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Homeostasis and T cell regulation

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Homeostatic regulation of cell numbers is an important principle in biology. Mechanisms that function to maintain or re-establish homeostasis in the immune system include interactions among antigen-presenting cells, regulatory T cells and cytokines. The vital role that homeostatic regulation plays in maintaining a functionally intact immune system is illustrated by the perturbation of the peripheral T cell repertoire that occurs after lymphopenic incidents, which frequently provoke either exacerbated immune or autoimmune responses. Recent studies show that transient states of lymphopenia occur in viral infections and in the neonatal state and might be involved in the development of autoimmune diseases. On the positive side, lymphopenia-provoked T cell expansion might enhance weak immune responses and thereby aid the rejection of tumours or the elimination of parasites.

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Abbreviations

IL interleukin

TCR T cell receptor

TGF- β transforming growth factor- β

Introduction

The immune system, similar to other biological systems, is subject to homeostatic regulation, which ensures that the total number of lymphocytes in the periphery is kept at more or less a constant level. The term ‘homeostasis’ was introduced by the American physiologist Walter Cannon to describe the tendency of an organism to restore its original status in the face of unexpected disturbances.

The principle of homeostatic regulation is clearly illustrated in the regulation of CD8⁺ T cell numbers after infection with lymphocytic choriomeningitis virus. After

encountering the virus, antigen-specific CD8⁺ T cells expand markedly such that after eight days about 50% of CD8⁺ T cells in the spleen are specific for the virus and the CD8⁺:CD4⁺ ratio has altered to 3:1 from its normal value of 1:2. These changes are transient, however, and are followed over the next 1–2 weeks by the death of approximately 90% of the activated T cells, resulting in the re-establishment of equilibrium conditions in the memory state [1]. Under steady-state conditions, the naïve T cells and the memory pool of T cells are under independent homeostatic control [2], which safeguards the preservation of a diverse repertoire of T cell receptor (TCR) specificities to cope with novel pathogens and minimizes the erosion of memory towards previously encountered pathogens.

Maintenance of the homeostatic equilibrium is achieved through cellular interactions, regulation of cell death and numerous cytokines that have distinct actions on different developmental stages of peripheral T cells [3,4]. Although re-establishment of the *status quo* is possible in a relatively undisturbed immune system, it is strongly compromised under conditions of extreme disturbance such as the acute depletion of lymphocytes or ‘lymphopenia’ that follows, for example, irradiation or chemotherapy. Total lymphocyte numbers will return to normal levels, but the composition of the T cell pool may be severely altered, especially if thymic function is also compromised. This is due to the fact that the naïve T cell compartment cannot be maintained by homeostatic mechanisms and depends crucially on thymic output for long-term maintenance [5–7].

This principle is illustrated by the prolific expansion and phenotypic conversion of naïve T cells that occurs after their transfer into hosts with lymphopenia [8]. Very few T cells with a naïve phenotype will persist under such conditions and the repertoire will be significantly altered. Because naïve T cells differ in their relative competitive fitness, which is determined by their avidity and ability to respond to homeostatic factors such as self-peptide bound by the MHC and possibly IL-7 [9*,10*], clones with the highest homeostatic expansion capacity dominate the repertoire [11], whereas clones that do not respond adequately to these signals die out. The presence of antigen during homeostatic regeneration of the peripheral T cells pool promotes an even more pronounced expansion of individual T cell clones.

This review summarizes recent advances in the understanding of principles underlying T cell homeostasis.

Regulation of homeostasis through competition

An important concept underlying the principle of homeostatic regulation is competition for limited resources. In brief, T cells have to compete with each other for signals and interactions that promote either their survival or their activation and maintenance after contact with antigen. Homeostatic proliferation can be dampened by the presence of large numbers of bystander T cells [12] and is strongly increased under conditions of lymphopenia, where such resources are available in excess to remaining or newly introduced T cells. Crucial resources for naïve T cells are IL-7 and TCR signals that act directly on T cells during lymphopenia-induced expansion [13], and, as shown in the human system, signalling by thymic stromal lymphopoietin (TSLP), whose action is mediated by dendritic cells [14].

It has been suggested that homeostatic proliferation of T cells is regulated by clonal competition for self ligands, because polyclonal CD4⁺ and CD8⁺ T cells proliferate when injected into TCR transgenic hosts, but not when injected into syngeneic polyclonal hosts [15^{*}]. Another study has shown that monoclonal T cells from TCR transgenic mice fail to proliferate when injected into the same strain, but divide not only in T-cell deficient *Rag*^{-/-} hosts, but also in TCR transgenic *Rag*^{-/-} mice, whose T cells have a different specificity [16^{*}]. Furthermore, the homeostatic expansion of naïve CD4⁺ T cells seems to be influenced by the diversity of the memory T cell repertoire [17].

The conclusion is that T cells ignore large numbers of competitors as long as their TCR specificity differs. Although this may well be one of the principles underlying homeostatic competition, several experimental caveats must be considered. Many *Rag*^{-/-} TCR transgenic strains seem to be lymphopenic, suggesting that their homeostatic regulation is compromised. Each TCR transgenic population has intrinsic characteristics that determine its fitness for competition and homeostatic expansion [9^{*}]. Although this is likely to be the same for polyclonal T cells, the overall fitness of these latter cells falls within a normal distribution with only a few clones representing extremes such as A18 or OT-II T cells, which have very low competitive fitness, and AND, OT-I and P14 T cells, which have extraordinary expansion capacities. It is possible, therefore, that proliferation of TCR transgenic T cells in another TCR transgenic strain simply reflects the relative state of lymphopenia in the adoptive host rather than the availability of different peptide-MHC ligands. For the transfer of polyclonal T cells, it is almost impossible to exclude the contribution of antigen-driven expansion, because TCR transgenic hosts might present transferred polyclonal T cells with an increased load of environmental antigens that are not cleared owing to the

restricted antigen specificity of the endogenous transgenic T cell population.

Regulation of homeostasis by CD25⁺CD4⁺ T cells

Homeostasis of peripheral CD4⁺ T cells is influenced by regulatory CD25⁺CD4⁺ T cells [18,19] via several different modes of action [20,21], and these cells are frequently credited with preventing autoimmunity. Many of the functions ascribed to regulatory T cells are extrapolated from experimental systems that involve their adoptive transfer into lymphopenic hosts, which develop autoimmune-like symptoms only as a consequence of excessive homeostatic expansion. In fact, there is little evidence that CD25⁺CD4⁺ T cells are directly responsible for preventing autoimmunity and, in contrast to depletion followed by adoptive transfer, their depletion from intact mice does not result in the onset of autoimmune syndromes.

Depletion studies in intact mice clearly show, however, that CD25⁺CD4⁺ T cells strongly influence immune responses. Removal of CD25⁺CD4⁺ T cells enhances immune responses to weak antigens such as tumour antigens and promotes the rejection of several transplantable tumour cell lines [22–24]. Isolation of CD25⁺CD4⁺ T cells from fresh melanoma samples has provided evidence for tumour antigen specificity [25]. Inflammatory responses to parasites such as malaria [26] are curtailed by CD25⁺CD4⁺ T cells, facilitating the escape of the parasites; in addition, CD25⁺CD4⁺ T cells prevent complete elimination of *Leishmania* parasites from the skin of resistant mice [27]. Depletion of CD25⁺CD4⁺ T cells enhances both CD4⁺ and CD8⁺ T cell immune responses to bacterial or viral infections [28–30], suggesting that an important function of these cells may be to limit the damage caused by exuberant effector cells that could cause immune pathology unless restrained.

It is not yet clear what capacity underlies the competitive advantage of CD25⁺CD4⁺ T cells in regulating the expansion of other T cells. Their constitutive expression of a high-affinity IL-2 receptor would equip them well to compete for IL-2, thereby depriving effector T cells of this cytokine; it has been also suggested that they are involved in IL-2-mediated inhibition of the division of memory CD8⁺ T cells [31]. In addition to competition for the resources that are commonly required for the expansion of activated T cells, CD25⁺CD4⁺ T cells may also use active interference strategies by secreting inhibitory cytokines such as IL-10 and/or TGF- β . Notably, T cells engineered *in vitro* by various means to secrete IL-10 suppress immune responses even in hosts that are replete in T cells [32,33]. Similarly, the importance of TGF- β as a crucial factor in the suppression of islet-specific CD8⁺ T cells by CD25⁺CD4⁺ T cells has been shown in T-cell-replete hosts, where the expression of a dominant-negative TGF- β 1 receptor type II transgene

in islet-specific CD8⁺ T cells has been shown to abrogate the control of these cells by CD25⁺CD4⁺ T cells [34].

Homeostatic dysregulation during lymphopenia

Many experimental models artificially create abnormally low numbers of lymphocytes, or lymphopenia, by using T-cell-deficient mouse strains, irradiation protocols, neonatal thymectomy or lymphocyte depletion; however, some physiological situations also cause at least transient states of lymphopenia. For example, many viral and bacterial infections cause substantial transient lymphopenia, and this has been shown to underlie the observed erosion of pre-existing CD8⁺ memory T cell clones [35,36]. Thus, even the memory T cell pool, which, in contrast to the naïve T cell pool, can maintain itself by homeostatic mechanisms, will suffer changes in repertoire distribution after a lymphopenic incident [9]. Restoration of the equilibrium by homeostatic expansion will initially favour memory clones with higher avidity for self-peptide–self-MHC complexes, such that the quantitative representation of memory clones after a lymphopenic incident is likely to look different from its representation before the incident.

Chronic infections of the immune system such as HIV infection progressively destroy the capacity of the immune system to maintain a homeostatic equilibrium [37]. A transient lymphopenic state also occurs naturally in the peripheral immune system of neonatal mice, in which adult numbers of T cells are not reached until day 7 in the lymph nodes and day 15 in the spleen [38]. As a consequence, naïve T cells proliferate and acquire the phenotype and function of activated or memory T cells [39,40,41], an effect that requires self-peptide–self-MHC interactions and is regulated by the size of the peripheral T cell pool.

Although the continuous production of new T cells generated in the thymus will supersede homeostatic expansion of the first cohort of T cells in the neonate, in the absence of continuous thymic output such T cells can expand to the same extent as T cells that are adoptively transferred into T-cell-deficient hosts. This has serious implications for the functionality of the immune system, because under such conditions remaining T cells or adoptively transferred T cells undergo excessive expansion, which frequently leads to immune pathology caused by exacerbated immune responses. Examples of this are inflammatory responses against commensal gut bacteria [42] and pulmonary hyperinflammation driven by *Pneumocystis carinii* [43], which occur after the transfer of naïve T cells into T-cell-deficient severe combined immunodeficient (SCID) or *Rag*^{-/-} hosts. Furthermore, it has been shown that lymphopenia and consequential systemic autoimmunity can be caused by massive deletion of the thymic T cell pool [44].

The excess expansion and consequential immune pathology seen after the transfer of small numbers of naïve T cells into lymphopenic hosts can be prevented by increasing the transfer inoculum or by the co-transfer of monoclonal TCR transgenic T cells with high potential for homeostatic expansion [45]. In this study, although 92% of the transferred T cells in recipients of small numbers of naïve T cells showed an activated phenotype, only 58% of T cells in mice that had received high doses of naïve T cells were activated. These findings are compatible with the hypothesis that competition with neighbouring T cells for limited resources may restrain the excessive activation and outgrowth of transferred T cells.

In clinical situations, lymphopenia is an obstacle to achieving transplantation tolerance, as demonstrated in an experimental model in which antibody-mediated T cell depletion preceded grafting with cardiac allografts [46]. However, tumour rejection is facilitated by lymphopenia-induced homeostatic proliferation that occurs concomitantly with tumour antigen presentation [47–50]. Thus, it seems that exacerbation of antigen-driven T cell expansion during lymphopenic states is a potential advantage if the aim is to increase responses to weak stimuli, but it constitutes a high risk situation for the development of autoimmunity. Thus, the development of autoimmune diabetes in the BB rat model is linked to their genetically determined state of lymphopenia [51], and recent studies indicate that lymphopenia might be also involved in the onset of diabetes in non-obese diabetic mice [52].

Conclusions

Maintaining relatively constant numbers of peripheral lymphocytes is a prime concern of the immune system. In an intact immune system, continuous competition among lymphocytes for access to survival signals and growth-promoting cytokines is sufficient to maintain equilibrium. Problems usually arise when lymphocyte numbers are markedly reduced and the correcting influence of the thymus is lost. Recovery from severe lymphopenia may permanently destabilize the peripheral T cell pool and result in immune pathology. The more moderate and transient lymphopenia seen in the neonatal state does not seem to have negative consequences for functionality of the immune system. It seems likely that a low degree or transient state of lymphopenia is not sufficient on its own to destabilize peripheral T cell pools but may do so in the context of additional, for example, inflammatory signals.

Lymphopenia and the resulting increase in T cell expansion in response to antigen can be exploited in a positive way to enhance weak immune responses. Furthermore, it will be important to unravel the contribution of lymphopenia and its correction by homeostatic control mechanisms to susceptibility to the development of autoimmune diseases. A lymphopenic incident may constitute the final

step in the cascade of several susceptibility traits that predispose an individual to the development of autoimmune disease. In this respect, the longstanding debate concerning associations of autoimmune diseases with infections, which are known to cause lymphopenia, might undergo yet another twist.

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