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Lymphopenia and Mechanisms of T-Cell Regeneration

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Abstract—Chronic lymphopenia, in particular, T-lymphocyte deficiency, increases the risk of death from cancer, cardiovascular and respiratory diseases and serves as a risk factor for a severe course and poor outcome of infectious diseases such as COVID-19. The regeneration of T-lymphocytes is a complex multilevel process, many questions of which still remain unanswered. The present review considers two main pathways of increasing the T-cell number in lymphopenia: production in the thymus and homeostatic proliferation in the periphery. Literature data on the signals that regulate each pathway are summarized. Their contribution to the quantitative and qualitative restoration of the immune cell pool is analyzed. The features of $CD4^+$ and $CD8^+$ T-lymphocytes' regeneration are considered.

Keywords: lymphopenia, regeneration, T-lymphocytes, thymus, homeostatic proliferation

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INTRODUCTION

T-lymphocyte deficiency—lymphopenia—develops under the influence of various factors: viral and bacterial infections, genetic and autoimmune diseases, benign and malignant tumors, injuries and surgical interventions, ionizing radiation, and drugs (Vatutin and Yeshchenko, 2016). While transient lymphopenia is not a health risk, once it becomes chronic, it increases the risk of death from a variety of causes, including cancer, cardiovascular diseases, and respiratory illnesses (Warny et al., 2020). Notably, in patients hospitalized with COVID-19, lymphopenia is also a reliable predictor of severe disease and poor outcome (Lee et al., 2021; Zaboli et al., 2021).

The regeneration of T-lymphocytes is ensured by the joint work of two mechanisms (Mackall et al., 1997b). The first is the maturation of bone-marrow precursor cells in the thymus. The second is the thymus-independent division of mature T-lymphocytes in the periphery (so-called "homeostatic proliferation"). The two pathways for T-cell regeneration work simultaneously, but their contribution to immune system repair is different. This review considers the signals that regulate the work of two T-lymphocyte regeneration pathways, questions of quantitative and qualitative restoration of the T-cell pool, and features of making up for the deficiency of $CD4^+$ and $CD8^+$ T-lymphocytes.

Arbbeviations: IL—interleukin; TCR—T-cell receptor; CFSE—5(6)-carboxyfluorescein diacetate-*n*-succinimidyl ether; IFNγ—interferon γ; MHC—major histocompatibility complex; TREC—T-cell-receptor excision circles.

MECHANISMS THAT TRIGGER T-CELL REGENERATION FOLLOWING LYMPHOPENIA

The thymus gland is a relatively autonomous structure that reacts poorly to the body's need for T-lymphocytes (Berzins et al., 1998). During the day, the thymus produces a number of naive T-cells equal to approximately 1% of its thymocytes (Scollay et al., 1980). It has been experimentally established that the presence of additional thymuses transplanted from syngeneic animals does not affect the productive function or size of the recipient's own thymus (Metcalf, 1963; Berzins et al., 1998). All engrafted thymuses work autonomously, and the number of mature T-lymphocytes in the periphery does not affect the production of naive T-cells.

In turn, the homeostatic proliferation of T-lymphocytes is not triggered by itself. The proportion of T-cells dividing in secondary lymphoid organs increases in response to a lymphocytes' absolute number decrease (Ge et al., 2002; Williams et al., 2007; Mitin et al., 2013). The signals that trigger the homeostatic division of T-lymphocytes are not fully understood.

Evidence suggests that, to start the process of homeostatic proliferation, cells require signals from various channels, including the T-cell receptor (TCR), cytokine receptors, and costimulatory mole-

cule receptors. Thus, the homeostatic division of naive T-lymphocytes depends on the interaction of their TCR with peptides present within the major histocompatibility complex (MHC) (Kieper and Jameson, 1999). An important role in this process is played by proteins that ensure the selection of cells in the thymus (Goldrath and Bevan, 1999; Min et al., 2005; Enouz et al., 2012). Such peptides have a low affinity for TCR. Normally, the stimulation they provide supports the viability of mature peripheral T-cells. However, in lymphopenia, even these weak interactions can initiate mitosis of T-lymphocytes. In addition, signals triggering homeostatic proliferation may come from commensal microorganisms. In experiments with sublethally irradiated $Rag1^{-/-}$ gnotobiont mice it was found that the absence of normal microflora antigens is accompanied by a decrease in the intensity of homeostatic division of adoptively transferred T-cells (Kieper et al., 2005). It is noteworthy that, unlike naive T-lymphocytes, memory T-cells are able to enter homeostatic division regardless of the signals coming through the TCR (Geginat et al., 2001, 2003).

Homeostatic proliferation requires cytokines with a common γ-chain, of which interleukin-7 (IL-7) has the greatest value for T-lymphocytes (Ku et al., 2000; Schluns et al., 2000; Fry and Mackall, 2001; Tan et al., 2001). In lymphopenia, the content of IL-7 in the blood serum increases, which is most often associated with a deficiency of cytokine-consuming cells (Bolotin et al., 1999; Guimond et al., 2009). High IL-7 concentrations reduce the threshold of T-lymphocyte sensitivity to activation in vitro (Porter et al., 2001). Apparently, this phenomenon promotes the naive T-cells proliferation in response to suboptimal stimulation with autologous peptides and products of commensal microorganisms. Experiments with $Rag2^{-/-}$ animals have shown that in T-lymphocytes, the level of anti-apoptotic factors expression and the rate of p27Kip1 cell-cycle inhibitor degradation increase under the influence of IL-7 (Li et al., 2006). These factors promote the survival of T-cells present in the periphery. IL-7 has such a pronounced effect on T-lymphocytes that its administration is accompanied by an increase in the number of immune cells even in mice without lymphopenia (Min et al., 2005). In turn, limiting the IL-7 availability by blocking the α-chain of the cytokine receptor (CD127) inhibits the T-cell homeostatic proliferation after the adoptive transfer to sublethally irradiated $Rag2^{-/-}$ mice.

In a number of studies, blocking CD127 did not affect the homeostatic proliferation of adoptively transferred T-lymphocytes (Schluns et al., 2000; Min et al., 2003). This and other inconsistencies in the experimental results led to the conclusion that the concept of "homeostatic proliferation" hides two processes that are triggered in conditions of lymphopenia: fast and slow division of T-cells (Min et al., 2005). Rapid homeostatic T-lymphocyte proliferation, also known as "spontaneous" or "endogenous," is characteristic of profound lymphopenia. Cells divide every day, often several times a day. In turn, slow homeostatic proliferation of T-lymphocytes is a feature of moderate or physiological lymphopenia. Cells divide once every 2–4 days or less frequently. The characteristics of each type of homeostatic proliferation known so far are summarized in Table 1 and will be discussed further.

Homeostatic proliferation can be triggered by signals from the costimulatory molecule CD28. Most studies indicate that blocking the interaction of CD28 with its ligand reduces the intensity of T-lymphocytes homeostatic division (Gudmundsdottir and Turka, 2001; Min et al., 2003; Hagen et al., 2004). However, costimulatory signals via CD28 are not always the limiting factor for triggering homeostatic T-cell proliferation (Prlic et al., 2001). The revealed differences may be associated with the use of different models of lymphopenia, in which fast (CD28-dependent) or slow (CD28-independent) homeostatic proliferation is more important for T-cell regeneration.

Thus, under conditions of T-lymphopenia, the regeneration of the immune system involves two pathways: the production of cells in the thymus and the homeostatic proliferation of lymphocytes in the periphery. Each of them is regulated by its own set of signals. It should be noted that the partial contribution of the two paths may vary depending on the situation. At the same time, an increase in the number of T-cells through one or another mechanism leaves its mark on the resulting pool of lymphocytes.

QUANTITATIVE T-LYMPHOCYTE REGENERATION

The thymus plays a central role in the initial formation of the T-lymphocyte pool. In the 1960s, Jacques Miller (Miller, 1961) showed that thymectomy in the early neonatal period leads to the development of profound lymphopenia and serious immunological defects in adult animals. Thereafter, in a large series of experiments, it was demonstrated that the thymus provides the microenvironment necessary for bone marrow progenitor cells maturation and selection of clones capable of low-affinity interactions with self-peptides presented within the MHC (von Boehmer et al., 1989). In other words, in the newborn organism, the thymus ensures the formation of a pool of CD45RA-positive naive $CD4^+$ and $CD8^+$ T-lymphocytes expressing a wide repertoire of T-cell receptors.

Experiments with transplantation of T-cell-depleted bone marrow into adult, lethally irradiated euthymic and nude mice showed that the thymus gland is involved in the formation of a T-lymphocyte pool not only in the neonatal period, but also at a more mature age (Miller, 1962; Zinkernagel et al., 1980). Based on these data, it was suggested that the age-

Table 1. Main characteristics of fast and slow homeostatic proliferation of T-lymphocytes

Parameter	Fast proliferation (spontaneous/endogenous) in subjects with severe lymphopenia	Slow proliferation in subjects with moderate/physiological lymphopenia
Division intensity	Once per day or more often	Once in 2–4 days or less
Dependence on cytokines	–	IL-7
Dependence on interaction with the peptide/MHC complex	+	+
Dependence on self or food antigens	+	+
Dependence on antigens of commensal bacteria	+	?
TCR affinity	High	Moderate or low
Dependence on CD28 costimulation	+	–
Dependence on TCR diversity in peripheral cells	+	–
Object of competition	Specific binding site	Soluble nonspecific stimulus
Properties of dividing cells		
Activation markers	$CD25^+/CD69^-$	$CD25^-CD69^-$
Differentiation	Effectors or memory cells ($CD44^{bright}CD62L^-$), regulatory T-cells	Naive cells or memory-like or memory ($CD44^{+/-}CD62L^+$) cells, which can restore the naive phenotype
Cytokine production after stimulation	IFNγ, IL-2	IL-2
Ability to localize in nonlymphoid tissues	+	–
Tendency to develop autoimmune diseases	Increases	Increases

TCR, T-cell receptor; MHC, major histocompatibility complex; IFNγ, γ interferon; IL-2, interleukin-2.

related thymus involution may reduce the T-lymphocytes regenerative potential. The presented hypothesis was confirmed by clinical data: the age of patients has a negative effect on the ability of the $CD4^+$ T-cell pool to recover. Thus, in children after intensive chemotherapy and bone-marrow transplantation, the thymus is often enlarged, which is associated with a relatively rapid increase in the number of naive $CD4^+$ T-cells (Mackall et al., 1995; Storek et al., 1995; Weinberg et al., 1995). In contrast, in adults, the recovery period is slow and is not accompanied by an increase in the size of the thymus (Forman et al., 1982; Moreland et al., 1994; Mackall et al., 1995; Storek et al., 1995).

In turn, the ability of T-lymphocytes to undergo homeostatic proliferation does not depend on age. While most of the abovementioned publications explore the issue of the immune regeneration in adults, the transfer of naive T-cells to neonatal mice with an immature peripheral T-lymphocyte pool also results in homeostatic cell expansion (Min et al., 2003): within 16–18 days, the transferred lymphocytes divide seven or more times. The intensity of homeostatic proliferation of transferred cells decreases as the peripheral T-cell pool is naturally filled with thymic emigrants (Mackall et al., 1993, 1997b). Therefore, homeostatic lymphopenia-induced proliferation is not only a response to the T-lymphocyte pool damage, but also an important physiological process that occurs in healthy organisms of any age.

T-cell involvement in homeostatic division corresponds to the depth of the immunodeficiency state (Dummer et al., 2002). In this work, the authors adoptively transferred different numbers of B6.PL ($Thy1.1^+$) cells into sublethally irradiated and intact C57BL/6 ($Thy1.2^+$) mice. On the seventh day after the transfer, it was noted that the administration of T-lymphocytes to intact animals did not cause cell division. In contrast, in irradiated mice, adoptive transfer resulted in an intense homeostatic proliferation of Thy1.1-positive $CD4^+$ and $CD8^+$ T-lymphocytes. An increase of the inoculum size caused the frequency of proliferating Thy1.1 $cells^+$ and the number of lymphocyte mitoses to decrease. After 10 weeks of observations, the absolute number of peripheral T-lymphocytes in the blood of all irradiated mice reached values characteristic of intact animals, which indicated the reconstruction of the immune system (Dummer et al., 2002). Similar results were obtained by other authors (Min et al., 2004), who adoptively transferred 10^4 to 10^7 $CD4^+$ T-cells into $Rag2^{-/-}$mice. After 1–2 months, assessing the number of these lymphocytes in the lymph nodes and spleen of animals, the authors noted that, regardless of the inoculum size, the $CD4^+$

T-cell count was comparable to that of intact healthy mice (Min et al., 2004). Since the thymus of $Rag2^{-/-}$ animals does not produce T-cells, the increase in their number occurs solely through homeostatic proliferation. It was found that mature T-cells dividing in the periphery are able to increase their number by 10 thousand to 800 thousand times (Miller and Stutman, 1984; Rocha et al., 1989).

It should be noted that homeostatic proliferation is not always able to completely restore the pool of T-lymphocytes. A single cyclophosphamide administration to mice decreases the absolute number of T-cells in the thymus and spleen (Grinko et al., 2020). However, while in the thymus of animals the number of T-lymphocytes is restored on the day 20th, this process is slowed down in the spleen. After 2 months, the total $CD4^+$ cell count reaches values characteristic of control animals; however, the size of naive $CD4^+$ T-lymphocyte subset remains reduced. These observations raise the question of how the T-cell pool forming under the pressure of lymphopenia corresponds to that of a normally functioning immune system.

QUALITATIVE T-CELL REGENERATION

As was noted above, the adoptive transfer of naïve T-cells to newborn mice, which have not yet formed their own pool of peripheral T-lymphocytes, is accompanied by homeostatic division of the transferred cells (Min et al., 2003). Under these conditions, proliferating naive T-lymphocytes do not retain their phenotype, but acquire characteristics of memory cells—namely, they express the corresponding surface markers (CD44) and acquire the ability to produce interferon γ (IFNγ). Phenotype conversion and change in functionality of T-cells undergoing homeostatic division have been noted by a number of researchers (Oehen and Brduscha-Riem, 1999; Murali-Krishna and Ahmed, 2000; Masopust et al., 2001; Dummer et al., 2002; Ge et al., 2002; Min et al., 2003). In some studies, cells that converted the phenotype during homeostatic proliferation were even called "surrogate" memory T-cells and were distinguished from "true" ones that are formed in response to an antigen (Lee et al., 2013; White et al., 2016).

Phenotype conversion is more characteristic of T-cells that have gone through fast homeostatic division. In turn, slow homeostatic proliferation effectively maintains a pool of immunocytes with the phenotype and functional characteristics of naive T-cells (Hazenberg et al., 2004; Bains et al., 2009). Thus, in adults, up to 90% of naive T-lymphocytes are formed through their proliferation in the periphery (den Braber et al., 2012). As a result, in humans, the content of TREC (T-cell receptor excision circles) molecules among naive T-lymphocytes declines by 90–99% with age (Jamieson et al., 1999; Harris et al., 2005; Kilpatrick et al., 2008). TRECs are formed during the rearrangement of T-cell-receptor gene segments in the thymus and serve as marker of the thymic origin of lymphocytes (Douek et al., 1998). It should be noted that the proportion of TREC-positive cells is reduced among both CD31-negative and CD31-positive naive $CD4^+$ T-lymphocytes (Kilpatrick et al., 2008). It can be concluded that even the so-called $CD31^+$ "thymic emigrants" are partly produced through the peripheral division of naive T-cells.

It is important that the formation of genes encoding TCR chains occurs exclusively in the thymus. In adults, the thymus gland produces a limited number of new, diverse naïve T-cells. Therefore, the regeneration of the T-lymphocyte pool mainly occurs due to the division of a limited number of clones present on the periphery (Mackall et al., 1996). The logical outcome of such proliferation is a gradual narrowing and bias of the TCR repertoire. For example, the TCR repertoire has been shown to be narrowed in adult HIV-infected subjects (Connors et al., 1997; Gea-Banacloche et al., 1998), which confirms that T-cells in these patients originate from a small number of lymphocytes proliferating in the periphery. Lymphopenia induced by the use of monoclonal anti-CDw52 antibodies for the treatment of rheumatoid arthritis also leads to the formation of a T-cell pool with low TCR diversity (Jendro et al., 1995). Similar results were obtained in the analysis of the T-cell repertoire formed during the initial (due to the expansion of mature donor T-lymphocytes) regeneration following bone-marrow transplantation (Gorski et al., 1994; Masuko et al., 1996; Roux et al., 1996). Interesting data are also presented in works performed using animal models (Min et al., 2004). Researchers administered 10^4–10^7 $CD4^+$ T-cells to $Rag2^{-/-}$ mice and noted that in animals from different groups, the regenerated T-lymphocyte pools differed significantly in the TCR diversity. In mice that received 10^7 T-lymphocytes, this index was higher than that in animals receiving smaller number of cells. However, the absolute $CD4^+$ T-lymphocyte count was comparable in mice of different groups.

Narrowing of the TCR repertoire due to homeostatic proliferation may reduce the effectiveness of the immune response (Fry et al., 2001). In the present study, thymectomized female mice, over 98% T-cells of which had been removed by administration of anti-CD4 and anti-CD8 antibodies, were transplanted with male skin flaps. Normally, such grafts should be rejected due to HY antigen incompatibility. However, adoptive transfer of 10^6 syngeneic T-lymphocytes and quantitative T-cell pool regeneration did not lead to a functional reconstruction of the mice immune system: the animals did not develop transplant rejection despite the absence of lymphopenia. Increasing the size of the inoculum contributed to a more effective immune response, and the optimal immune response was achieved with an inoculum size equal to a tenth of

the total T-cell number in an intact organism. The presented data allow us to conclude that, in the absence of the thymus, peripheral expansion can restore not only the number of T-lymphocytes, but also their ability to develop an immune response against antigens. At the same time, the regeneration of the T-lymphocyte pool from a state of deep lymphopenia, combined with the inability to enrich the TCR repertoire, can lead to a decrease in the body's resistance to pathogens and tumors, and accelerate the development of age-related immunodeficiency (Roux et al., 2000; Kozlov, 2014).

Homeostatic proliferation negatively affects the viability of T-cells. It has been noted that, in mice with genetically determined lymphopenia, homeostatic division of T-lymphocytes is often accompanied by their death, which prevents the accumulation of cells and the restoration of the immune system (Goldrath et al., 2000). The mathematical model created on the basis of experiments confirmed that the lymphopenia-induced T-lymphocyte division is accompanied by the active death of these cells (Min et al., 2004). The researchers reasoned that, if only 1% of adoptively transferred T-cells made seven mitoses, then the number of divided lymphocytes would increase by 128 times and significantly narrow the repertoire of clones present in the body. However, the pool of T-cells formed under these conditions is usually characterized by a relatively wide variety of TCRs. Consequently, the cells filling it cannot be descendants of a small number of lymphocytes. Since regeneration leads to the formation of a T-cells pool limited in size, the researchers believe that active death of T-lymphocytes occurs during homeostatic division. Indeed, compared with cells that did not take part in homeostatic proliferation, regenerating T-lymphocytes are more prone to activation-induced apoptosis (Fry et al., 2001). It should also be taken into account that the intensive division of T-lymphocytes shortens their telomeres and decreases their reserve proliferative capacity. This phenomenon, known as "replicative senescence," has been identified in both CD4- and CD8-positive T-lymphocytes proliferating under lymphopenia (Weng, 2008).

Another significant effect of T-cell regeneration through homeostatic proliferation is an increase in the likelihood of autoimmune diseases development. Since interaction with self-peptides is an important stage in triggering homeostatic proliferation of T-lymphocytes, clones carrying TCRs with a higher affinity for self-peptides more often enter the division cycle. By narrowing the TCR repertoire and provoking an increase in the number of autoreactive clones, lymphopenia-induced homeostatic proliferation gradually creates favorable conditions for the development of autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, type I diabetes, etc. (Schulze-Koops, 2004; Datta and Sarvetnick, 2009). These effects have been repeatedly noted in clinical practice with the use of radiation, chemotherapy, and immunosuppressive therapy (King et al., 2004; Marleau and Sarvetnick, 2005; Baccala and Theofilopoulos, 2005; Khoruts and Fraser, 2005; Krupica et al., 2006).

Thus, the thymus-dependent mechanism of T-lymphocyte regeneration provides a complete restoration of the immune system, due to the formation of new T-cells of various specificities. However, this pathway is of priority only in the early period of life, and with age, its contribution to the immune system regeneration decreases. In turn, homeostatic proliferation maintains a pool of T-lymphocytes that is numerous and diverse in TCR specificity throughout the lifespan of the organism. At the same time, the efficiency of the immune system regeneration through homeostatic division largely depends on the state and diversity of T-cells preserved in the periphery. After deep lymphopenia, homeostatic proliferation forms a pool of T-lymphocytes with a narrow TCR repertoire, a high propensity to respond to autoantigens, and low viability. In this regard, homeostatic proliferation is sometimes considered to be a negative phenomenon (Baccala and Theofilopoulos, 2005; Kozlov, 2006).

FEATURES OF CD4- AND CD8-POSITIVE T-LYMPHOCYTES REGENERATION

It is noteworthy that, in most cases, lymphopenia is a consequence of a $CD4^+$ T-cell deficiency, while a selective lack of $CD8^+$ T-lymphocytes is rare (Societies, 1999). For example, in cancer patients, chemotherapy leads to a short-term decrease in the number of $CD8^+$ T-cells, B-lymphocytes, and natural killer cells, but to long-term deficiency of $CD4^+$ T-cells, the number of which is not restored even a year after the treatment completion (Mackall et al., 1997a). After bone-marrow (hematopoietic stem cell) transplantation, the number of $CD8^+$ T-lymphocytes also recovers significantly faster than the count of $CD4^+$ T-cells (Atkinson et al., 1982; Forman et al., 1982; Favrot et al., 1983; Guillaume et al., 1998).

In experiments with sublethally irradiated mice, it was shown that, 4 days after the T-cell adoptive transfer, lymphocytes actively proliferate in the lymph nodes and spleen (Mitin et al., 2014). At the same time, the frequency of dividing $CD8^+$ T-lymphocytes is twice that of $CD4^+$ T-cells. Mathematical modeling of the T-lymphocytes regeneration after chemotherapy also showed that the average rate of increase in the number of $CD8^+$ T-cells (0.085 ± 0.035 cells/day) was 3.1 times higher than the corresponding $CD4^+$ T-lymphocyte values (0.027 ± 0.007 cells/day) (Mackall et al., 1997a). The mean cell doubling time during regeneration in the same work was 12.6 and 28.2 days for $CD8^+$ and $CD4^+$ T-lymphocytes, respectively. The most rapid number increase was observed for $CD8^+CD57^+$ and $CD8^+CD28^-$ T-lymphocytes.

In turn, the number of $CD28^+$ and $CD45RA^+CD8^+$ T-cells increased commensurate with the increase in the number of $CD4^+$ T-lymphocytes. Notably, unlike $CD4^+$ T-cells and their naive subset, the regeneration of which was negatively correlated with the age of patients, the increase in $CD8^+$ T-cells and naive $CD8^+$ T-lymphocyte count was not associated with either the patients age or the size of their thymus glands. These data allow us to conclude that regeneration of $CD4^+$ T-lymphocytes in lymphopenia is largely dependent on the thymus. In turn, $CD8^+$ T-lymphocytes, especially their highly differentiated subsets, actively divide on the periphery, thereby replenishing the lost T-cells.

The features of homeostatic proliferation described above can have serious consequences. For instance, $CD8^+CD28^-$ and $CD8^+CD57^+$ T-lymphocyte subsets are characterized by altered functionality, low viability, and impaired proliferative activity after stimulation through TCR (Lum et al., 1982; Damle and Engleman, 1983; Autran et al., 1991). Moreover, the narrow repertoire of antigen-recognition receptors inherent in $CD8^+CD28^-$ and $CD8^+CD57^+$ T-cells (Gorochov et al., 1994; Posnett et al., 1994), may limit their functionality as effectors. Together, these factors lower the body's ability to resist cancer and reduce the effectiveness of immune-stimulating anticancer therapy.

The differences in $CD4^+$ and $CD8^+$ T-cells regeneration during lymphopenia may be related to the viability of individual lymphocyte subsets. It was found that, in mice, the lifespan of naive $CD4^+$ T-cells is significantly lower than that of naive $CD8^+$ T-lymphocytes (den Braber et al., 2012). T-cell death during homeostatic proliferation is also elevated among $CD4^+$ T-lymphocytes compared with that of $CD8^+$ T-cells (Fortner et al., 2010). Maintaining T-cell viability is an active process (Raff, 1992). Lymphocytes receive signals for survival by interacting with cells expressing class I or II MHC (Brocker, 1997; Kirberg et al., 1997; Tanchot et al., 1997). In the absence of these interactions, mature CD4- and CD8-positive T-cells are unable to persist in circulation for more than a few weeks. At the same time, the rate of disappearance of $CD4^+$ T-cells is higher than that of $CD8^+$ T-lymphocytes (Nešić and Vukmanović, 1998). It should be noted that the conditions needed to receive signals that are essential for survival are different for $CD4^+$ and $CD8^+$ T-cells (Kieper et al., 2004). Indeed, $CD4^+$ T-lymphocytes require direct close contact with dendritic cells in secondary lymphoid organs (Brocker, 1997), while $CD8^+$ T-cells can establish a sufficient contact with any cell, even outside the lymphoid tissues (Dai and Lakkis, 2001).

Not only the viability, but also the homeostatic proliferation, of T-lymphocytes depends on their interaction with the peptides present within the MHC (Mackall et al., 1996). Division of $CD8^+$ T-lymphocytes can be triggered by contact with any class I MHC inside and outside the lymphoid organs and induction of homeostatic division of $CD4^+$ T-cells are possible only after contacting the class II MHC on antigen-presenting cells located in T-dependent zones of secondary lymphoid organs (Dai and Lakkis, 2001). Apparently, this can explain the fact that $CD8^+$ T-cells compared with $CD4^+$ T-lymphocytes enter homeostatic division earlier and divide more intensively (Jameson, 2002).

It should be noted that $CD4^+$ and $CD8^+$ T-lymphocyte subsets occupy similar niches and, therefore, compete during regeneration (Freitas and Rocha, 2000; Dummer et al., 2001). But while the $CD4^+$ T-cell selective deficiency is compensated by proliferation of both subsets, the $CD8^+$ T-lymphocyte deficiency is compensated predominantly by $CD8^+$ T-cells (Cosgrove et al., 1991; Rahemtulla et al., 1991; Ge et al., 2001). The transfer of CFSE-labeled T-lymphocytes together with a large number of unlabeled $CD4^+$ T-cells to a lymphopenic animal leads to a decrease in the intensity of homeostatic proliferation of $CD4^+CFSE^+$, but not $CD8^+CFSE^+$ T-cells (Ernst et al., 1999). In turn, the same situation, but with an excess of $CD8^+$ T-lymphocytes, leads to suppression of homeostatic division of all $CFSE^+$ T-cells. Apparently, in the setting of lymphopenia, $CD8^+$ T-lymphocytes have a competitive advantage over $CD4^+$ T-cells.

Thus, $CD4^+$ and $CD8^+$ T-lymphocytes are located within the same niche of the immune system. However, these cells have features that have a significant impact on their regeneration in lymphopenia. Indeed, $CD4^+$ T-lymphocytes compared to $CD8^+$ T-cells have more stringent requirements for receiving signals that promote survival and trigger proliferation, are characterized by less viability in a resting and activated state, and cannot homeostatically divide or increase their numbers as productively. These features make $CD4^+$ T-cells less competitive than $CD8^+$ T-cells, which, apparently, results in the widespread selective deficiency of CD4-positive, but not CD8-positive, T-cells.

CONCLUSIONS

For the full regeneration of T-lymphocytes in lymphopenia, two mechanisms are necessary: the production of T-cells in the thymus and their homeostatic proliferation. The partial contribution of each mechanism to the restoration of the immune system depends on many factors and can differ significantly. In the thymus, long-lived naive T-cells with a wide repertoire of antigen-recognizing receptors are created, but, undergoing involution, this primary lymphoid organ reduces its productive function. On the contrary, homeostatic proliferation, regardless of the age of the organism, multiplies the T-lymphocytes

present on the periphery, but can reduce their diversity and viability.

Despite the numerous studies, the process of T-cell regeneration in lymphopenia is fraught with many unresolved issues. First, is it possible to restore the functional activity of the thymus in older people? Although it has been shown that the age-related involution of the thymus can be regulated by the use of keratinocyte growth factor and a number of interleukins (IL-7, IL-12, and IL-15), as well as by decreasing steroid sex hormones and increasing the level of the Foxn1 transcription factor expression on epithelial cells (Holland and van den Brink, 2009; Bredenkamp et al., 2014), effective approaches to restoring the productive function of the gland have not been developed. Second, what is the biological role of T-cell phenotype conversion? What molecular mechanisms trigger the differentiation of naive T-lymphocytes during homeostatic proliferation? What role do surrogate memory T-cells and regulatory T-lymphocytes formed in the process of homeostatic division play in maintaining the body's immune homeostasis? Third, is it possible to avoid the negative effects of homeostatic proliferation during the regeneration of the immune system from a state of deep lymphopenia? What approaches will increase the viability of dividing T-cells and, thereby, increase the efficiency of the immune system's recovery? The solution of the questions raised will open up new opportunities for maintaining the immune system in people with lymphopenia of various origins and will allow us to proceed to the development of therapeutic approaches that reduce the risk of morbidity and mortality, as well as increase the length and quality of human life.

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COMPLIANCE WITH ETHICAL STANDARDS

The author declares that she has no conflict of interest. The work did not involve animals or human beings as experimental subjects.

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