The Role of Cytokines in Lymphocyte Homeostasis

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ABSTRACT

The size of lymphocyte populations is regulated by replication and death. Cytokines produced by non-lymphoid cells provide key survival and replication signals for several lymphocyte subpopulations. The availability of these cytokines thus serves as a homeostatic regulatory mechanism by determining the upper limit of the population size. IL-7 is required for survival of naive CD4⁺ and CD8⁺ cells and memory CD8⁺ cells. IL-15 is required for survival of memory CD8⁺ cells. IL-12 and IL-4 also promote memory CD8⁺ survival. BAFF is required for survival of mature B cells. Antigen receptor signals, together with these cytokine signals, are required for survival of mature B cells and naive T cells. The list of extracellular survival signals for lymphocytes remains incomplete, and the intracellular pathways leading to survival are poorly understood.

INTRODUCTION

The total pool of lymphocytes in a healthy adult is a relatively fixed size, despite a continuous influx of new cells and replication of existing cells. The subsets of lymphocytes that show relatively constant numbers include subpopulations of thymocytes and progenitor B cells, peripheral naive CD4⁺ or CD8⁺ T cells, memory CD4⁺ or CD8⁺ T cells, mature or follicular B cells, $\gamma\delta$ T cells, and natural killer (NK) cells. This implies the existence of homeostatic mechanisms maintaining lymphocyte numbers in different niches.

Lymphocyte numbers are not regulated through control of production from stem cells. By contrast, erythrocyte production from stem cells is increased when oxygen is low in blood; hence the body senses a need for more erythrocytes and increases their production. The production of lymphocytes is not increased when their peripheral numbers are low. Rather than regulating lymphopoiesis, the number of lymphocytes is regulated after their initial production by survival and homeostatic proliferation of mature lymphocytes. If the number of lymphocytes is low, homeostatic proliferation generates more from the peripheral pools. If the number is high, excess lymphocytes die.

Whether a lymphocyte survives or dies appears to depend on whether it successfully acquires extracellular signals that are in limiting amounts. Each type of lymphocyte population requires a different signal(s), which thus defines separate niches for each subpopulation. A lymphocyte does not continuously inhabit the

physical niche that provides survival signals because lymphocytes are motile cells. Peripheral T cells are especially itinerant, continuously recirculating from lymph to blood and back to lymph. The T cell probably contacts its extracellular survival signals while transiting across surfaces in the lymphoid organs. It must take up these survival factors with its receptors, thus consuming them. Therefore, if one T cell trails behind another T cell along the same surface, it will find its survival factors have been depleted until the stromal cells replenish those survival factors. The rates of depletion and recharging of survival factors must account for the limit in population size of motile lymphocytes, something like the growth rate of grass limiting the population of grazing animals in a fenced pasture.

Two lymphocyte survival or trophic signals that have been identified include the γ c cytokines interleukin-7 (IL-7) and interleukin-15 (IL-15). During exposure to foreign antigens, lymphocytes themselves produce other γ c cytokines, interleukin-2 (IL-2), interleukin-4 (IL-4) and interleukin-9 (IL-9), likely resulting in the temporary enlargement of activated lymphocyte populations. For some lymphocyte types, antigen receptor signals are also required for survival, whereas immune co-stimulation does not appear to be involved, and there are certainly other essential survival signals yet to be identified that regulate lymphocyte homeostasis. In this review, we will discuss the different lymphocyte subpopulations and the extracellular stimuli that are currently thought to regulate homeostasis.

THYMOCYTE DEVELOPMENT

The development of T cells begins as precursor cells from the bone marrow enter the thymus. Early work suggested that the cytokine IL-7 acted as a growth factor for thymocytes (44). In the thymus, IL-7 is primarily a product of the stromal epithelium and following secretion becomes associated with the extracellular matrix (28).

The absence of an IL-7 signal blocks thymocyte development at an early stage as first reported in IL-7 or IL-7 receptor deficient mice (38,46,69). Expression of an IL-7 transgene restored lymphocyte development in IL-7 deficient animals (50). Human thymocyte development also requires an IL-7 signal (34,49). Various lines of evidence suggested that the requirement for IL-7 during thymocyte development was to promote

cell survival rather than to serve as a growth factor (5), and IL-7 was shown to promote the survival of the first three stages of pro-T cells by preventing the induction of apoptosis (27). Thus IL-7 may be a homeostatic regulator of the population size of pro-T cells, however it has yet to be shown that increasing thymic IL-7 (by transgenic overexpression, for example) would increase the number of pro-T cells.

In the $\alpha\beta$ thymocyte lineage, successful rearrangement of a T cell receptor (TCR) β gene induces the transition from the pro-T cell stage to the pre-T cell or double positive (DP) ($CD4^+CD8^+$) stage. DP T cells no longer depend on IL-7 and actually down-regulate expression of the IL-7 receptor. The number of DP cells is determined by the amount of stroma, which presumably provide trophic surfaces for thymocyte survival—thus, homeostatic regulation of the population size of DP cells is apparently imposed by thymic stroma via unknown stimuli. DP cells undergo negative and positive selection to produce functional single positive T cells that weakly recognize self-peptides, ensuring a competent T cell repertoire. DP cells that fail positive selection (more than 90%) die because they fail to acquire the “trophic” signal provided by TCR. The cells that emerge from the thymus (about 10^6 /day in the mouse) are naive $CD4^+$ or $CD8^+$ T cells that then enter the naive peripheral T cell pools.

NAIVE $CD4^+$ AND $CD8^+$ T CELLS

Naive T cells may require trafficking through secondary lymphoid organs (8) for survival and proliferative signals. Part of this requirement may be that naive T cells need low levels of stimulation through the TCR from class I and class II major histocompatibility complex (MHC) molecules complexed with self-peptide (13,16,24). Naive $CD8^+$ T cells rapidly disappear when transferred into syngenic MHC class I deficient animals (reviewed in Reference 60).

Some controversy exists as to whether naive $CD4^+$ T cells require signals through self-peptides presented by MHC class II as initially suggested (10). In a recent experiment these cells proliferated equally well in MHC class II $^+$ or II $^-$ hosts (11). One possibility is that naive $CD4^+$ cells, in that study, had a short lifespan that was not prolonged by class II, whereas naive $CD8^+$ cells had a longer lifespan in a class I bearing host than in a host lacking class I (15,61).

TCR ablation was induced in peripheral T cells by acute Cre-LoxP removal of the gene segment encoding the receptor's constant region. This resulted in loss of naive T cells over time, with faster decay rates for $CD8^+$ T cells than $CD4^+$ T cells (47). Therefore, the absence of a TCR signal did not immediately promote death, but was necessary for the long-term maintenance of naive T cells.

Cytokines provide a second signal, in addition to TCR signals, for homeostatic survival and proliferation of naive T cell populations. Naive T cells require cytokines that signal through the γc chain (32). It was further shown that the cytokines IL-4, IL-7 (2,67), and IL-6 (65) prolong the survival of naive T cells and enhance homeostasis (39). Though IL-6 has no proven role in vivo for naive T cells (although plasma cells may depend on it), loss of IL-4 or IL-7 shortened the lifespan of naive T cells in thymectomized mice (3).

Using cytokine-deficient mice, it was shown that naive T cells could undergo homeostatic expansion in IL-4 $^{-/-}$ and IL-15 $^{-/-}$ hosts, but not in IL-7 $^{-/-}$ hosts. Hence, exposure to IL-7 is essential for the maintenance of the naive T cell pool. IL-7 is required for prolonged survival of naive T cells in that these cells disappear over a one-month period when transferred into IL-7 $^{-/-}$ hosts (63). The overall size of the naive T cell pool is therefore based on the levels of available IL-7. Decreases in cellular content reduce the competition for the available IL-7, resulting in increased cytokine levels, which then drives residual T cells to undergo homeostatic proliferation, in conjunction with signals received from self-antigens through the TCR. In peripheral lymphoid organs, IL-7 has recently been reported to be produced by dendritic-like cells, and this production increases following lymphocyte depletion (45).

MEMORY T CELLS

Naive T cells migrate through secondary lymphoid tissues (spleen, lymph nodes, and Peyer's patches) where their TCRs can respond to antigenic peptides in the cleft of a MHC molecule on the surface of antigen presenting cells (APCs) such as dendritic cells. Together with engagement of the TCR, the T cell requires co-stimulation through CD28 or other surface molecules, which is provided by activated dendritic cells. However, co-stimulation is not thought to be an essential component of T cell homeostatic expansion (48). It should be noted that this process of foreign antigen presentation by dendritic cells is different from that which occurs when naive T cells encounter self-antigen. In the maintenance of naive T cell homeostasis, self-peptides would be presented by dendritic cells that are not activated by infectious agents (i.e., bacteria and viruses), hence co-stimulation would not ordinarily be available, and as noted above, is not required.

Following activation by antigens, T cells proliferate vigorously and produce cytokines such as IL-2, IL-4, and IL-9, which probably mimic IL-7 and IL-15 to the extent that they allow a temporary increase in size of the T cell compartment. For example, IL-2 functions as a growth factor and temporary survival factor, but then programs T cells for elimination via the Fas/FasL pathway and activation-induced cell death (AICD). This process is self-limiting and massive cell death follows decay of antigenic stimulation. Mice deficient in IL-2 or IL-2 signaling accumulate high numbers of lymphocytes and demonstrate striking enlargement of peripheral lymphoid organs (53). CTLA-4, which like CD28 binds B7, delivers a key inhibitory signal to T cells during activation. Blocking CTLA-4 enhances T cell proliferation, and mice deficient for CTLA-4 develop a fatal lymphoproliferative disorder (66).

From the pool of activated cells, the development of memory T cells has engendered several theories. Generation of memory could be either a stochastic process or an instructional process, with a small subset of cells learning to avoid death. Memory cells could also arise from a unique subset of effector cells, rather than from effector cells in general, or could originate from cells that express a full-range of effector activity but are produced late in the course of an immune response, having been exposed to foreign antigen a shorter time (reviewed in Reference 58). Memory T cells are of two types: those in an activated state (resem-

Table 1. Mediators of Lymphocyte Homeostasis

<u>The γc Cytokines</u>		
IL-7	Naive CD4 ⁺ and CD8 ⁺ T cells Memory CD8 ⁺ T cells (possibly $\gamma\delta$ T cells) (possibly pro-T cells)	Tan et al. (63) Schluns et al. (55) Moore et al. (41) Kim et al. (27)
IL-15	Memory CD8 ⁺ T cells NK and NK-T cells	Lodolce et al. (35) Kennedy et al. (23)
IL-4	(expendable cofactor for memory CD8 ⁺ T cells)	Huang et al. (22)
<u>Other Cytokines</u>		
IL-12	(expendable cofactor for memory CD8 ⁺ T cells)	Kieper et al. (25)
<u>Antigen Receptors</u>		
TCR	Naive CD4 ⁺ and CD8 ⁺ T cells	Kieper et al. (24)
BCR	Mature B cells	Lam et al. (31)
<u>Other Factors</u>		
BAFF	Mature B cells	Schiemann et al. (54)
LKLF	(possible intracellular signal for memory CD4)	Schober et al. (56)

bling effector cells), displaying activation markers such as CD69 and CD25, and those in a resting state, with slow turnover and no activation markers.

Memory T cells are more metabolically active than naive cells (59) and do not need antigen stimulation for survival (4,33,42). CD4⁺ or CD8⁺ memory T cells can survive in MHC class II or class I deficient hosts for long periods of time (43,62) and in the absence of a functional TCR (47).

Memory CD8⁺ T Cells

Experiments stimulating the innate immune system with Poly I:C or LPS induced a burst of proliferation of polyclonal memory CD8⁺ T cells. This did not occur in interferon-gamma (IFN- γ) deficient mice, and it was shown that the IFNs stimulated secondary cytokines (59), one candidate being IL-15.

IL-15 is produced by nonlymphoid cells. The IL-15 receptor consists of a unique IL15R α chain and two components shared with the IL-2 receptor (IL-2R β and γ c) (76). IL-15^{-/-} mice showed a deficiency in memory CD8⁺ T cells, especially those expressing CD122 (IL-2R β). Mice lacking the IL-15R α chain were lymphopenic despite apparently normal lymphocyte development and had a selective reduction in memory phenotype CD8⁺ T cells (35,73). The same was true for mice deficient in IL-15 (23). An IL-15 transgene induced massive increases in T cells (14) and treatment with IL-15 accelerated restoration of lymphocytes in lymphopenic mice (36,76), indicating that it is a homeostatic regulator.

The homeostatic activities of IL-15 are distinct from IL-2, which does not trigger T cell expansion and actually programs for cell death (70). Hence, the total pool size of memory CD8⁺ T

cells is maintained through a balance of IL-15 (promoting life), and IL-2 (promoting death) (29). Despite this strong role of IL-15 in memory T cell survival, a portion of CD8⁺ memory T cells (approx. 30%) are independent. The cells are CD122 low and account for the residual cells found in IL-15 deficient mice (59).

IL-7, in addition to IL-15, was also shown to promote survival of memory CD8⁺ T cells (55). The absence of IL-7 blocked homeostatic expansion in immunodepleted hosts but had only a partial effect in normal hosts, suggesting the interactions of other cytokines. Because both IL-7 and IL-15 are required for normal numbers of memory CD8⁺ cells, it has been suggested that IL-15 stimulates homeostatic proliferation, whereas IL-7 signals for survival (55). An IL-7 transgene induced increases in memory CD8⁺ cells and restored CD8⁺ memory cell numbers in IL-15 deficient mice. Therefore, the requirement for IL-15 in the generation and maintenance of memory CD8⁺ is dispensable in the presence of excess IL-7 (26).

Recently it was shown that IL-12, after lymphodepletion, also contributed to the homeostatic expansion of CD8⁺ memory T cells together with self-peptides and MHC, while addition of IL-2 did not promote growth and survival and in fact inhibited the IL-12 driven expansion (25). It is likely that one function of cytokines in memory CD8⁺ T cells survival is induction of anti-apoptotic proteins like Bcl-2, however there must be other functions still to be determined. IL-4, given to naive CD8⁺ T cells along with TCR stimulation in vitro, was also shown to promote the generation of long-term memory CD8⁺ T cells following transfer in vivo (22), perhaps by up-regulating CD122 (58); however there is no evidence for a physiological role in homeostasis, since IL-4 deficient mice had normal levels of CD8⁺ memory T cells (68).

Memory CD4⁺ T Cells

Unlike memory CD8⁺ T cells that rely on γ c-cytokine-mediated survival signals, memory CD4⁺ T cells proliferate and survive in γ c-cytokine-depleted hosts (57). Clearly neither IL-7 nor IL-15 is necessary for the homeostatic expansion of CD4⁺ memory T cells and contact with MHC is also not essential (64). Thus, if a cytokine(s) serves as a homeostatic regulator of CD4⁺ memory T cells, it has yet to be identified. Another possibility is OX40, a molecule shown to be required with CD28 co-stimulation during antigen-driven expansion of CD4⁺ T cells, which stimulates expression of anti-apoptotic proteins (17,51), but whether such a molecule has a role in lymphocyte homeostasis remains to be determined.

That distinct intracellular mechanisms control CD8⁺ versus CD4⁺ memory T cells is suggested by the different anti-apoptotic proteins expressed. In CD8⁺ memory T cells, Bcl-2 is up-regulated, while in CD4⁺ memory T cells expression is observed for Bcl-X_L (18,59) or possibly other pro-life factors such as lung Kruppel-like factor (LKLf) (56).

NK CELLS

In mice deficient for the common γ c receptor chain that is shared by IL-2, IL-4, IL-7, and IL-15, it was noted that NK cells were among the immune cells absent—with a 350-fold reduction reported (6,9). However, mice lacking IL-7 or its receptor did not display any NK deficiency (37,41). IL-2 is known to be an activator of NK cells, but at high amounts, yet IL-2 deficient mice had only slight decreases in NK cells (reviewed in Reference 72). The mystery was resolved when mice deficient in IL-15 or IL-15R α were shown to have a striking deficiency in NK and NK-T cells as well as subpopulations of intestinal epithelial lymphocytes (IELs) (23,35). IL-15 was shown to maintain the survival of NK cells in the absence of serum and could promote its survival function through the up-regulation of anti-apoptotic proteins (7). It remains to be shown that IL-15 is actually a homeostatic regulator of NK cells, since raising the level of IL-15 has yet to be shown to increase the NK population (as IL-15 increases memory CD8⁺ cells), nor have survival of NK cells following transfer into IL-15^{-/-} mice been examined. So there may be another NK regulator.

$\gamma\delta$ T CELLS

$\gamma\delta$ T cells require IL-7 for development. Mice lacking IL-7 had a decreased frequency and number of thymic $\gamma\delta$ T cells (41), and mice without an IL-7 receptor had an absence of $\gamma\delta$ T cells from the skin, gut, liver, and spleen (37). The requirement for IL-7 is partly for rearrangement of the TCR γ gene (12). There may also be a function for IL-7 in survival of $\gamma\delta$ T cells, however this has yet to be shown by transfer of $\gamma\delta$ T cells into IL-7^{-/-} hosts.

B CELLS

The requirements for homeostasis of B cells are less well understood than for T cells. In the mouse (but not humans), dif-

ferentiation and selection of B cells in the bone marrow requires IL-7. IL-7 deficient mice show a block in pro- to pre-B cell development (69). Newly formed B cells (called transitional B cells) then leave bone marrow and migrate to the spleen, a complex process regulated by chemokines and nonhematopoietic elements (1). Signaling through the B cell receptor (BCR) is important to generate a mature B cell pool (40). Even after their development, the mature B cell depends on signals through BCR, as addressed using conditional knock-out mice (31). Many mutations that interrupt BCR signaling also inhibit the maturation of B cells (reviewed in Reference 30). In addition to the BCR, other factors that enable differentiation of transitional B cells into long-lived lymphocytes are still being discovered.

Recently a number of investigators identified a cytokine that enhanced B cell survival. BAFF/BLyS/TALL-1/TNFS13B is a member of the TNF family and is produced by myeloid cells. BAFF deficient mice show depletion of peripheral B cells and negligible IgM responses after challenge with antigen (54). BAFF transgenes induce peripheral B cell expansion and autoimmunity (19). The receptor for BAFF remained a puzzle because two TNF family receptors originally thought to bind BAFF, BCMA, and TACI, could not account for the full activity of BAFF (71). Recently a third, very specific receptor for BAFF was identified, BAFF-R or BR3, which binds only BAFF. Mice harboring a natural mutation of the BAFF-R gene demonstrate poor peripheral B cell survival similar to that seen with BAFF-deficient mice (20,74). Hence, through mechanisms still to be resolved, BAFF promotes survival of mature B cells, heightens humoral immune responses, and synergizes in the B cell response to CD40L (52). Because BAFF deletion reduces the B cell pool and overexpression expands it, BAFF appears to be a major homeostatic regulator of mature B cell populations. APRIL is a BAFF homolog with some overlapping receptor specificities, and its injection also induces B cell increases (75); thus it may also prove to be a homeostatic B cell regulator.

Once activated B cells differentiate into antibody-secreting plasma cells, IL-6 may play a role in their survival. Plasmacytomas and multiple myelomas have been shown to require IL-6 for survival through activation of signaling pathways still to be dissected (21).

CONCLUDING REMARKS

The requirements for survival factors in the maintenance of peripheral homeostasis differs between B and T cells throughout their different developmental stages. The need for a survival stimulus during homeostasis is mediated through specific cytokines, resulting in the regulation and control of lymphocyte development, function, and peripheral population size. IL-7 is essential during lymphocyte development and is a required signal for the maintenance of naive CD4⁺ and CD8⁺ T cells as well as memory CD8⁺ T cells. The cytokine IL-15 is necessary also for the homeostasis of memory CD8⁺ T cells and NK cells. Recognition of self-peptides through MHC class I and II is needed by naive T cells, in addition to IL-7, while memory T cells are independent of the MHC. Together this pool of knowledge demonstrates the elegant regulatory mechanisms that maintain homeostasis of peripheral lymphocytes. Still many

questions remain to be answered.

The most striking omission in our understanding is what regulates the survival of memory CD4⁺ T cells since the $\gamma\epsilon$ cytokines and TCR do not appear to be required. By contrast, CD8⁺ memory T cells depend on two critical cytokines, IL-7 and IL-15, and can also be regulated by IL-12 and IL-4. What maintains the CD122^{lo} memory CD8⁺ cells that are independent of IL-15. What is the precise microenvironment in which these signals are delivered? Little is known about the homeostasis of B cells and new factors remain to be discovered. Even the $\gamma\epsilon$ cytokines have unknown cofactors in their action on T cells, since *ex vivo*, IL-7 can only support their survival for a week or two, whereas *in vivo*, T cells can survive for years.

In addition to cytokines, signaling through the antigen receptors regulates survival in some populations. This is most evident in B cells and naive CD8⁺ cells, yet the picture in naive CD4⁺ T is controversial, perhaps because their lifespan is fairly brief anyway.

The nature of the intracellular survival signals delivered either by cytokines or antigen receptors remains elusive and is too complex an issue to deal with in this discussion. The induction of antiapoptotic factors like Bcl-2 or Bcl-X_L is only part of the lymphocyte survival signal. In addition, survival signals repress activation of death proteins including Bim, Bad, and Bax, stimulate cellular metabolism, and there could be other effects. Further understanding of these intracellular pathways that regulate lymphocyte homeostasis should offer keys to clinical problems of stimulating the immune response, repressing it, and treating lymphoma.

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