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HOMEOSTATIC EXPANSION AS A BARRIER TO LYMPHOCYTE DEPLETION STRATEGIES

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Introduction

Purpose of review—Following lymphodepletion, lymphocytes repopulate the immune space both through enhanced thymopoiesis and proliferation of residual non-depleted peripheral lymphocytes. The term homeostatic proliferation (alternatively homeostatic expansion or lymphopenia-induced proliferation) refers to the latter process. Homeostatic proliferation is especially relevant to reconstitution of the lymphocyte compartment following immunodepletion therapy in transplantation. Repopulating lymphocytes can skew toward an effector memory type capable of inducing graft rejection, autoimmunity, or, in the case of allogeneic bone marrow transplantation, graft *versus* host disease. Here we review recent studies exploring the biologic mechanisms underlying homeostatic proliferation and explore implications for therapy in transplantation.

Recent findings—Two immune-depleting agents, alemtuzumab and rabbit antithymocyte globulin, have been well-characterized in their abilities to induce an effector-memory phenotype in repopulating lymphocytes. Additionally, we have gained new understandings of the mechanisms by which the cytokines Interleukin-7 (IL-7) and Interleukin-15 (IL-15) regulate this process. Recent studies have also explored the functions of non-cytokine and signaling molecules in lymphopnenia-induced proliferation. Finally, we have seen the promise and limitations of several therapeutic approaches, including recombinant IL-7 therapy, $CD8^+$-targeted antibodies, and peri-transplant cyclophosphamide, to treat post-transplant lymphopenia and reduce the risks of immune dysregulation following homeostatic proliferation.

Summary—Immune dysfunction following homeostatic proliferation is a special challenge in transplantation. A deeper understanding of the underlying biology has led to a number of promising new therapies to overcome this problem.

Keywords

Homeostatic proliferation; transplantation; lymphodepletion; autoimmunity

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Conflict of Interest

Laurence Turka owns equity in and has a family member employed by Novartis.

I. Introduction

Following lymphodepletion, lymphocytes repopulate the immune space both through enhanced thymopoiesis and proliferation of residual non-depleted peripheral lymphocytes. The term homeostatic proliferation (alternatively homeostatic expansion or lymphopenia-induced proliferation) refers to the latter process. Early studies of homeostatic proliferation showed that T cells surviving lymphodepletion divided, developed memory phenotype and function, and then acted in a dominant fashion to render animals resistant to cardiac or renal allograft tolerance *via* costimulatory blockade.[1,2] In line with these findings, recent studies have shown that lymphopenia itself is enough to break stable costimulatory blockade-based peripheral tolerance.[3] In a mouse model of MHC-mimatched cardiac transplantation, lymphopenia (achieved either by irradiation or anti-$CD4^+$/$CD8^+$ monoclonal antibodies) induced acute T and B cell-mediated rejection, accompanied by a T cell shift toward a $CD44^{hi}$ effector-memory (EM) phenotype and the appearance of donor-specific antibodies. The process of homeostatic proliferation can be divided into “slow” (one cell division per 24–36 hours) or “fast” (one division per 6–8h) kinetics. While slow proliferation occurs in response to a “sensing of empty space”, rapid proliferation is primarily a gut antigen-driven process.[4] Slow homeostatic proliferation predominates in homeostatic proliferation following lymphodepletion in mouse models. Furthermore, both T and B cells can undergo homeostatic proliferation. In this review, we will focus on recent developments in the slow homeostatic proliferation of T cells following lymphodepletion, which we believe is most relevant to understanding rejection and autoreactivity following transplantation.

II. Pharmacologic lymphocyte depletion promotes autoimmunity and the expansion of alloreactive lymphocytes

Alemtuzumab (anti-CD52) is a potent lymphocyte depletional agent that has been used as induction therapy for transplantation and for treatment of multiple sclerosis. $CD4^+$ cells and, to a lesser extent, naïve $CD8^+$ cells, are most susceptible to alemtuzumab-induced lymphodepletion.[5,6,7,8] A larger population of naïve T cells may remain undeleted, however, as peripheral lymph nodes may be a reservoir for these cells following alemtuzumab induction.[9] Alemtuzumab therapy leads to skewing toward memory $CD4^+$ and $CD8^+$ phenotypes in renal transplant recipients; those with evidence of rejection (by biopsy, new or donor-specific antibodies) following alemtuzumab therapy have an increased proportion of $CD8^+$ effector memory cells ($CD45RO^-CD62L^-$).[10] These same patients further have decreased frequencies of regulatory T cells (T_{regs}) among $CD4^+$ cells. While other work, in contrast, has suggested an increased frequency of $Foxp3^+$ cells following alemtuzumab induction.[11] It is possible that in this instance Foxp3 expression may be only a transient marker of T cell activation.[12,13, 14] Among patients with multiple sclerosis, homeostatic proliferation following alemtuzumab therapy leads to recovery of a highly activated, proliferative, oligoclonal, and memory-like population of $CD4^+$ and $CD8^+$ cells.[15] In particular, the CD8 pool is dominated by a terminally-differentiated, effector memory $CD28^-CD57^+$CD8 population expressing perforin and Granzyme B. Such as population is known to be associated with autoimmunity, and indeed in this study of 87 patients, two thirds developed (primarily thyroid) autoimmunity.

Rabbit antihymocyte globulin (rATG) depletes naïve but not central memory or effector memory T cell subsets in kidney transplant patients.[16] Early studies of immune monitoring of $CD4^+$ cells following ATG induction has indeed revealed a residual population of $CD25^+CD45RO^+CD45RA^-$ (*i.e.*, EM) cells but also transient expression of Foxp3,[17] which, again, may only be a marker of $CD4^+$ activation. Nonetheless, administration of mouse ATG in a mouse model of T_{reg}-dependent autoimmune diabetes increased the prevalence of $Foxp3^+$ and $CTLA\text{-}4^+$ cells while delaying the onset of autoimmunity.[18] Perhaps Treg induction (transiently) counterbalances memory T cell expansion following ATG induction. Recent examination of the kinetics of lymphocyte depletion following rATG given as induction therapy in renal transplantation found that rATG durably depletes the T cell compartment to counts below 250 $CD3^+$ cells/uL at six months, compared to minimal T cell depletion following basiliximab or no induction therapy.[19] In contrast to prior studies, this recent investigation found no increase in thymopoiesis (*i.e.*, $CD31^+$ cells among $CD4^+$ or $CD8^+$ cells) one month following rATG induction. Rather, peripheral cytokine-mediated signaling by IL-7 and IL-15 via Stat5 increased in the first month following rATG therapy, particularly among memory T cell subsets. These studies indicate that T cell recovery following ATG comes from peripheral T cell pools rather than heightened thymopoiesis.

III. New insights into the immunobiology of homeostatic proliferation: IL-7, IL-15, and non-cytokine regulators

In humans, unlike mice, the majority of proliferating T cells derives from the periphery rather than the thymus.[20] Therefore, peripheral cytokine signaling is essential to maintain the lymphoreplete state and repopulate the T cell compartment in lymphopenia. IL-7 is the primary cytokine responsible for T cell homeostatic proliferation. In young thymectomized and elderly adults, circulating IL-7 levels are higher than those of healthy controls.[21] IL-7 in these patients with low or no thymic function appears to stimulate T cell proliferation *via* STAT5 signaling. IL-7 itself has been described as a “rheostat” to maintain the T cell compartment.[22] In lymphopenia, excess IL-7 stimulates T cell proliferation. Proliferating T cells consume IL-7, and levels fall to the basal state as the T cell compartment repopulates. This mechanism prevents excess proliferation and preserves T cell homeostasis. A recent study found that IL-7-induced proliferation requires intermittent (rather than continuous) signaling and that TCR engagement provides this interruption.[23] T cells with inadequate affinity for peripheral (self) TCR ligands die following prolonged IL-7 signaling; this mechanism maintains a population of T cells with appropriate affinity for self ligands.

In addition to IL-7, IL-15 signaling is important for $CD8^+$ T cell survival and proliferation.[24,25,26] While IL-15 enhances homeostatic proliferation of memory $CD8^+$ cells, IL-15 alone is not enough for homeostatic proliferation of naïve CD8 T cells. [27] In naïve $CD8^+$ cells, MHC I engagement is also necessary for homeostatic proliferation.[28] Emerging data show that memory $CD4^+$ may also be responsive to IL-15.[29,30,31] Finally, TGB-β may attenuate IL-15 signaling and act as a brake on homeostatic proliferation-driven autoimmunity.[32,33, 34,35,36,37]

In the past year, a number of studies have shown the importance of cell-intrinsic signaling, non-cytokine TCR regulation, and trafficking molecules in regulating homeostatic proliferation.

The protein tyrosine phosphatase gene product PTPN2, which dampens TCR signaling in $CD4^+$ and $CD8^+$ cells, is implicated in human autoimmunity.[38,39] T cell knockout of PTPN2 in a mouse model resulted in more rapid lymphopenia-induced $CD8^+$ proliferation compared to control animals. Adoptive transfer of PTPN2-deleted $CD8^+$ cells into congenic hosts resulted in effector/memory differentiation and autoimmunity compared to adoptive transfer of control $CD8^+$ cells..[40] This response was IL-7-independent. miRNA-181a enhances TCR signaling, in part by suppressing expression of other protein phosphatases.[41] Thus, miRNA-181 or another miRNA might inhibit PTPN2 expression and thereby dampen lymphopenia-induced proliferation.

It has been suggested that transcription factors may regulate the ability of hematopoietic stem cells to repopulate the lymphocyte compartment. For example, *Hoxb4* signaling may promote a hematopoietic stem cell $CD4^+$ central memory ($CD44^{hi}CD62L^+$) phenotype in response to lymphopenia.[42] In competitive adoptive transfer experiments, Hoxb4-overexpressing central memory cells contributed less than wild-type central memory cells to reconstitution of lymphoid organs.

Finally, the integrin CD18 (lymphocyte function-associated antigen-1, or LFA-1) functions in naïve T cell trafficking between the gut and secondary lymphoid organs[43,44] and is implicated in gut autoimmunity.[45] Adoptive transfer of $CD4^+$ $CD18^{-/-}$ cells into $Rag^{-/-}$ hosts has shown the requirement of CD18 both for fast and slow lymphopenia-induced proliferation.[46] The above studies have illustrated the importance of non-cytokine regulators of homeostatic proliferation that skew toward an effector memory phenotype in homeostatic proliferation.

IV. Clinical implications for autoimmunity after treatment of lymphopenia and strategies to prevent autoreactivity

Recombinant IL-7 has come into use to promote T cell recovery in lymphopenia. The therapeutic goal has been to expand the population of mature lymphocytes rather than to induce thymopoiesis.[47,48] While studies of T cell subsets suggest that IL-7 administration to humans with refractory malignancies increases naïve T cell fractions,[49] these results need to be interpreted with caution. IL-7 administration in lymphopenic hosts may have markedly different effects. A recent Phase I trial of IL-7 administration in allo-HSCT skewed repopulating $CD4^+$ and $CD8^+$ cells toward an effector-memory ($CD45RA^-CCR7^-$) phenotype.[50] Recent studies of IL-7 administration to mice have suggested that $CD4^+$ single-positive (miR181a -expressing) thymocytes are more sensitive to IL-7-induced proliferation than are peripheral $CD4^+$ cells.[51] In these animals, peripheral lymphopenic $CD4^+$ proliferation in response to IL-7 had a strong TCR co-stimulation requirement; these proliferating cells were primarily slow rather than fast-proliferating cells. These data suggest that thymopoiesis provides an important contribution to resolving lymphopenia and that IL-7 therapy affects slowly rather than quickly-proliferating cells under conditions of homeostatic

proliferation. Prior studies have suggested that PI3K signaling is essential for proliferation of these $CD4^+$ cells, particularly in $CD31^+$ recent thymic emigrants.[52,53]

Another potential approach to overcoming homeostatic proliferation as a barrier to transplantation is to delete potentially pathologic $CD8^+$ cells specifically in transplant recipients. Yamada *et al* employed this approach with the use of anti-CD8 mAbs at the time of lymphodepletion in a mixed chimerism model of MHC mismatched renal transplantation in nonhuman primates;[54] their findings of decreased T_{mem} responses in CD8-depleted antimals are encouarging. The same group subsequently studied alefacept, a fusion protein of the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) adhesion molecule.[55] This agent is thought to interrupt cytotoxic effector memory T cell proliferation by blocking the interaction between effector-memory $CD2^+$ cells and LFA-3. Alefacept therapy for psoriasis preferentially depleted $CD4^+CD45RO^+$ effector memory cells, which correlated with clinical improvement in skin lesions.[56] Alefacept preferentially and reversibly depleted $CD8^+$ effector memory ($CD28^-CD95^+$) cells in a nonhuman primate transplantation model[57]; $CD28^-$ cells in this model were $CD2^{hi}$, helping to explain alefacept's ability to preferentially deplete $CD8^+$ cells.

Post-transplant cyclophosphamide administration is an attractive approach to prevent GVHD by depleting alloreactive $CD8^+$ cells that might otherwise survive induction therapy.[58,59] Recent data suggest that post-transplant cyclophosphamide administration primarily targets rapidly-dividing allo-specific cells, relatively sparing naïve cells essential to maintenance of immunocompetence following HSCT.[60] $CD4^+Foxp3^+$ T_{regs} appear resistant to cyclophosphamide and recover quickly following cyclophosphamide induction for allogeneic bone marrow transplantation.[61] Sparing of T_{regs} may partly underlie the mechanism by which cyclophosphamide prevents GVHD.

Finally, in contrast to T_{conv} cells, T_{regs} require IL-2 is essential for Treg survival and proliferation, both in lymphopenia and the lymphoreplete state.[62] This observation has led to low-dose IL-2 as therapy to promote Treg proliferation in hepatitis C-associated vasculitis[63] and GVHD following stem cell transplantation.[64] IL-2 therapy for GVHD restores pStat5 signaling and proliferation of T_{regs} without affecting T_{convs}.[65] Thus, T_{reg}-specific therapy may ultimately find a place in transplant immunosuppression protocols alongside more generalized lymphodepletion strategies and targeted effector-memory cell deletion.

V. Conclusion

Lymphodepletion for induction transplant therapy is double-edged sword. On the one hand, highly effective agents such as alemtuzumab and rATG are able to prevent early T cell mediated rejection. On the other hand, repopulated T cells skew toward allo-specific, effector-memory phenotypes following lymphodepletion. An interesting concept in tumor immunobiology turns the concept of homeostatic proliferation on its head. The conditions of homeostatic proliferation could be used to cultivate $CD8^+$ cells specific to tumor antigens, allowing for specific immunotherapy.[66,67] This type of approach remains experimental in mouse models. But exploring the spectrum of homeostatic proliferation can improve our understanding of this important phenomenon, not only as it relates to transplantation but also

to HIV therapy and autoimmunity. The use of recombinant IL-7 in transplantation treatment of lymphopenia may be a tight rope to walk if this therapy skews repopulating T cells toward an effector memory phenotype capable of autoreactivity. Alternatively, targeted deletion of effector memory $CD8^+$ cells upon transplantation—with depleting antibodies or cyclophosphamide—is an intriguing way to solve this problem, so long as these approaches do not increase the risks of infection unacceptably. Finally, the role of T_{regs} in controlling autoimmunity or alloreactivity following lyphodepletion merits further investigation. IL-2 therapy may not adequately enhance T_{reg} function to overcome the problems of homeostatic proliferation. A deeper understanding of T_{reg} biology, however, may ultimately lead to Treg-specific therapies that ameliorate the EM-skewing induced by lymphodepletion.

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Abbreviations

EM	Effector memory
HP	homeostatic proliferation
GVHD	Graft *versus* host disease
IL-2	Interleukin-2
IL-7	Interleukin-7
IL-15	Interleukin-15
T_{mem}	memory T cell
rATG or ATG	rabbit antithymocyte globulin
T_{reg}	regulatory T cell
TCR	T cell receptor

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Key Points

- Repopulating lymphocytes can skew toward an effector memory type capable of inducing graft rejection, autoimmunity, or, in the case of allogeneic bone marrow transplantation, graft *versus* host disease.
- In the past year, we have gained new understandings of the mechanisms by which the cytokines Interleukin-7 (IL-7) and Interleukin-15 (IL-15) regulate this process. Recent studies have also explored the functions of non-cytokine and signaling molecules in lymphopnenia-induced proliferation.
- Additionally, we have seen the promise and limitations of several therapeutic approaches, including recombinant IL-7 therapy, $CD8^+$-targeted antibodies, and peri-transplant cyclophosphamide, to treat post-transplant lymphopenia and reduce the risks of immune dysregulation following homeostatic proliferation.