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Homeostatic cytokines in immune reconstitution and graft-versus-host disease

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ABSTRACT

For numerous patients, allogeneic stem cell transplantation (SCT) is the only therapeutic option that could potentially cure their disease. Despite significant progress made in clinical management of allogeneic SCT, acute graft-versus-host disease (aGVHD) remains the second cause of death after disease recurrence. aGVHD is highly immunosuppressive and the adverse effect of allogeneic SCT on T cell regeneration is typically more important than the levels of immunosuppression normally seen after autologous SCT. In these patients, immune reconstitution often takes several years to occur and restoring immunocompetence after allogeneic SCT represents an important challenge, principally because clinical options are limited and current methods used to accelerate immune reconstitution are associated with increased GVHD. Interleukin-7 and IL-15 are both under clinical investigation and demonstrate the greatest potential on peripheral T cells regeneration in mice and humans. However, awareness has been raised about the use of IL-7 and IL-15 after allogeneic SCT with regards to potential adverse effects on aGVHD. In this review, we will discuss about recent progress made in lymphocyte regeneration, the critical role played by IL-7 and IL-15 in T cell homeostasis and how these cytokines could be used to improve immune reconstitution after allogeneic SCT.

1. Introduction

Allogeneic stem cell transplantation (SCT) was developed to treat hematologic malignancies and congenital or acquired hemopathies. Despite important side effects, SCT remains the only curative treatment for several patients with hematologic cancers. Graft-versus-host-disease (GVHD) is the second cause of death after disease recurrence and occurs when donor T cells react against normal host tissues. Simultaneously, graft-versus-leukemia (GVL), which is also mediated by donor T cells, provides a survival advantage to transplanted patients through the elimination and control of minimal residual disease [1]. In humans, it is still unclear as to whether T lymphocytes that mediate GVHD or GVL effects are the same [2,3]. Following SCT, donor stem cells migrate inside the bone marrow (BM) where they engraft and later differentiate into white blood cells, megakaryocytes and erythrocytes. While the regeneration of innate immune cells occurs relatively early post-SCT, lymphocyte regeneration is typically slow and T cell recovery can take several years to occur, sometimes never recovering completely [4,5]. Following T cell depletion, lymphocyte regeneration occurs via two distinct pathways; via thymopoiesis, which recapitulates lymphocyte differentiation as it occurs early in life and via a thymic independent pathway termed homeostatic peripheral expansion (HPE) which relies on the intensive proliferation of mature lymphocytes contained within the stem cell graft [6,7]. Because thymic involution occurs early in humans and thymic function is further compromised by chemotherapy and GVHD, peripheral homeostatic mechanisms become essential during this period in order to promote T cell regeneration and provide immunocompetence [8,9]. Yet, in these patients, even a mild GVHD (grade 1–2) can significantly affect T cell regeneration and induce profound lymphopenia. IL-7 and IL-15 are two homeostatic cytokines with the greatest effect on lymphocyte homeostasis and immune reconstitution after SCT [10,11]. However, awareness has been raised about the use of these cytokines T to accelerate T cell regeneration in the setting of allogenic SCT since both cytokines can worsen GVHD [12,13]. In this review, we will discuss about IL-7 and IL-15 homeostatic cytokines and their dual role in promoting lymphocyte reconstitution and GVHD in the setting of allogeneic SCT.

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2. Immunobiology of IL-7

Interleukin-7 is a glycoprotein of 25 kDa that belongs to the common gamma chain (γC) family and is located on chromosome 8 in humans and chromosome 3 in mice [14–16]. While stromal cells from primary and secondary lymphoid organs constitute the main reservoir of IL-7 [17], hepatocytes, epithelial cells from the guts, keratinocytes, endothelial cells and fibroblasts also produce IL-7 [18–22]. More recently, dendritic cells and macrophages have been shown to produce IL-7 but the effect on T cell homeostasis remains largely unexplored [23,24].

Interleukin-7Rα is expressed by common lymphoid progenitors (CLP) [25], immature thymocytes prior to their double positive stage and later on single positive thymocytes [26,27]. Expression of IL-7Rα is high on most peripheral T cells including recent thymic emigrants (RTE) [28]. Following T cell activation, IL-7Rα expression is down modulated and then re-acquired during the formation of memory lymphocytes [29,30]. Interleukin-7Rα stimulation on T cells induces IL-7Rα endocytosis and degradation [31–33]. In B lymphocytes, expression of IL-7Rα is limited to immature pro-pre B cells [29]. Finally, IL-7Rα mRNA is detected in DCs and stroma cells of primary and secondary lymphoid organs [4,24,34].

While the IL-7Rα chain provides the specificity to bind IL-7, the dimerization between IL-7Rα and the γ_c chain is necessary for IL-7 signaling (Fig. 1) [35,36]. Interleukin-7 induces the activation of Janus kinase 1 (JAK1) and JAK3 which catalyze the phosphorylation of signal transducer and activator 5A (STAT5A) and STAT5B proteins. Following their translocation inside the nucleus, Stat5A and B bind B cell lymphoma (BCL-2) and myeloid cell leukaemia sequence 1 (MCL-1) promoters and induce transcription of these cell survival genes. More recently, studies have also demonstrated that T cell survival was also controlled in part by down-modulation of pro-apoptotic proteins BCL-2 associated X protein Bax [37], BCL-2 antagonist of cell death (Bad) [38], and BCL-2-interacting mediator of cell death (Bim) [39]. Interleukin-7 signaling can induce the activation of phosphoinositide 3-kinase (PI3K) [40,41] and the mitogen activated kinases (MAP kinases) [42] pathways to promote T cell proliferation. Finally, IL-7 can modulate glucose uptake and cell metabolism which are essential for survival, proliferation and migration of T cells [43,44]. Thus, IL-7 signaling in T lymphocytes is essential and required for the peripheral maintenance of T lymphocytes in humans and mice.

3. Immunobiology of IL-15

Interleukin-15 is a glycoprotein of 14–15 kDa that belongs to the common γC cytokine family and is located on chromosome 4 in humans and 8 in mice. Although IL-15 mRNA is detected in several types of cells (fibroblasts, keratinocytes, neural cells, monocytes-macrophages and DCs) [45–47] protein synthesis is tightly controlled and detected only in fewer cell types including monocytes/macrophages and dendritic cells (DCs) [48,49] IL-15 exists under 2 different splicing isoforms; a long and a short form that differ according to the length of their signal peptide. While both isoforms give raise to the same IL-15 protein, only the isoform with long signal peptide is secreted [50].

Interleukin-15R is composed of 3 chains; the IL-2/15Rβ, the common γ_c and the high affinity IL-15Rα chain. Interleukin-15Rα is expressed by memory $CD8^+$ T cells, NK cells, DCs and macrophages [51] whereas CD122 (IL-2/IL-15β) expression is the highest on activated/memory $CD8^+$ T cells, NK and NK T cells [52–54]. Following Toll-Like Receptor (TLR) stimulation and/or in response to type I and II interferons (IFNs), IL-15Rα mRNA is up-regulated in DCs and IL-15 signaling in these cells induces functional maturation and survival of these cells [55]. IL-$15^{-/-}$ and IL-$15R\alpha^{-/-}$ mice present an important deficit in memory $CD8^+$ T cells, NKT and NK cells as well as intra-epithelial CD8αα lymphocytes, indicating a dominant effect of IL-15 on these cells [53,54]. IL-15 is normally trans-presented from IL-15 producing APCs to responding cells [56,57]. While trans-presentation of IL-15 is mediated by IL-15Rα chain, IL-15Rβ is essential for IL-15 response [56,58].

Because of the shared IL-2/IL-15βγ chain, it was originally postulated that IL-2 and IL-15 would induce similar effects on responder cells [59]. Surprisingly however, some of the effects mediated by IL-2 differ considerably from effects mediated by IL-15, and IL-2Rα (CD25) expression appears essential in order to instruct responsiveness to IL-2 rather than IL-15. While CD122 (IL-2/IL-15β) stimulation induces the phosphorylation of Janus kinase 1 (JAK1), CD132 (γc chain) stimulation induces the phosphorylation of Janus kinase 3 (JAK3). The recruitment of JAK1 and JAK3 leads to the phosphorylation of STAT3 and STAT5 and the recruitment of bcl-2 and MCL1, which in turn promotes cell survival (Fig. 1) [60,61]. Other signaling pathways triggered by IL-15 include Lck and Syk [62,63], the activation of phosphatidylinositol-3-kinase (PI3K), the kinase AKT [64] and the Ras/Raf/MEK/mitogen-activated protein kinase (MAPK) [65] that ultimately lead to the activation of fos/jun for proliferation and survival of T cells. Finally, cell proliferation can be enhanced upon IL-15 signaling through IL-15Rα [66].

	IL-7	IL-15
Cytokine structure	Glycoprotein of 25 kDa	Glycoprotein of 14–15 kDa
Location	Chromosome 8q12-13	Chromosome 4q31
Protein production	Thymic epithelial cells	Dendritic cells, monocytes, epithelial cells and fibroblasts
Central lymphoid organs	Thymic medulla stromal cells Follicular dendritic cells and reticular fibroblatic cells	
Peripheral tissus	Hepatocytes, keratinocytes, intestinal epithelial cells, dendritic cells	
Receptor	IL-7Rα B cell precursor T cell precursor Stromal cell Naive and memory T cells	IL-15Rα Monocytes Dendritic cells Memory $CD8^+$ T cells
Function	B cell development Thymopoiesis	Proliferation and differentiation of NK, T and B cells.
	T cell homeostasis Selection of memory T cells	Maintenance of memory $CD8^+$ T cells

4. The role of homeostatic cytokines in T cell homeostasis

The role played by thymopoiesis is important early in life and patients that undergo thymectomy during this period normally remain lymphopenic for most of their life. At birth, recent thymic emigrants are produced and exit the thymus to seed the empty peripheral niche. The degree of homeostatic proliferation (HP) that occurs during this period is critical in order to maintain/increase TCR diversity and immunocompetence [67]. As T cell counts