a privilege: their dynamics does not depend on concentration of memory T cells. The dynamics of and the average life time of memory T cells depend on total amount of T cells. (1) The new naïve T cells are produced in thymus and fill the peripheral pool of naïve T cells; (2) natural decay of naïve T cells; (3) memory T cells production from naïve cells in the result of antigenic stimulation; (4) memory T cells self-sustaining due to antigenic stimulation; (5) removal of the excess of memory T cells. Shading gradients illustrate differences in telomere length. Darker areas correspond to longer telomeres.

The important characteristic of the pool of the peripheral lymphocytes is its 'antigenic repertoire'. By this term we mean the total number of various antigens which can be recognized by the cells at a given time, and the number of the lymphocytes for each specific antigen. The memory cells and the naïve cells play different roles in the antigen repertoire: the naïve cells are responsible for its diversity, and memory cells provide enlarged initial value of lymphocytes for a relatively small number of experienced pathogens. So for humans the diversity of naïve T cells is about 2.5×10^7 specificities, and memory cells is $(1–2) \times 10^5$ specificities (Arstila et al., 1999). The peripheral pool of T lymphocytes is about 10^{12} cells and if the number of naïve cells is about the same as the number of memory cells, then per one of 2×10^5 specificities there are at average about 5×10^6 memory cells, and per one of 2.5×10^7 specificities there are at average 2×10^4 naïve cells. In particular 1 ml of lymphoid tissue (an average lymph node) contains 20 naïve lymphocytes/specificity. At ages between 90 and 100 when the concentration of naïve T cells declines ten times, there are only two naïve lymphocytes/specificity in 1 ml of lymphoid tissue. Due to possible variations in distribution of cells some regional nodes may have a smaller concentration of cells specific to distinct antigen. This will lead to a delay of the immune response and thus to an increase of a severity of the infections.

The essence of immune response is the rapid and repeated divisions of antigen specific lymphocytes. In the course of immune response lymphocytes undergo approximately 15–20 divisions. Total proliferative capacity of human T lymphocyte is about 40–45 divisions and depends on the telomere length. Telomers are the end parts of the chromosomes, which become shorter in every cell division. The lymphocyte reaches its unresponsiveness state when the telomere length reaches about one half of its initial value. Since the average length of telomeres in peripheral lymphocyte shorten with individual's age, the process of immunesenescence includes not only decline in the lymphocytes' number, but also the decline in their proliferative capacity (Effros, 1998; Globerson and Effros, 2000).

Fig. 2d shows the results of linear regression analysis of telomere length as function of age in two subpopulations of peripheral blood T lymphocytes (Rufer et al., 1999). One can see that the rates of telomere shortening in subpopulations of naïve and memory T cells are similar and equal to 30 and 25 bp/year, respectively (for $CD4^+$ T cells). The corresponding results for granulocytes and $CD4^+$ T cells are presented on Fig. 2e. We assume that the rate of telomere shortening in granulocytes may be considered as preliminary estimate for the rate of telomere shortening in the progenitor of naïve cells.

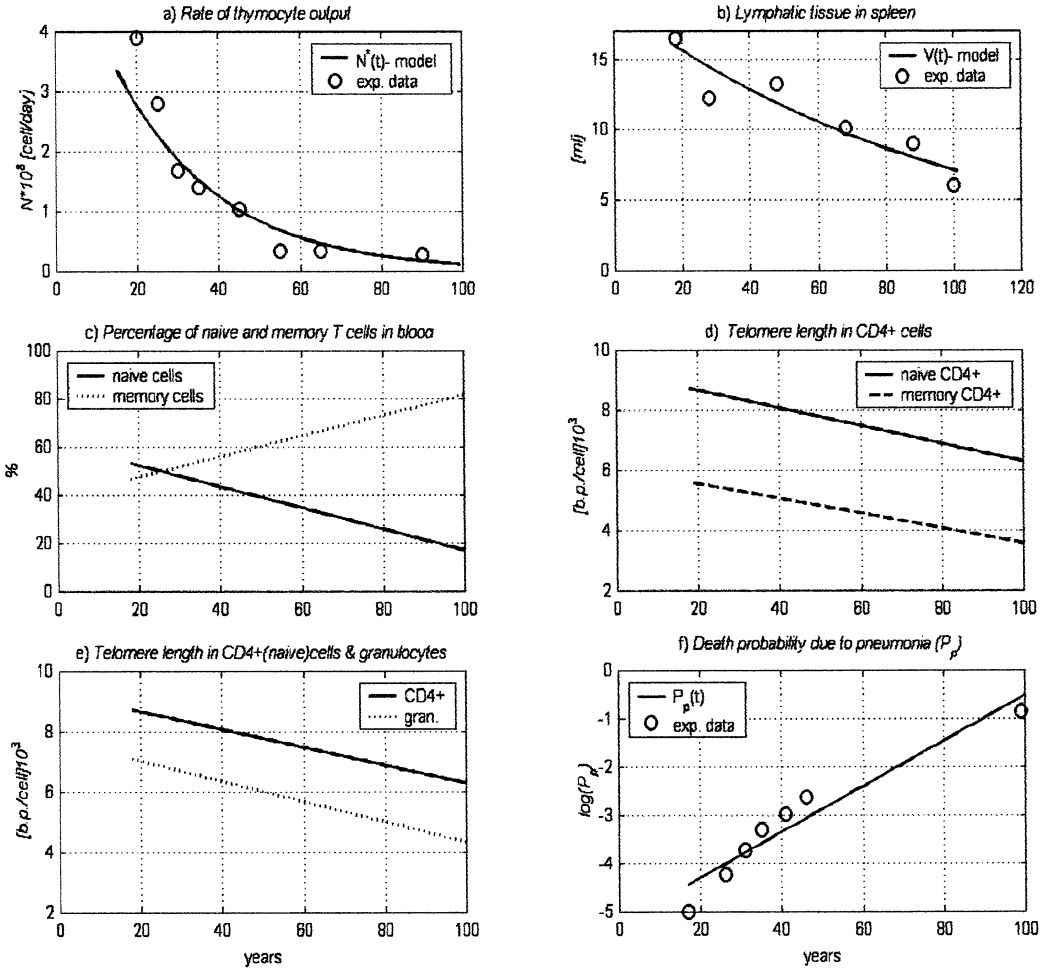

Fig. 2. The age dependent traits of human immune system; (a) the volume of lymphoid tissue in thymus [2] (these values are used in estimation of the rate of production of naïve T cells); (b) the volume of lymphoid tissue in spleen (these values are used in the estimation of the whole lymphoid tissue dynamics); (c) percentage of naïve and memory T cells in the blood (used in the estimation of populations of respective cells in peripheral lymphoid tissue); (d) telomere lengths in naïve and memory CD4+ cells [13]; (e) telomere lengths in naïve CD4+ cells and granulocytes [31]; (f) the logarithm of probability of death due to pneumonia (used as an indicator of immune resistance).

3. Mechanisms of aging in the immune system

Many characteristics of the immune system change during the aging process. However, most significant shifts are observed in T cell populations. In this paper we suggest a model of age related changes in this system (Fig. 2).

The involution of thymus is one of the most important features of aging in the immune system. The shrinkage of the thymic lymphoid tissue starts right after puberty. The 4–5-fold reduction is observed at age 35–40. At age 50 on average only 10% of the initial amount of lymphoid tissue is left. After this age the amount of lymphoid tissue diminishes slowly or stays about the same (Douek and Koup, 2000; McCune et al., 2000; Zhang et al., 1999). Thus, this tissue is the weakening source of naïve T lymphocytes and thymic hormone (Consolini et al., 2000). The age dependence of the rate of naïve T cells production is shown in Fig. 2a. It is obtained from the volume of lymphoid tissue in thymus (Sapin and Etingen, 1996). We assume that lymphoid tissue consists mainly of lymphocytes, (the mass of one lymphocyte is about 2.5×10^{-10} g) and that daily rate of naïve T cell production is 0.7–1% of the total number of thymocytes.

The age related changes in the peripheral immune system are less explored. Based on estimates of concentration of T cells in the blood the conclusion is often made that the total number of lymphocytes in an organism does not experience substantial changes during aging. Histologic findings, however, shows that lymphoid tissue tends to be replaced by connective and lipoid tissues. The process starts after 18–20 years and continues for the rest of the life. The rate of this process may differ in different groups of lymph nodes. For example, the amount of lymphoid tissue declines 3-fold in the intestine and 1.5–2 fold in the upper respiratory tract between ages 18 and 85. However,

changes in the same tissues in the urinary bladder are insignificant (Sapin and Etingen, 1996). The decline in the volume of the intact peripheral lymphoid tissue (IPLT) indicates the decline of the pool of the peripheral lymphocytes. The individual variability in the rate of the IPLT decline increases dramatically with the age. For estimation of model parameters we used data on the decline of lymphoid tissue in the spleen Fig. 2b (Sapin and Etingen, 1996). Fig. 2c shows the results of linear regression analysis which describe percentages of naïve and memory T cells in peripheral blood as functions of age (Fagnoni et al., 2000). These results give us simple approximation of changes in peripheral lymphoid tissue with age. Fig. 2f shows age dependence of the force of mortality due to pneumonia in the semi-logarithmic scale (Dolejs and Kozak, 2000; Bordin et al., 1999). This data are used as a measure of immune dependent vulnerability of individual organism.

4. Mathematical model

The mathematical model of age related changes in peripheral T cell population in the immune system is represented by the system of the following seven ordinary differential equations:

$$\frac{dN}{dt} = \frac{N^*}{V} - \alpha_1 \frac{L}{V}\, N - \mu_N N - \frac{dV}{dt}\frac{N}{V},$$

$$\frac{dP_N}{dt} = (P^* - P_N)\frac{N^*}{NV},$$

$$\frac{dM}{dt} = \rho_1\alpha_1 \frac{L}{V}\, N + \rho_2\alpha_2 \frac{L}{V}\, M + \mu_M(C^* - N - M) - \frac{dV}{dt} \times \frac{M}{V},$$

$$\frac{dP_M}{dt} = \rho_1\alpha_1 \frac{L}{V}(P_N - P_M - \lambda_N)\frac{N}{M} - \rho_2\alpha_2\lambda_M \frac{L}{V}.$$

$$\frac{dN^*}{dt} = -k_T N^*,$$

$$\frac{dV}{dt} = -k_V V,$$

$$\frac{dP^*}{dt} = -k_P P^*,$$

As initial conditions the following values were used: $t_0 = 6570$; $N(t_0) = 1.31 \times 10^9$; $M(t_0) = 1.21 \times 10^9$; $P_N(t_0) = 8.8 \times 10^3$; $P_M(t_0) = 5.7 \times 10^3$; $N^*(t_0) = 4 \times 10^8$; $V(t_0) = 1500$; $P^*(t_0) = 8.3 \times 10^3$.

5. Model variables

- $N^*(t)$, rate of naïve T cells influx in IPLT at the age t (cell/day);
- $V(t)$, volume of IPLT at the age t, (ml);
- $P^*(t)$, length of telomere repeats in naïve T cells produced at the age t, (bp/cell);
- $N(t)$, concentration of naïve T cells in IPLT at the age t, (cell/ml);
- $M(t)$, concentration of memory T cells in IPLT at the age of t (cell/ml);
- $P_N(t)$, average length of telomere repeats in naïve T cell at the age t (bp/cell);
- $P_M(t)$, average length of telomere repeats in memory T cell at the age t (bp/cell).

Function $L(t)$ describes total antigenic load at the age t (g/day).

The first equation describes the dynamics of concentration of the naïve T lymphocytes (N) in the IPLT. The first term characterizes the inflow of naïve T cells/unit of volume of (IPLT). It is equal to the rate of the arrival of the T lymphocytes from thymus (N^*) divided by V, the current volume of IPLT. The second term describes the decline of the concentration of the naïve T cells as a result of antigen stimulation. It is proportional to antigen load L/V, where L is the total antigen load at the age t. The third term describes the natural death of naïve T cells. The last term describes changes in N as a result of changes in the volume of IPLT. (At age 80 this volume is about 25–40% of its value at age 18–25 years.)

The second equation describes the dynamics of average telomere length P_N in the pool of naïve T cells. The rate of this process depends on $(P^* - P_N)$, where P^* is the telomere length in the cells, which just left thymus and relative rate of this pool replenishment.

The third equation describes age dependent changes of concentration of memory T cells M in IPLT. The first term corresponds to the inflow of the new memory cells, which are produced as a result of antigen stimulation of naïve T cells. Coefficient ρ_1 is equal to the average number of memory T cells originated from one naïve cell. The second term describes the self-sustaining process of regulation of total concentration of the memory T cells. The third term describes the regulation process of the total concentration of T lymphocytes in IPLT. Here C^* is the homeostatic concentration of T cells in IPLT. The last term describes changes in M as a result of changes in the volume of IPLT.

The fourth equation describes the changes in average telomere length among memory T cells. The rate of this process depends on the term $(P_N - \lambda_N - P_M)$ which is the difference between average length of telomere in the naïve and memory cells minus λ_N which is the average telomere loss during immune response. This value is

multiplied by the relative (to the value of M) rate of production of the new memory cells. The second term characterizes the telomere loss in memory T cells in the process of self-reproduction.

The last three equations describe the changes in the naïve T cells (N^*) production, IPLT-volume (V) and the telomere length in newly produced naïve T cells (P^*). The relative rates (k_T, k_V, k_P) in this equations are estimated from the data presented in Fig. 2a,b and e (granulocyte), respectively.

6. The results of simulation

The parameter values of the model were either evaluated using published data, or estimated to fit available data. In particular, the values of α_1 and L/V were estimated taking into account that their product (equal to the fraction of proliferating naïve T cells in normal conditions) was about 10^{-4}–10^{-5}. The value of $1/\alpha_1$ is equal to the concentration of antigens necessary to provide stimulation of the majority of naïve cells. The values of model's parameters are given in Table 1.

Fig. 3 shows age trajectories of the model variables (Fig. 3a, b, d and e) and characteristics of T cell populations (Fig. 3c and f) corresponding to the values of coefficients and initial conditions specified above.

Comparison of two curves in Fig. 3a gives an opportunity to evaluate the influence of the reduction of the volume of the lymphoid tissue on the rate of inflow of naïve lymphocytes into the unit of volume of this tissue. The lower (dashed) line corresponds to the constant $V = 1500$ ml; the upper (solid) line corresponds to the case with volume reduction. The dynamics of V shrinking is shown in Fig. 3b. Fig. 3d shows the dynamics of two variables in the model: $P_N(t)$, the average telomere length in the naïve cells and $P_M(t)$, the average telomere length in memory cells (dashed line). Comparison of these trajectories with the data presented in Fig. 2d shows that the model gives a good description to the data. (Shaded areas around the curves depict the scatter range of the values of $P_N(t)$ and $P_M(t)$. These distributions are asymmetric. Horizontal shaded line on the level 4000–4400 nucleotide pairs corresponds to the Heiflick's limit (H). The cell stops division when telomere becomes shorter than 4000 nucleotide pairs. Fig. 3c shows age dynamics of concentration of naïve T lymphocytes (solid line) and T memory cells (dashed line). When comparing these trajectories with respective regression lines of Fig. 2c one has to keep in mind that in this figure the results are shown in percent of T cells of respective types in the blood. Hence one has to assume that relative concentrations of cells of these two types in the blood reflect the dynamics of their absolute concentrations in lymphoid tissue. Under this assumption the modeling trajectories are close to those shown in Fig. 2c: the concentrations are the same at age 23–25 years; the monotone substitution of the naïve cells by memory cells is going further. Some inconsistency is observed at the end of the age-interval. The solution produced by the model gives a smaller number of naïve cells than respective measurements show. This may be related to survival to older ages of individuals with higher level of naïve cells. Fig. 3f shows the dynamics of two variables R_N and R_M characterizing the resistance of the organism due to response of naïve T cells and memory cells, respectively. These variables characterize replication potentials of the pools of respective cells: $R_N = V \cdot N(P_N - H)$, $R_M = V \cdot M(P_M - H)$, H denotes the Heiflick's limit.

Thus, the model describes two important phenomena, determining the process of aging in T immune system: gradual replacement of naïve cells by memory cells (Fig. 2c and Fig. 3e) and parallel decline of telomere length in these two subpopulations (Fig. 2d, e and Fig. 3d).

Table 1
Parameters of the model

Parameter	Interpretation	Dimension	Value
α_1	Coefficient of sensitivity of naïve T cells to antigen load	ml/g	1.5×10^4
α_2	Coefficient of sensitivity of memory T cells to antigen load	ml/g	1.7×10^4
μ_N	Death rate of naïve T cells in the absence of antigen load	one/day	1.8×10^{-4}
μ_M	Death rate of memory T cells due to competition for space in IPLT	one/day	0.05
ρ_1	Number of memory T cells produced by one naïve cell	–	100
ρ_2	Number of memory T cells produced by one memory cell	–	1.1
λ_N	length of telomere repeats lost during transformation of naïve cells to memory cell	bp/cell	3050
λ_M	Length of telomere repeats lost during self replication of memory cells	bp/cell	500
C^*	Low limit for normal concentration of memory T cells in intact lymphoid tissue	cell/ml	2.5×10^9
k_T	Rate of diminishing of naïve T cells production with age	one/day	1.1×10^{-4}
k_V	Relative rate of reduction of the IPLT volume with age	one/day	2.7×10^{-5}
k_P	Relative rate of the telomere repeats reduction in the progenitor of naïve cells	one/day	1×10^{-5}
L	Antigen load	g/day	2.5×10^{-6}

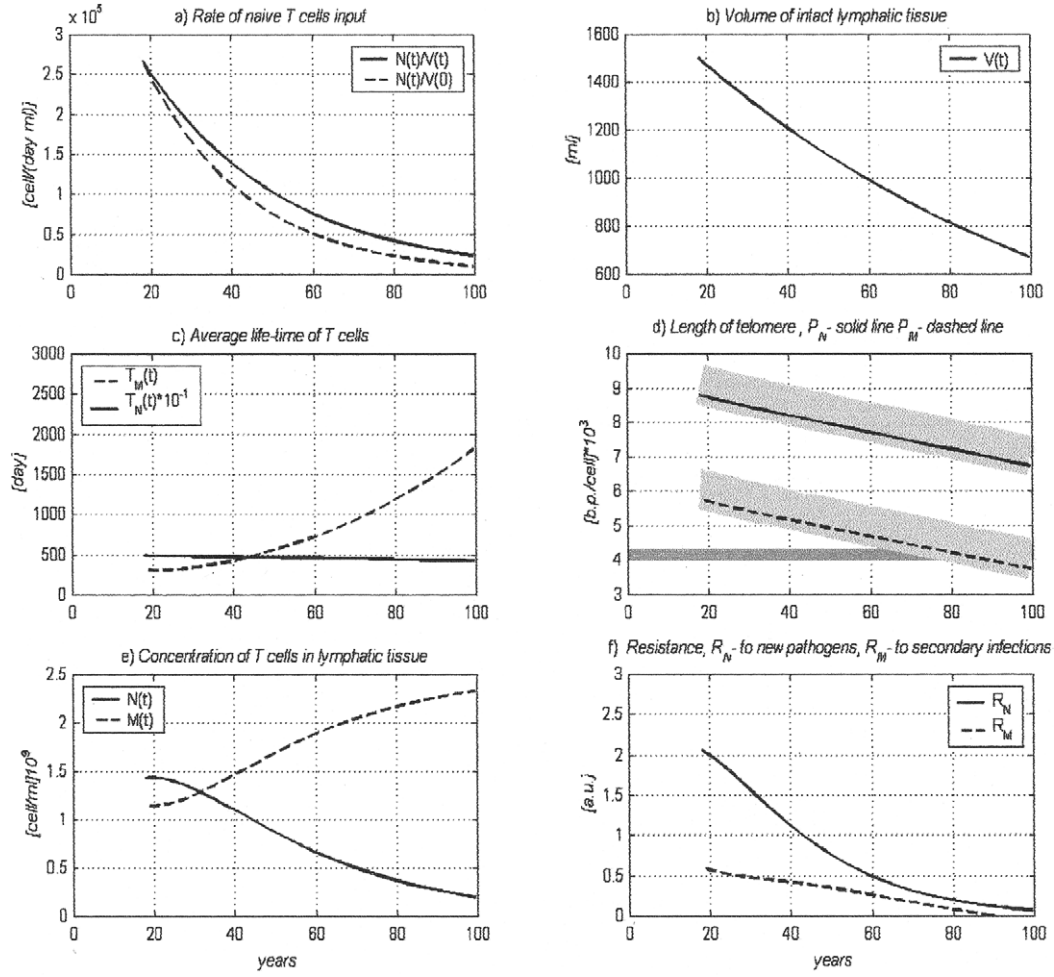

Fig. 3. Mathematical modeling of age related changes in peripheral T cells population. (a) Changes in the rate of naïve T cells input/the unit of volume caused by shrinkage of peripheral lymphoid tissue; (b) the dynamics of the peripheral lymphoid tissue volume ($V(t)$ on Fig. 2b); (c) the average life-time of naïve and memory T cells: the average life span of memory T cells increases with age; (d) the dynamics of the telomere length in the naïve (solid line) and memory (dashed line) T cells; horizontal half-tone strip corresponds to the value of critical length for replicative senescence; strips contour lines depicts variance of telomere lengths; (e) the dynamics of concentrations of naïve ($N(t)$) and memory ($M(t)$) T cells in intact lymphoid tissue; (f) the resistance to infections related to populations of naïve (R_N) and memory (R_M) T cells.

7. Discussion

The model described above is based on the following basic assumptions:

- the pool of naïve cells replenish from thymus and decreases because of antigen stimulation and natural death of the cells;
- the pool of memory cells increases due to proliferation and differentiation of naïve T cells and self-sustaining memory cells. It decreases because of competition for the space in the lymphoid tissue and natural death;
- the processes of cell division are accompanied by the reduction of the telomere length.

The pool of peripheral T cells besides naïve and memory T cells includes other populations of T cells, for example, CTLs. However, these cells are not permanently present in the lymphoid tissue. They do not participate in recirculation and, hence, their influence on fulfillment of the niches and the process of homeostatic regulation is small.

The assumption that the new naïve T cells arrive only from thymus yields that these cells are characterized by large mean life time (between 4000 and 5000 days or 11–13 years) (see Fig. 3c, dashed line). The assumption about the constancy of concentration of T lymphocytes in peripheral lymphoid tissue restricts the growth of the concentration of memory T cells by the value of C^* minus current concentration of naïve T cells. We assumed that one naïve T cell produces 100 memory T cells and that the average life span of 'redundant' memory cells is 20 days. An increase in the number of memory cells yields the reduction of their mean life span.

An increase in the mean life span of memory cells is associated with the slowing down of the average rate of telomere shortening. It happens when the mean lifetime of these cells becomes about 200–400 days and a substantial part of memory cells originates from naïve cells with larger telomere length. The data shows that in human memory cells the decline in telomere length is going with the same rate or faster as it is in naïve cells (Rufer et al., 1999).

The accelerated decline in telomere length in memory cells is explained by repeated immune reactions and by divisions of these cells (Burns et al., 2000; Franceschi et al., 1999). This process is described in equation for P_M by the term $\rho_2\alpha_2\lambda_2(L/V)$. The values of respective parameters are given in the Table 1. The value $\lambda_M =$ 500 bp/cell corresponds to 10–16 divisions of secondary immune response. However, self-replication of memory cells increases their competition and decreases their average lifetime.

Thus, the results of modeling show that suggested mechanism of homeostasis of T lymphocytes peripheral pool maintenance describes age dependent changes in this important component of the immune system. It is interesting to note that one of the consequences of thymus involution and reduction of inflow of naïve T cells is an increase in average life span of memory cells (from 1 year in age 20, up to 3 years after age 80, see Fig. 2c). These long living cells, however, have minimal

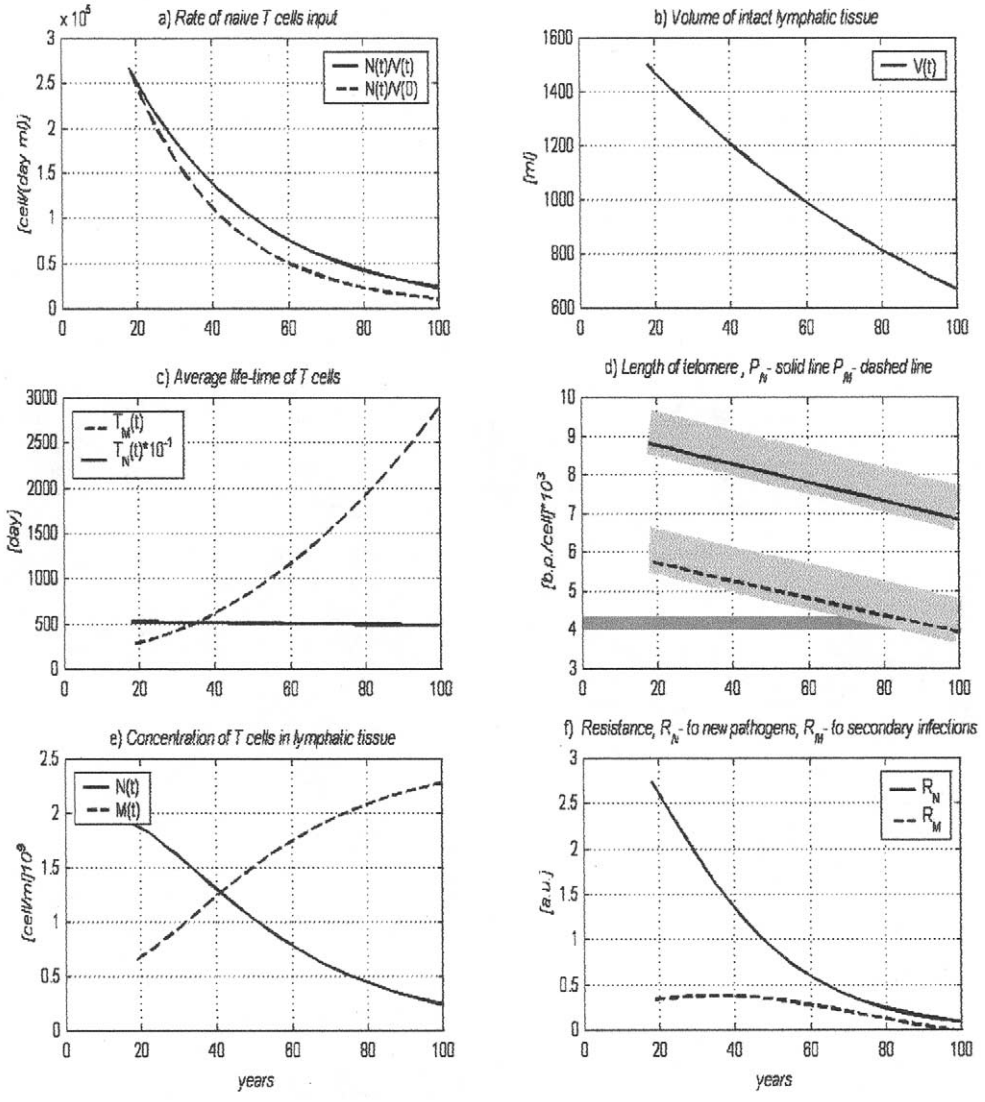

Fig. 4. Mathematical modeling of age related changes in peripheral T cells population in the case of 50% reduction of the antigenic load. (a, b) did not change; (c) the average life span of naïve T cells did not change, but the average life span of memory T cells increased compared with Fig. 3c; (d) the average levels of the telomere length in naïve (solid line) and memory (dashed line) T cells is slightly higher then on Fig. 3d; (e) the intersection of trajectories of naïve ($N(t)$) and memory ($M(t)$) T cells concentrations happens in older age then on Fig. 3e; (f) only small increase in absolute value of resistance to infections in old age takes place in the case of reduced antigenic load. Relative increase is about 50–70% and may be notable.

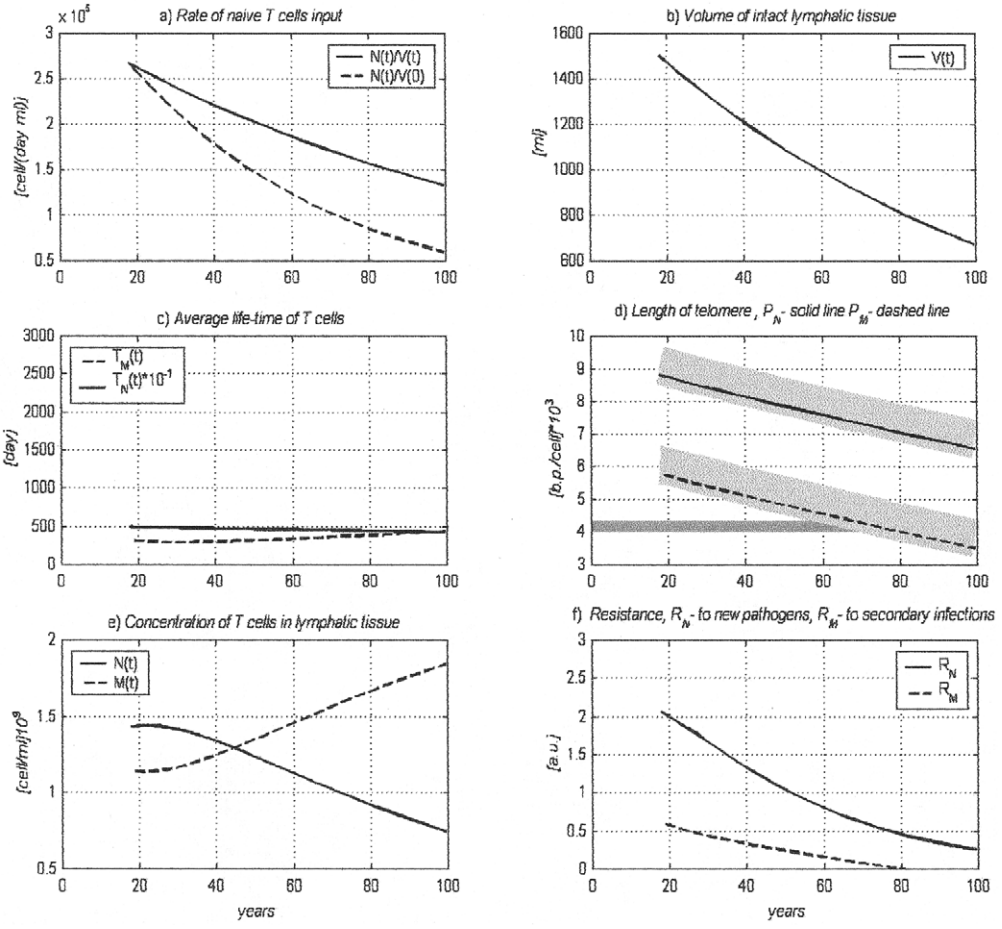

Fig. 5. Mathematical modeling of age related changes in population of peripheral T cells in the case of reduced rate of thymus involution. (a) Rate of increase of naïve T cells/unit of volume; (b) did not changed; (c) average life span of naïve T cells did not change, but life span of memory T cells decreased compared with Fig. 3c and especially with the case of reduced antigenic load on Fig. 4c; (d) average levels of the telomere length in the naïve (solid line) and memory (dashed line) T cells declined in comparison with Fig. 3d, Fig. 4d; (e) crossover of the trajectories of naïve and memory T cells concentrations happens in older ages than in Fig. 3e and Fig. 4e; (f) substantial increase in resistance to infections in old age due to naïve T cells and declined resistance associated with memory T cells.

replicative potential (dashed line in Fig. 2d intersects the line associated with the Heiflick limit). Thus, in the old organism the immune defense is provided by the 'senile' memory T cells and by a small number of naïve T cells. Memory cells that save their replicative potential are shown by the grey strip above the dashed line. These results are in concert with the data on low efficiency of vaccinations in old ages. As a result the resistance of an organism, associated with the pool of its memory cells at age 80 becomes reduced despite the large size of a pool of these cells.

Let us consider how the rate of aging changes as a result of the reduction of the antigen load, for example because of changes in environmental conditions and nutrition. Fig. 4 shows the results of modeling when the antigen load is reduced by 50%.

The solution is characterized by a clear delay in age related transformation of the immune system in middle ages and non-significant changes at age 80 years and older. In particular, the reduction in the antigen load yields an increase in the mean life span of memory cells, which leads to a substantial increase in resistance in the middle ages and to a small increase in resistance after age 80. Thus, the reduction of the antigen load (given that this process did not influence the dynamics of reduction of the volume of intact lymphoid tissue) did not substantially change the level of resistance in old age.

The amount of lymphoid tissue in thymus plays an important role in the functioning of the T cell immune system. It is established that healthy centenarians have a certain amount of lymphoid tissue in their thymus. Fig. 5 shows the trajectories of aging of the immune system with a 50% reduction of the rate of the thymus involution. The most important difference between trajectories shown in Figs. 4 and 2 is substantial reduction of the life time of the memory T cells (300–400 days in Fig. 5c and 4 years in Fig. 3c). This phenomenon yields much earlier decline in resistance associated with the pool of memory T cells. The higher

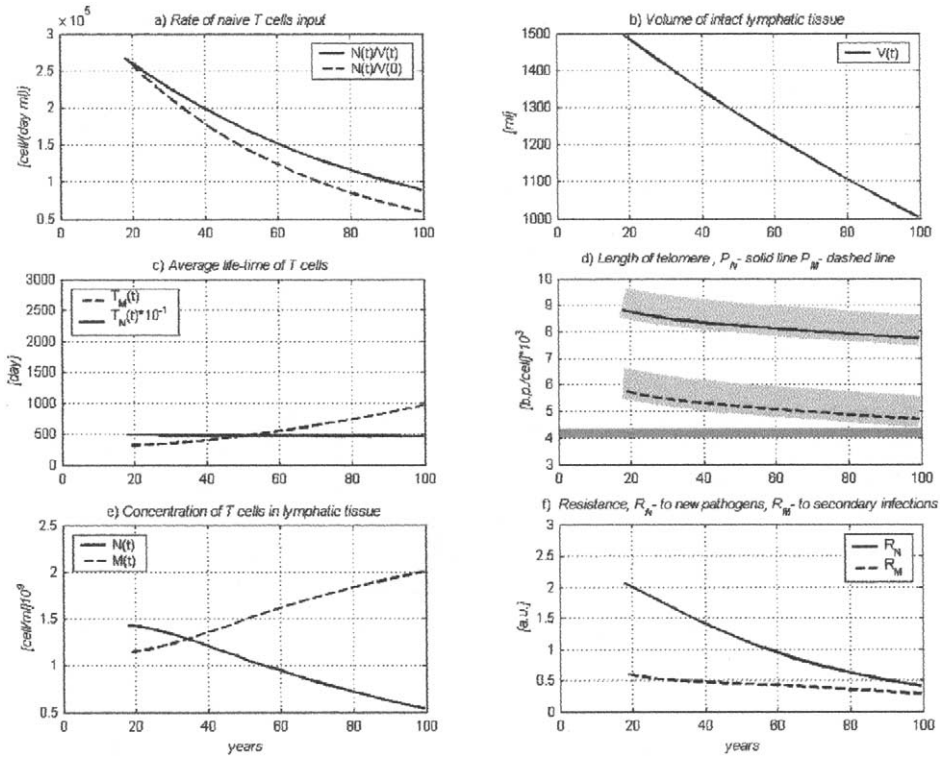

Fig. 6. Mathematical modeling of age related changes in population of peripheral T cells in the case of reduced rate of: telomere loss in steam cells, peripheral lymphatic tissue shrinking, and thymus involution.

inflow of naïve cells enhances the defense ability of a pool of naïve cells in later ages. However, the substantial decline of replicative potential associated with the reduction of telomere length makes this enhancement not so significant (see Fig. 5).

The results of numerical experiments show that the immunosenescence is the outcome of the several related processes. Manipulations with one component of this process do not produce substantial improvement of the immune system functioning.

Thus, effective immune defense in late age may be based on combined slowing down of the several age-depending decay processes in the immune system. Fig. 6 illustrates the hypothetical case of relatively successful immunosenescence.

Compared with Fig. 3, model's solution on Fig. 6 is the result of:

- 2-fold slowing down of the declining rate of naïve T cell production;
- 2-fold slowing down of the IPLT volume reduction rate;
- 3-fold slowing down of the telomere repeats reduction rate.

The distinguishing features of the resulting solution are:

- preservation of the memory cells protective capacity (Fig. 6f, dashed line);
- relatively high naïve cells protective capacity (Fig. 6f) solid line;
- relative shortening of the memory cells life time.

The latter may cause an increase in the incidence of acute infection. Interestingly, that slowing of telomere repeats reduction rate alone did not influence the rate of immunosenescence. Note that mathematical model discussed above did not take into account the influence of immune response on the antigenic load. In more realistic model more effective response must diminish antigenic load and vice versa.

These results show that the aging of T system of immunity is a complex phenomenon, which includes several interrelated processes. The changes in only one process do not improve much the function of the immune system in old ages. Our model does not include several other mechanisms, which may influence the dynamics of the aging process in the immune system. For example, the assumption about the exponential decline of the volume of intact peripheral tissue may be violated since this process depends on the strength and duration of inflammatory responses in peripheral tissues.

The life time and repertoire of the cells in the immune system may differ in subpopulation of T lymphocytes recirculating through mesenteric nodes, lymphoid tissue where they originated from. The naïve T cells in their turn do not have preferences in the place of their circulation. These features of T cells were not taken into account in the model. It would also be interesting to consider how the aging process of the immune system can be modulated by persistence of antigens in lymphoid tissues, the HIV infection, bone marrow transplantation etc.

Especially important is the investigation of factors slowing down the aging of the immune system and restoration of its functioning in old ages (Beverley and Grubeck-Loebenstein, 2000). The mathematical model of aging of the immune system may play a useful role in testing various hypotheses related to such kind of impacts. Some aspects of modulation of anticancer immune defense as well as autoimmune response may also be effectively studied using mathematical model of immunosenscence.

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