Allergy and Immunology

AIMS Allergy and Immunology, 5(1): 18–32.
DOI: 10.3934/Allergy.2021002
Received: 10 November 2020
Accepted: 23 December 2020
Published: 24 December 2020

http://www.aimspress.com/journal/Allergy

Review

Homeostatic proliferation as a physiological process and a risk factor for autoimmune pathology

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Abstract: The most important functions of the immune system are the guarantee of multicellularity, the maintenance of genetic homeostasis, and the protection of the organism from various infectious agents. The maintenance of homeostasis within the immune system also plays an important role in the normal functioning of the organism and is realized through several mechanisms. For example, after the resolution of the immune response, the excessive amount of lymphocytes is eliminated via apoptosis due to the competition for the survival factors and because of the lack of specific stimulation, and the excessive amount of antibodies is corrected by idiotype–anti-idiotype interactions. The restoration and maintenance of the lymphocyte count are performed due to the migration from the bone marrow and thymus and the process of homeostatic proliferation that plays the most important role (after the involution of the thymus) for T-lymphocytes. Because of the non-uniformity of the definitions that are met in the published literature, the authors provide the definition of the process of homeostatic proliferation of T-lymphocytes that will be used further in the text. Homeostatic proliferation (HP) is a physiological process to restoration of the peripheral T-lymphocyte pool after lymphopenia of any etiology through the antigen-specific proliferation of lymphocytes under the influence of IL-7 and IL-15, which can acquire pathological features depending on the severity of lymphopenia. Homeostatic proliferation can be conventionally divided into a fast and slow type depending on its intensity. Although such division is highly conventional, there are certain physiological peculiarities of fast and slow HP that can influence the functioning of the immune system, change the T-cell receptor landscape, and lead to the development of pathologies. It is worth noting that fast HP predominantly involves memory effector T-cells, while slow HP also influences naive T-cells. In the present review, the authors discuss the most important physiological and pathological aspects of the homeostatic proliferation of T-lymphocytes.

Keywords: homeostatic proliferation; lymphopenia; T-cell homeostasis; autoimmune diseases; TCR diversity; IL-7; IL-15

1. Introduction

To protect the organism from various antigen challenges (different infectious agents or altered self-antigens), the immune system has to maintain the diversity and size of the peripheral pool of T-lymphocytes at a constant level that is kept within a narrow range [1]. Before the involution of the thymus, restoration of the T-cell pool occurs due to the migration of naïve T-lymphocytes from the thymus, and with age, homeostatic proliferation (HP) starts to play the key role [2]. HP is a physiological process induced by lymphopenia and targeted for the restoration and maintenance of the peripheral pool of T-lymphocytes [3–5]. HP requires free lymphocyte niches that become free in the conditions of lymphopenia and occurs in the T-cell zones of lymph nodes and spleen [6], which is confirmed by the disturbance of the process of HP in mice deprived of secondary lymphoid organs [7]. The main factors that provide HP are the signal from the T-cell receptor (TCR), signals of co-stimulation, as well as IL-7 and IL-15 [8–12]. At the same time, the intensity of HP directly depends on the TCR signal strength, which is determined by the avidity of the interaction between TCR and peptide in the Major Histocompatibility Complex (MHC). For HP of low intensity (slow HP), it is enough to have a "tonic" TCR signal and elevated levels of IL-7 and IL-15. It is of a polyclonal character and, probably, does not lead to negative consequences by maintaining the diversity of TCR. HP of high intensity (fast HP) on the other hand primarily depends on a strong TCR signal, is of oligoclonal character, and leads to the changes in the TCR landscape and formation of lymphocytes with the memory-like T-cells, increasing the risk of the development of autoimmune pathologies [13–18]. We define the TCR landscape not only as the diversity of TCR but also as the frequency of occurrence of each specific TCR. Thus, the strength of TCR signal that T-lymphocytes receive in the conditions of lymphopenia not only influences the rate of restoration of the T-cell pool but also determines qualitative changes in the immune system that occur during HP.

2. Background of the negative influence of homeostatic proliferation

It is well-known that during maturation, thymocytes go through the stages of positive and negative selection. Positive selection results in the selection of T-lymphocytes capable of recognizing antigenic determinants in complex with MHC. Negative selection results in the elimination of lymphocytes that have a high affinity to self-antigens in MHC complexes [19]. Lymphocytes with relatively high affinity to self-antigens die as a result of apoptosis. Lymphocytes with moderate affinity to self-antigens become T-regulatory cells (Tregs), and lymphocytes with relatively low affinity represent effector T-lymphocytes capable of recognizing foreign antigens. It should be noted that the affinity of TCR to cognate antigens differs in various populations of T-lymphocytes. The majority of self-reactive T-cells have a significantly lower absolute affinity to self-antigens than effector T-lymphocytes to foreign antigens, and the absolute affinity of TCRs of anti-tumor lymphocytes to neoantigens lies somewhere in the middle [20]. The mechanisms of central tolerance and, in particular, negative selection are not completely efficient and some potentially self-reactive T-lymphocytes with a high affinity of TCRs to self-antigens can get into the peripheral

bloodstream [21–24]. This leads to the risk of the development of autoimmune diseases and requires the mechanisms of peripheral tolerance [25]. It should be noted that because of the limited size of the pool of T-cells, there is a compromise observed between the diversity of TCRs and the number of the existing cells of a given specificity. If the TCR repertoire is too diverse, the rate of occurrence of lymphocytes of a given specificity becomes too low for timely reaction to a pathogen. However, if the repertoire is not sufficiently diverse, foreign antigens may be missed. The minimal TCR repertoire that provides the optimal balance between the diversity and the number of T-lymphocytes of a given specificity is called protecton [19,26]. According to some data, in humans, the general diversity of TCRs of naïve T-lymphocytes reaches 10^8 variants [27]. The mechanisms described above are involved in the formation of the TCR specificity landscape of naive T-lymphocytes (Figure 1).

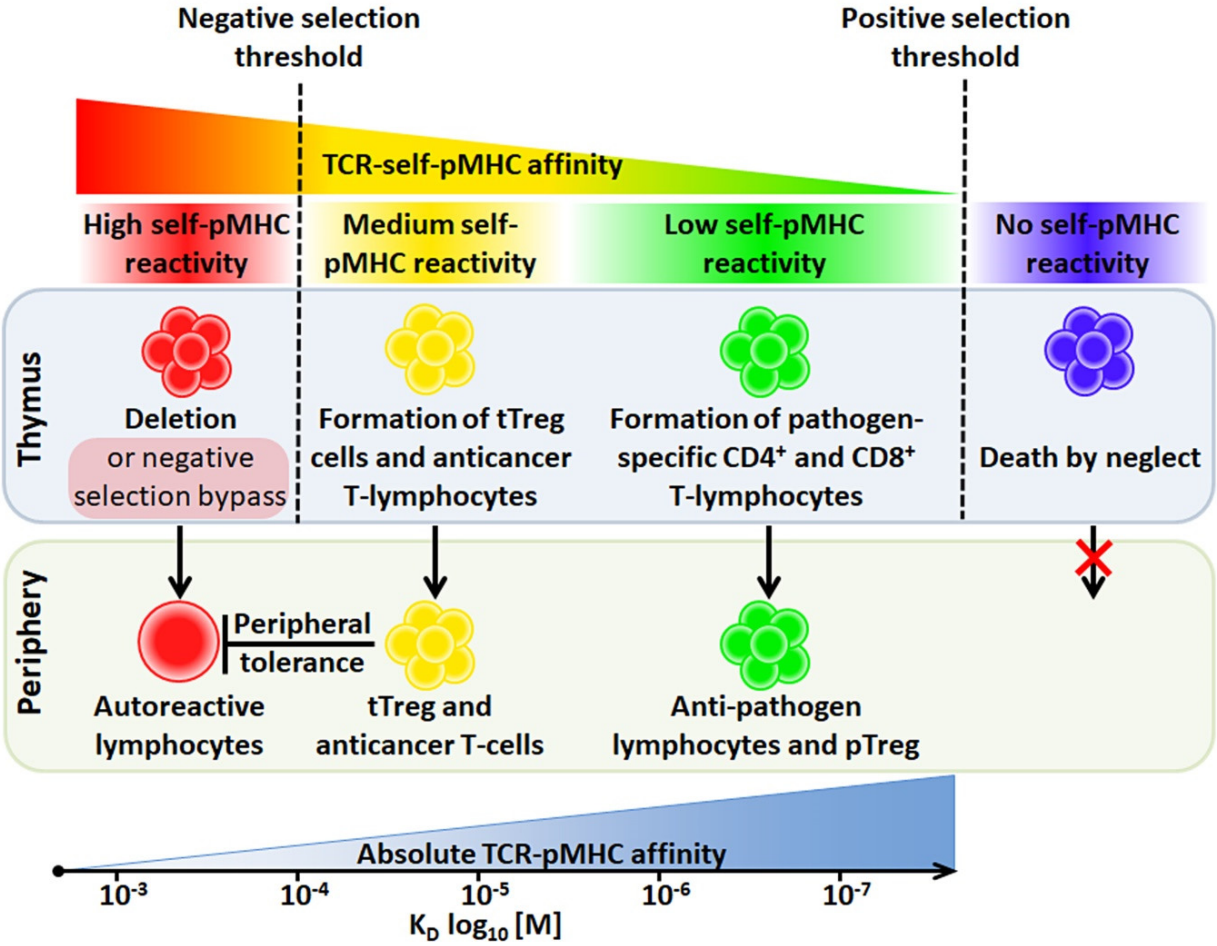

Figure 1. Thymic selection, TCR landscape and average TCR affinities to different types of pMHC. In the thymus, relatively strong interactions of TCR with self-pMHC lead to negative selection and deletion of self-reactive T cells, or alternatively, T-cell differentiation into Tregs. T-cells with low but sufficient to survival TCR affinity to self-pMHC become anti-pathogen effector T-lymphocytes with high TCR affinity to foreign antigens. Due to negative selection is not completely efficient some self-reactive T-cells may leave the thymus and must be inhibited by Tregs in the periphery to maintain self-tolerance.

After leaving the thymus, some effector T-lymphocytes are differentiated into peripherally-induced pTregs when they face antigens of symbiotic microflora. Thus, the general repertoire of TCRs of T-lymphocytes is characterized by the presence of thymic tTregs with relatively high affinity to self-antigens, effector T-lymphocytes with high affinity of TCRs to foreign antigens and low affinity to self-antigens, pTregs with high affinity to antigens of commensal microflora, as well as some self-reactive T-lymphocytes [28,29]. It should be mentioned that TCR specificity spectra of the described subtypes of T-cells barely overlap [30,31].

Well-known, a combination of genetic predisposition (including SNP mutations in the genes of MHC, enzymes, cytokines, or their receptors) with an action of unfavorable environmental factors is essential for autoimmune disease development [32,33]. In this context, the escape of self-reactive T-lymphocytes from the negative selection in the thymus, as well as the presence of anti-tumor T-lymphocytes with intermediate affinity to self-antigens, create an additional risk of the development of autoimmune processes. At the same time, the realization of autoimmune pathology requires certain disturbances in the mechanisms that provide peripheral tolerance. The authors believe that such disturbances can occur in cases with lymphopenia during the process of HP, which is confirmed by the association between lymphopenia and different autoimmune diseases [34–37]. So, signs of autoimmunity are frequently observed in various pathologies that are accompanied by lymphopenia, such as rheumatoid arthritis, Sjogren's syndrome, insulin-dependent diabetes mellitus, Crohn's disease, systemic lupus erythematosus, HIV-infection, etc. [34,38].

3. Homeostatic proliferation of effector T-lymphocytes

During life, the human organism is affected by numerous physical, chemical, and infectious factors that require a reaction from the immune system side, and often associated with loss of immune equilibrium and development of lymphopenia. Obviously, there are mechanisms aimed at returning to the initial state or attaining a new equilibrium state by the immune system. For example, it is observed during the resolution of the immune response when the excessive amounts of lymphocytes eliminate via apoptosis because of the lack of specific antigen stimulation, and the excessive amount of antibodies is corrected via idiotype–anti-idiotype interactions according to the immune network theory of Niels Jerne [39]. Another example is the process of restoration of the number of lymphocytes after lymphopenia, which occurs via the proliferation on the periphery and is limited by the number of vacant niches that provide the lymphocytes with the factors of survival. In both cases, homeostatic mechanisms get involved that target the quantitative return to the steady-state conditions of the immune system. However, at the same time, its qualitative characteristics can change. In general, a dynamic equilibrium in the immune system is controlled by universal mechanisms that include TCR, humoral, and co-stimulating molecule signals. As was mentioned above, these three groups of stimuli (TCR signals, humoral, and co-stimulating signals) play the most important role in the process of HP. Moreover, the contribution of one or another type of signals differs for slow and fast HP.

3.1. Slow homeostatic proliferation

Slow HP occurs in the conditions of moderate lymphopenia. The division of cells is observed rarer than 1 time per day; at the same time, $CD8^+$ lymphocytes are divided faster than $CD4^+$

cells [13,40]. In regular conditions, for the maintenance of homeostasis and basal activity, T-lymphocytes require a "tonic" TCR signal from the interaction between the TCR and peptide in the complex with the MHC on dendritic cells. As a result, partial phosphorylation of ζ-chain of TCR complexes occurs. [41–43]. This is observed in the lymphoid organs in course of the continuous monitoring of dendritic cells by T-lymphocytes for exogenous antigens [43]. In the conditions of lymphopenia, IL-7 and IL-15 are produced. IL-7 is produced by the cells of the reticuloendothelial system, stromal cells of the thymus, and bone marrow [44]. IL-15 is produced by the cells of monocyte/macrophage lineage [45], epithelial [46], and dendritic cells [47]. Both IL-7 and IL-15 along with IL-2 belong to the common cytokine receptor γ-chain family and bind with receptor complexes that contain γ-chain/IL-2R-γ—CD127, CD215, and CD25, respectively. In the majority of cases, the effect of IL-7 and IL-15 was mediated by the activation of three signal pathways: JAK-STAT, PI3-K-Akt, and RAS-RAF-MAPK [48,49]. The activation of the mentioned signal pathways under the influence of IL-7 and IL-15, as well as tonic TCR signal, provide the required level of activation for the survival and proliferation of T-lymphocytes during slow HP. As it was mentioned earlier, such proliferation occurred in the conditions of moderate lymphopenia and had a polyclonal character maintaining the diversity of the TCR repertoire. It is interesting to note that the blocking of TCR-pMHC interaction or the introduction of neutralizing antibodies against IL-7 leads to the inhibition of slow HP [13,50,51]. It should be mentioned that IL-7 is important for slow HP of $CD4^+$ and $CD8^+$ lymphocytes, while IL-15 is more important for $CD8^+$ cells [52,53]. Polyclonality of slow HP is determined at the first stage of selection in the thymus (during positive selection) when lymphocytes are selected that have TCRs capable of recognizing self-antigens in the complex of the MHC. Thus, each T-lymphocyte in the diversity of T-cells can receive a weak "tonic" signal from the TCR and get involved in slow HP under the effect of the elevated levels of IL-7 and IL-15 in the conditions of lymphopenia. This provides not only a quantitative restoration of the pool of T-cells but also the maintenance of the diversity of the TCR repertoire (Figure 2).

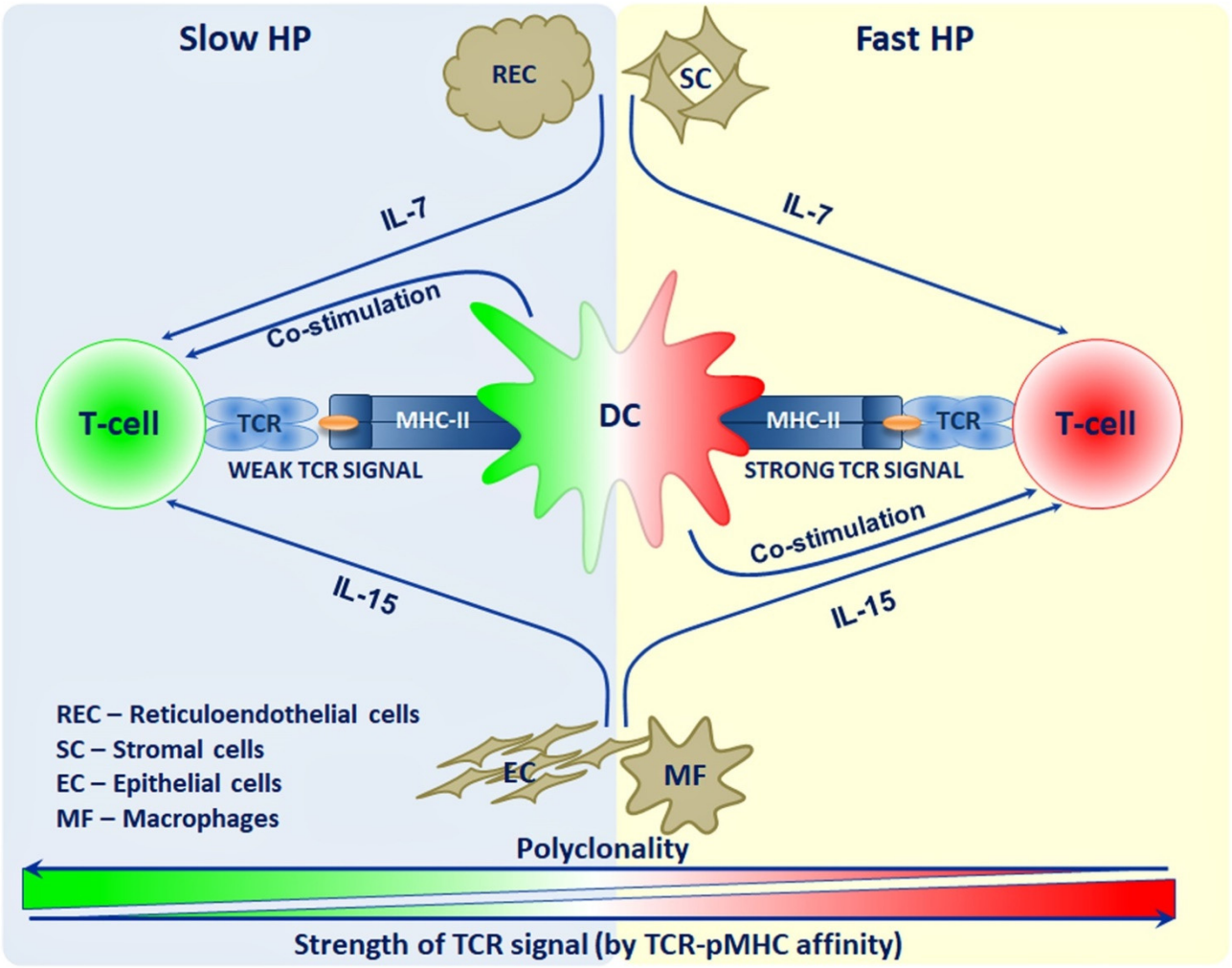

Figure 2. Slow and fast homeostatic proliferation principles. HP provided by TCR signal, elevated levels of IL-7 and IL-15, and co-stimulation molecules such as OX40 and CD24 (classic co-stimulatory interactions, such as CD28/B7, CD40/CD40L, and 4-1BB/4-1BBL—are not required for HP of T-cells) [11,12,54]. Slow HP provided by weak (tonic) TCR signal and has benefit preserving TCR diversity. While fast HP provided by strong TCR signal, lead to a decrease of TCR diversity and transient acquiring of "memory-like" phenotype by T-cells. There is some evidence Tregs cannot inhibit fast HP.

3.2. Fast homeostatic proliferation

Fast HP (in some publications—spontaneous proliferation) is observed in the conditions of "severe" lymphopenia, when a great number of lymphocytic niches become unoccupied. The division of cells occurs more often than 1 time per day. For fast HP of $CD8^+$ lymphocytes, it is enough to contact the epitope in the MHC-I or MHC-II complexes on dendritic cells or B-cells. At the same time, for the induction of fast HP of $CD4^+$ lymphocytes, the TCR has to contact with the epitope in the MHC-II complex on $CD11^+$ dendritic cells [55]. Fast HP requires a strong TCR signal. It is less dependent on cytokines IL-7 and IL-15 and leads to the formation of cells with effector or

memory-like phenotype [13,18]. As was noted before, the strength of the TCR signal, i.e. the avidity of the interaction of TCR-pMHC, is the most important factor that determines the intensity of HP. Recent studies showed that weak and strong TCR signals activated different pathways of intracellular signaling. Thus, a weak TCR signals generated elevated phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) and reduced phosphatidylinositol (3,4,5)-trisphosphate (PIP3) levels, whereas strong TCR signals reduced PI(4,5)P2 and elevated PIP3 levels [56]. Low PIP3 levels generated by weak TCR signals were sufficient to activate phosphoinositide-dependent kinase-1 to phosphorylate AKT on Thr-308 but insufficient to activate mTOR complex 2 (mTORC2), whereas elevated PIP3 levels generated by a strong TCR signal were required to activate mTORC2 to phosphorylate Ser-473 on AKT [56]. Different proteoforms of Akt generated by weak and strong TCR signals have different substrate specificity and activate different descending signal pathways. Thus, various strength of the TCR signal determines the activation of different intracellular signal pathways, which determines cell fate [56]. This provides a materialistic background for the division of HP depending on the strength of the TCR signal into slow and fast (Figure 2).

Earlier, the authors shortly described the mechanisms of the formation of the naïve TCR repertoire in the thymus, which occurred due to the action of the factors *Aire* and *Fezf2* [57]. Further formation of the general TCR repertoire is observed in the periphery [58]. In both cases, the determining role is played by the repertoires represented by antigens in the MHC complexes (pMHC). Thus, the diversity of the TCR repertoire of T-lymphocytes depends on the diversity of the representing antigens: the landscape of recognition (TCR) is formed by the landscape of presentation (pMHC). As it was mentioned before, one of the required conditions for fast HP of T-cells is a contact between the TCR and peptide-MHC complex. The avidity of this interaction determines the strength of the TCR signal and the capability of T-cells to compete for the factors that provide proliferation. Thus, urgent restoration of the T-cells pool as a result of fast HP cannot take place with the complete preservation of TCR diversity due to not all possible antigens are present simultaneously in the body, which cannot provide a fast antigen-specific proliferation of the entire diversity of T-lymphocytes. As a result, only 30% of T-lymphocytes get involved in this process. Primarily, these are the cells with relatively high affinity to self-antigens and antigens of commensal flora [10,15,17,36]. Experiments *in vivo* showed that antigens of commensal microflora also played an important role in the provision of fast HP; it significantly reduced in germ-free lymphopenic mice [59]. However, this may be due not only to the absence of microbial antigens, but also to the absence of costimulation provided by the commensal flora in germ-free mice [60]. Still, fast HP is observed in these animals, which highlights the involvement of self-antigens and food antigens in its induction [59,61]. This indirectly confirms the role of fast HP as a factor that provides oligoclonal expansion of self-reactive T-cells.

As it was mentioned above, HP is a process that is induced by lymphopenia. Such a “traditional” view on this process requires some specifications. Earlier, it was suggested that in lymphopenic conditions, lymphocyte niches got vacant and the competition for the factors of survival reduced, which led to HP of T-cells [50,62–65]. However, the fact that fast HP can be observed without lymphopenia in animals with a normal level of T-lymphocytes can indicate that the number of peripheral T-lymphocytes is not a factor that directly regulates fast HP [61]. Thus, when polyclonal T-lymphocytes are introduced to TCR transgenic mice that have a pool of T-lymphocytes presented by monoclonal TCR repertoire (i.e. all TCR have common specificity) and primarily naïve phenotype, fast HP of the transferred T-lymphocytes is observed [66]. Besides, even in lymphopenia,

the presence of the preserved pool of memory-like T-cells prevents fast HP of the transferred naïve T-lymphocytes [67]. Hence, the most important factor of fast HP is not lymphopenia itself but a decrease in the number of memory T-cells. At the same time, the presence of clonal competition confirms the high antigenic specificity of fast HP [66]. Thus, monoclonal T-lymphocytes enter to HP process after the introduction to the recipients with another clonotype and are not divided after the introduction to the recipients with identical clonotype. Besides, the introduction of monoclonal T-lymphocytes to transgenic recipients with the same clonotype that underwent sublethal irradiation did not lead to their proliferation. At the same time, polyclonal T-lymphocytes got involved in fast proliferation in these conditions [66]. Hence, for fast HP of a certain clone of naïve T-lymphocytes, a decrease in the number of memory T-cells of the identical specificity is required. Taking into account that different groups of draining lymphatic nodes have antigens specific to the respective tissues, it would be logical to suggest the presence of tissue-specific or organ-specific homeostatic proliferation that may be mediated by the appearance of specific vacant niches during the elimination of some clone of effector or memory T-cells. *In vivo* studies demonstrated HP associated with the intestine that was primarily observed in mesenteric lymphatic nodes and led to the appearance of effector and memory-like T-cells [68]. Based on this fact, it could be suggested that in the physiological conditions, fast HP targets the maintenance of the diversity of TCR of memory T-cells [61] and it barely depends on the presence or absence of general lymphopenia. At the same time, slow HP targets the maintenance of the diversity of TCR of naïve T-lymphocytes and memory T-cells and primarily depends on lymphopenia and an increase in the concentration of IL-7 and IL-15.

3.3. General effects of homeostatic proliferation

It should be mentioned that there is another possible role of HP—it can be a component of antitumor immunity. The results of the studies showed that the induction of HP in the lymphatic nodes with the presentation of a tumor antigen caused the favorable autoimmune anti-tumor response. On the periphery, HP with the recognition of self-antigens leads to the development of the autoimmune response to these antigens including tumor ones. Such a response results from polyclonal homeostatic expansion in lymph nodes and is characterized by $CD8^+$ cellular cytotoxicity and an increase in the concentration of IFNγ, as well as the formation of memory T-cells [69]. However, the presence of potentially self-reactive T-lymphocytes also contributes to the development of the pathological character of HP. It should be mentioned in this context that there are data that indicate that the shift in the emphasis of homeostatic proliferation from $CD8^+$ cells to $CD4^+$ lymphocytes can be one of the causes of the development of autoimmune diseases [15].

One of the most important studies that confirm the association between lymphopenia and HP with the development of autoimmune diseases in humans is the study conducted by Jones et al. in 2013 that included 80 patients with multiple sclerosis. All patients received lymphocyte-depleting humanized monoclonal antibody alemtuzumab (monoclonal antibody that binds to CD52), which caused severe lymphopenia in the majority of patients. Within a year and a half, 46% of patients developed autoimmune diseases, and 20% developed asymptomatic carriage of autoantibodies. Patients with a manifestation of autoimmune disease were characterized by a decrease in the migration from the thymic and a narrowing of the TCR repertoire. Thus, the study on humans showed that HP caused by alemtuzumab significantly increased the risk of the development of autoimmune diseases and was accompanied by the generation of activated, highly proliferating

effector and memory-like T-cells that had high potential for the production of inflammatory cytokines, which indicated the prevalence of fast HP in these patients [70].

HP is a physiological process that proceeds differently in people. Some factors can increase its negative influence on the organism: genetic predisposition, severity, rate, and duration of lymphopenia, current inflammatory background in target-tissues, as well as the effectiveness of thymopoiesis. Lymphopenia is observed in many patients with autoimmune diseases [34]. For example, in patients with rheumatoid arthritis, the rate of naïve T-cells pool restoration is insufficient, which is shown by a significant decrease in the number of $TREC^+$ lymphocytes in this patients [71]. Such disturbance is observed from the beginning of the disease and does not depend on the stage, which indicates the primary defect in the generation of naïve T-lymphocytes. However, a decrease in the number of naïve $TREC^+$ cells does not lead to the changes in the number of memory T-cells, which indicates an enhancement of homeostatic proliferation in these patients. Apparently, a disturbance of thymopoiesis and the rate and severity of lymphopenia provides a significant impact on the shaping of the pathological nature of HP.

Besides the negative impact on the TCR landscape, HP may lead to telomere attrition and increased numbers of senescent and exhausted T-cells because T-cells undergoing slow HP do not express the high levels of telomerase necessary to prevent replication-driven telomere length erosion [72,73]. Also, a previous study showed that recurrent HP results in global gene expression changes, including the up-regulation of both cytotoxic and inhibitory molecules that explain how HP could lead to the simultaneous auto-inflammatory and immunodeficiency syndromes frequently observed in lymphopenic patients [74]. Moreover, recurrent HP may cause epigenetic dysregulation as extensive demethylation of genome discrete sites and leads to up-regulation in the expression of corresponding genes [75]. Thus, HP influences the fate of T cells and the body as a whole, has a complex character, and can have both physiological and pathological features.

3.4. The role of Treg cells in the homeostatic proliferation

Tregs are an important factor in the maintenance of the immune equilibrium. It is well-known that these cells provide peripheral auto-tolerance and can suppress different immune-mediated reactions in response to a wide spectrum of physiological and pathological stimuli, including microorganisms, tumor cells, allogeneic grafts, and fetal cells [76,77]. There are few studies dedicated to HP of Tregs. Still, some of them show that these cells can get involved in fast HP even in the absence of severe lymphopenia [78,79]. At the same time, there were no studies on the evaluation of the functional activity of such HP-derived Tregs, which provides the rationale for further studies. It should be mentioned that mechanisms of homeostatic maintenance of Treg cells differ from the mechanisms of effector cells that were described in detail in a recent review [77].

Treg cells are the main cells that provide peripheral tolerance. For this reason, the issue of their functional activity arises in the lymphopenia during HP. According to some data, Tregs can suppress HP of effector lymphocytes with the CTLA-4-mediated mechanism [80–82]. However, our data (unpublished) and some studies show that Tregs cannot effectively suppress the proliferation of effector $CD4^+$ and $CD8^+$ lymphocytes that receive a strong signal from TCRs in the presence of IL-7 or IL-15 (conditions typical for fast HP) [83,84]. Thus, during fast HP, when T-cells receive a strong TCR signal and the levels of IL-7 and IL-15 are elevated, the conditions for the acceleration of proliferation of potentially self-reactive T-lymphocytes are created. This provides an additional

mechanism of the negative influence of HP on the immune equilibrium and becomes a risk factor for the development of autoimmune diseases.

It should be mentioned that incapability of Treg cells to suppress fast HP of effector cells can be associated with both the direct negative influence of HP conditions on Tregs (deprivation of IL-2 due to a decrease in the number of its producers) and acquisition of the resistance to the suppressor influence of Tregs by the effector cells [83,84]. However, this issue requires additional studies.

4. Conclusion

The influence of homeostatic proliferation on the immune system is many-sided. Even though it exerts physiological function, in some cases, this process can acquire pathological features [2,4,13,15,18]. Earlier, it was demonstrated that various factors influenced the character of HP. The most important of them is decreased thymopoiesis and the rate and severity of lymphopenia [34,71]. In cases with moderate lymphopenia, humoral factors are sufficient for the maintenance of the TCR diversity and the restoration of the T-cell pool takes place without its qualitative alterations [41,42]. However, when a certain degree of lymphopenia is reached, the mechanisms of urgent restoration of the peripheral population of lymphocytes get activated that require a higher rate of proliferation and depend on a strong TCR signal [10,13,17,18]. Thus, the degree of lymphopenia influences the intensity of homeostatic processes and may lead to qualitative changes that can negatively influence the general state of the immune system. In this case, negative effects are limited to a clonal expansion of lymphocytes with relatively high affinity TCR [10], the transition of these lymphocytes to memory-like T-cells [3,18], and a decrease in the activity of Tregs due to IL-2 deprivation [77]. In general, this reflects qualitative-quantitative transition, when the changes in the rate of the physiological process cause functional disturbances in the immune system that result in the development of pathology.

Conflict of interests

All authors declare no conflicts of interest in this paper.

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