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Clinical Strategies to Enhance T cell Reconstitution

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Abstract

Strategies to enhance T cell recovery are of increasing clinical importance to overcome long lasting T cell deficiencies, which occur in association with infections, autoimmunity and chemo/radiotherapy as well as aging of the immune system. In this review we discuss those strategies that are close to or in the clinic. Interleukin-7, sex steroid modulation, keratinocyte growth factor, growth hormone and cellular therapies using ex vivo generated T cell precursors are currently being tested in recipients of a hematopoietic stem cell transplantation and patients with malignancies or HIV/AIDS.

Keywords

T cell reconstitution; bone marrow transplantation; Interleukin-7; Keratinocyte Growth Factor; Growth Hormone; Sex Steroid Modulation; OP9-DL1

T cell deficiencies can occur through infection (such as HIV), autoimmune diseases, chemo/radiotherapy or as a consequence of aging of the immune system (especially the thymus). T cell deficiency has been associated with an increased risk of infection and malignancies and a failure to respond to vaccination. For example, much of the late morbidity and mortality following hematopoietic stem cell transplantation (HSCT) can be attributed to delayed T cell reconstitution, leading to increased opportunistic infection and malignant relapse. There is also a growing body of evidence suggesting that early lymphocyte reconstitution, following both allogeneic and autologous HSCT, is a good prognostic indicator of disease outcome [1–5].

Several strategies to enhance immune reconstitution have been developed in preclinical models (reviewed in[6]), but few have made it into clinical trials. We will focus on those strategies which are close to entering the clinic.

Interleukin-7

Interleukin 7 (IL-7) is a 25kD glycoprotein produced by stromal cells in the thymus and bone marrow [7], as well as by keratinocytes and enterocytes [8]. IL-7 binds the IL-7 receptor (IL-7R) which consists of the α-chain (also known as CD127) and the common cytokine receptor γ-chain (γc) [9]. IL-7R is expressed on many cells of the immune system including common lymphoid precursors, triple negative (CD3−CD4−CD8−) and single positive (CD3+CD4+CD8− or CD3+CD4−CD8+) thymocytes, CD4+ and CD8+ T cells, developing B cells, γδ T cells,

thymic dendritic cells (DCs) and monocytes, as well as nonhematopoietic cells such as intestinal epithelial cells and keratinocytes (reviewed in [8]).

IL-7 is a non-redundant cytokine for both T and B cell development in mice. Mice treated with anti-IL-7 antibodies, and those deficient in IL-7Rα or IL-7 exhibit severely impaired lymphocyte development. Thymic cellularity is profoundly decreased in both types of knockout mice [10,11], and while a small number of αβ T cells develop, γδ T cells are absent [12]. In humans, a defect in the IL-7Rα results in a complete lack of T cells and severe combined immunodeficiency syndrome (SCID) [13]. Interestingly, in contrast to mice IL-7 does not appear to be a requirement for normal B cell development in humans [13].

IL-7 promotes both the survival and differentiation of immature triple negative and mature single positive thymocytes [14,15]. It is also essential for the production of γδ T cells [12] and thymic dendritic cells [16]. In the periphery, IL-7 has been identified as a key regulator of peripheral T cell survival and function. It has anti-apoptotic effects, possibly through the upregulation of Bcl-2 [17], and while it is not essential for the initiation of a T cell-mediated antigenic response, it is necessary for the generation of memory T cells [18–21]. IL-7 has also been shown to be a non-redundant regulator of homeostatic expansion of $CD4^+$ and $CD8^+$ naïve and memory T cells in settings of lymphopenia [17].

Preclinical studies in mouse HSCT models have demonstrated that post-transplant IL-7 administration can enhance T cell reconstitution in recipients of a syngeneic or allogeneic HSCT through increased thymopoiesis, increased homeostatic proliferation of transferred and *de novo* - generated mature T cells and decreased peripheral T-cell apoptosis [22–28]. IL-7 treatment not only increased T cell numbers but also enhanced their function. However, IL-7 did not show any effect on the T cell repertoire [25].

One of the concerns about the use of IL-7 in the setting of an allogeneic HSCT has been whether IL-7 may lead to or exacerbate graft versus host disease (GVHD). As demonstrated in a number of studies, IL-7 does not lead to GVHD in the setting of a T cell-depleted (TCD)-BMT [25]. However, depending on the dose of T cells and the duration and dose of IL-7 administration, the cytokine may exacerbate GVHD when it is administered in a T cell-replete HSCT [27,28]. Finally, IL-7 administration preserved the graft-vs-leukemia (GVL) activity of a T cell-replete allograft [25].

CYT 99 007 (Cytheris, Inc.), a recombinant non-glycosylated form of human IL-7, has been studied in phase I clinical trials. As of March 1, 2007, 61 patients have been treated with subcutaneous CYT 99 007 in five different phase I dose-escalation trials conducted in various clinical settings, in a dose range varying from 3 to 60 mcg/kg/dose (R. Buffet, personal communication). In general, administration of IL-7 was associated with little toxicity, and immunologic efficacy was demonstrated in these early studies. Repeated doses of CYT 99 007 induced a dose-dependent sustained expansion of $CD4^+$ and $CD8^+$ T cells with memory and naïve phenotypes, including Recent Thymic Emigrants (RTEs) defined as $CD45^+CD31^+$ T cells [29]. As expected, expansion resulted from an increase in both T cell proliferation and survival, assessed through the expression of Ki-67 and Bcl-2 markers, which also appeared to be strongly linked to the IL-7 dose. Consistent with the homeostatic role of IL-7, the magnitude and duration of T cell expansion seemed to be more pronounced in patients with lower T cell counts at baseline. The same T cell expansion profile was observed in a patient treated with CYT 99 007 after an allogeneic HSCT (Perales, unpublished observation). Studies of a potentially less immunogenic glycosylated formulation of IL-7 (CYT107, Cytheris) are currently underway.

Sex Steroid Modulation

Apart from their conventional roles in sexual dimorphism, differentiation and development, sex steroids are known to be involved in many other biological systems, including the immune system. The effects of sex steroids on the immune system might be responsible for gender disparity in susceptibility to autoimmune disease, and decreased T cell immunity during pregnancy. However, sex steroids appear to affect most hematopoietic developmental stages, as well as the function of mature immune cells [30–45].

Most studies agree that thymic atrophy becomes most pronounced at the time of puberty, concomitant with an increase in circulating sex steroids [46–51]. The link between sex steroid ablation (via surgical or chemical castration) and reversal of age-related thymic atrophy is well established. When mice or rats are castrated before puberty, thymic atrophy is delayed and if they are castrated later in life thymic atrophy is reversed [52–57]. Castration and the subsequent reversal of thymic atrophy results in an increase in RTEs, resulting in an increase in peripheral naïve T cells [57]. Increased T cell numbers translate to an increase in peripheral T cell function [57].

Administration of estrogens, progesterone or testosterone leads to reversible thymic atrophy, which resembles that observed with age [55,58–63]. Furthermore, the thymic enlargement/regeneration observed following castration is inhibited or reversed in a dose-dependent manner by the administration of testosterone or estrogen [55,59,64].

LHRH agonist administration results in a reversible inhibition of testicular steroidogenesis and spermatogenesis in males (chemical castration) [54]. LHRH agonist administration leads to an increase in thymic weight and reversal of age-related thymic structural defects, including the appearance of a clear distinction between cortex and medulla and an obvious corticomedullary junction [54,65–67].

Many groups have studied the expression of classical intracellular androgen receptors (iARs) in the thymus. iARs have been shown to be present in both male and female thymi [68], in whole thymus homogenate [20,58,68–73], thymic stroma [68,74], purified thymocytes [20,75] and all thymocyte subsets (based on expression of CD4 and CD8) [76]. Thymic stroma and thymocytes express both estrogen receptor α (ERα) and estrogen receptor β (ERβ) [77–79].

Because ARs and ERs have been identified on both thymocytes and thymic stromal cells, sex steroids may either act directly on thymocytes to affect apoptosis, proliferation and/or differentiation, or act indirectly via the thymic stroma. The mechanisms by which sex steroids act on the thymus remain to be fully elucidated. Olsen *et al.* (2001) used Tfm mice that have a point mutation in the androgen receptor and significantly larger thymi than androgen-sensitive mice to study the affect of androgen receptor signalling in the thymus [80]. BMT experiments were used to show that the presence of a functional androgen receptor on the stromal components of the thymus but not the thymocytes is essential for normal age-related thymic atrophy and the regeneration seen following sex steroid ablation [80]. Similar experiments were carried out using ERα knockout mice (ERKOs), ERβ knockout mice (BERKOs) and double knockouts (DERKOs) [81,82]. Again, BMT experiments were used to demonstrate that it was the expression of ERα, or lack thereof, on the thymic stromal cell components that predominantly mediated the changes in thymic cellularity observed [81].

Studies from Boyd and collegues [56,57] have identified very early effects on hematopoietic thymic precursors following surgical castration. Early thymic progenitors (ETPs) are decreased in number with age [56,83] and surgical castration restores ETP numbers [56]. Normalization of triple negative thymocyte proportions were also observed [56,57]. Medina et al. (2001) have also shown that early bone marrow lymphoid progenitors are negatively regulated by estrogen

[34]. These data, along with early in vitro studies [84,85], suggest that while the major mode of action of sex steroids is via the thymic stroma, there may also be direct effects on thymocytes and their precursors.

Several recent studies have taken advantage of the above observations and identified sex steroid modulation as a therapy to enhance immune reconstitution.

A study by Roden *et al.* demonstrated that surgical castration of mice led to an increase in thymus, lymph node and spleen size, as well as peripheral T cell numbers and T cell proliferation (to antigen specific and nonspecific stimuli) [86]. The T cell repertoire of these mice was similar to that of sham-castrated controls, suggesting that sex steroid ablation does not lead to the peripheral expansion of particular T cell clones [86]. Castration following induction of lymphopenia by cyclophosphamide treatment enhanced BM and thymic recovery as well as peripheral lymphoid reconstitution and function [86] (Goldberg *et al.* unpublished observation).

Several studies demonstrated that immune reconstitution following autologous and allogeneic HSCT was enhanced by surgical castration [57,87,88]. BM precursor cells including LSKs (Lineage- Sca-1-, ckit- cells that represent a population enriched for hematopoietic stem cells), common lymphoid precursors (CLPs), pro-B, pre-B and immature B cells were all positively affected. Similar results were observed in the thymus, with enhanced recovery observed in all thymocyte subsets [87,88]. In both autologous and allogeneic HSCT models castration led to an increase in the number of splenic T and B cells. T cell function determined by delayed type hypersensitivity was significantly increased in castrated vs sham-castrated allogeneic HSCT recipients. Importantly, castrated allogeneic HSCT recipients did not experience worse GVHD, and GVT activity remained intact [88].

Sutherland *et al.* (2005) showed that chemical castration of humans using an LHRH agonist, which is both reversible and transient led to enhanced thymic function [57]. In a small cohort of 10–16 patients, 60% of patients showed increased numbers of RTEs, as measured by TREC levels. Blood lymphocyte counts were also significantly increased, as were $CD4^+$ and $CD8^+$ T cells and NK cells.

These preliminary clinical data, along with the large body of preclinical data support sex steroid ablation as a potential adjunct therapy to follow treatments which induce immunosuppression. Clinical trials testing the efficacy of chemical sex steroid ablation (using Lupron) as a means to enhance immune reconstitution after allogeneic and autologous HSCT are underway in Australia and the USA, and the effects on T cell recovery are promising (personal communication – Richard Boyd).

Keratinocyte Growth Factor

Keratinocyte Growth Factor (KGF), or fibroblast growth factor 7 (FGF7), is an epithelial mitogen produced predominantly by cells of mesenchymal origin, including fibroblasts in the mammary gland, lung, skin, prostate, stomach and bladder as well as smooth muscle cells and microvascular endothelium (summarized in [89]). More recently, Gray *et al*. described a population of thymic fibroblasts as the major producers of KGF within the thymic stroma [90]. Interestingly, thymocytes also produce KGF and the expression of KGF increases during their differentiation [91]. KGF causes epithelial cell proliferation and differentiation in several tissues, including intestine (gut epithelial cells), skin (keratinocytes), and thymus (thymic epithelial cells (TECs)). KGF acts through a single receptor, FGFR2IIIb, which is expressed predominantly but not exclusively by epithelial cells [89]. In the thymus, FGFR2IIIb is expressed on TECs but not on thymocytes [92]. KGF is currently an FDA-approved drug for oral mucositis

prophylaxis in patients receiving high-dose therapy, such as myeloablative conditioning prior to a HSCT[93,94].

While thymus size and thymocyte subsets are not altered in $KGF^{-/-}$ mice, these mice are more susceptible to thymic damage (such as irradiation), resulting in a significant delay in thymic recovery [95].

KGF administration results in an increase in thymus size in both old and young mice or mice treated with irradiation, cyclophosphamide or dexamethasone [95]. Furthermore, KGF adminstration leads to an increase in peripheral T cell numbers in aged mice [95]. When $KGF^{-/-}$ mice were used as recipients of syngeneic or allogeneic BMTs, defective thymopoiesis and T cell reconstitution were observed. However, when used as donors these disruptions were not observed [95], suggesting that the KGF required for post-irradiation thymic recovery is produced by non-haematopoietic cells of host origin.

Min *et al.* (2007) observed that a single course of KGF treatment reversed age-related decreases in thymocyte numbers and restored the disrupted thymic microenvironment, as well as peripheral T cell function [96]. Continued treatment led to an increase in thymic cell numbers [96].

Rossi *et al.* (2007) showed that KGF treatment led to the expansion of TECs and differentiation of immature TECs. Although these stromal changes were transient, they led to a long-lasting augmentation of thymocyte development and T cell export [97]. Stromal exposure to KGF was required for these changes to occur, while thymocyte precursor exposure did not appear to play a role [97]. Wnt5b, Wnt10b, BMP2 and BMP4 were upregulated *in vivo* following KGF treatment, and thymii from $Smad4^{-/-}$ (required for canonical BMP signaling) mice did not increase in size following KGF treatment, suggesting an essential role for BMP signaling in the mechanism of KGF-induced enhanced thymopoiesis. Furthermore, blocking p53 and NFκB suppressed upregulation of Wnt10b upon KGF treatment, suggesting that KGF signaling involves both p53 and NFκB pathways [97].

KGF treatment of recipients prior to syngeneic [98] and allogeneic [95,98] HSCT leads to enhanced thymopoiesis and peripheral T cell reconstitution [95,98]. Moreover, pretreatment with KGF could significantly decrease GVHD morbidity and mortality in allogeneic HSCT recipients [92,99–101].

Studies by Ferrara and colleagues suggested that the ameliorating effect of KGF on GVHD was due to protection of gut epithelium from damage associated with conditioning [101]. However, Blazar and colleagues demonstrated that KGF decreased GVHD in the absence of conditioning [100], suggesting that KGF can protect target tissues from GVHD in other ways. The authors suggest that KGF may protect against T cell mediated damage [100]. Rossi *et al.* also used a conditioning-free GVHD model to assess whether treatment with KGF led to cytoprotection of TECs [92]. KGF pretreatment prevented the loss of thymus size and cellularity, which are associated with GVHD. Furthermore, thymocyte subset proportions remained intact and the GVHD-associated decrease in percentage of DP thymocytes was not observed [92]. Thymic architecture was preserved following pretreatment with KGF, as were cortical and medullary TEC subsets [92].

In a recent study, rhesus macaques were treated with KGF (single or multiple doses) prior to $CD34^{+}$ peripheral blood progenitor transplantation [102]. KGF improved thymic-dependent T cell reconstitution, when compared to untreated recipients. Thymic architecture was restored in the KGF-treated groups 12 months after transplant, while thymi from control mice remained atrophic. Naïve T cell numbers were increased following KGF treatment, as were T cell receptor excision circles (TRECs) and T cell receptor diversity. Furthermore, the increases in

thymic T cell reconstitution led to an increase in peripheral T cell function, as measured by the humoral response to a T cell-dependent neo-antigen [102].

In summary, KGF enhances thymopoiesis through its protective and trophic effects on TECs, which results in increased production of IL-7 by TECs, as well as increased resistance to apoptosis and epithelial cell recovery. A better preservation or recovery of the thymic microenvironment should allow for enhanced seeding of T cell precursors resulting in improved T cell production.

These preclinical data suggest that KGF can be used to enhance T cell reconstitution in lymphopenic patients. At present, studies are underway at our center to assess whether KGF administration can enhance T cell recovery in patients who have received a T cell-depleted allogeneic HSCT.

Growth Hormone

Growth hormone (GH) is predominantly produced and stored by the anterior pituitary [103]. However, several studies have shown that it is also produced by hematopoietic cells [104–107]. GH receptor (GHr) is expressed by developing thymocytes, all hematopoietic cells in the bone marrow, as well as B cells, T cells and macrophages in the periphery (reviewed in [108]). GH is believed to affect the immune system via its stimulatory effects on insulin-like growth factor 1 (IGF-1), but may also have a direct effect. IGF-1 and GH serum levels decrease with age in humans (Reviewed in [108]).

In both rodents and humans, macrophages are the main source of IGF-1 in the hematopoietic system [109,110], but production has also been observed in thymic epithelial cells [111,112] and BM cells [113,114]. IGF-1 receptors are expressed by NK cells, B cells, and T cells (differential expression depending on activation state), as well as erythrocytes and monocytes (Reviewed in [108]). *In vitro* and *in vivo* assays have shown enhanced hematopoiesis and immune function following GH or IGF-1 treatment [108]. Conversely, some studies have suggested that GH deficient mice have significantly smaller thymi (reversible with administration of GH), diminished B cell production and myeloid deficiencies [115]. However, these abnormalities are not observed in humans with GH deficiency. Studies by Welniak et al. (2002) suggest that the results observed in the GH deficient dwarf mice are variable and are dependent on stress, weaning age and conditions under which the mice are housed [108].

Hematopoietic progenitors in the spleen and BM are increased following administration of GH to adult mice [116]. GH hormone administration following sygeneic bone marrow transplantation in mice leads to enhanced hematopoiesis (analyzed by colony-forming unit-cultures) and erythropoiesis, as well as enhanced recovery of leukocytes and platelets [117]. While the augmentation of peripheral neutrophil recovery was substantial, lymphocyte recovery was only marginally enhanced (albeit statistically significantly) [117].

Following allogeneic HSCT and GH administration thymic cellularity is increased, as are peripheral T cell and B cell numbers [118]. In addition, mice that were treated with GH following BMT rejected third-party grafts significantly faster than control HSCT mice [118]. Studies treating mice with IGF-1 following HSCT support these findings. IGF-1 treatment following allogeneic HSCT significantly increases peripheral T cells numbers and T cell proliferation without exacerbating GVHD [119], and reconstitution is also enhanced following syngeneic HSCT [120].

Growth hormone enhances immune reconstitution predominantly through stimulating IGF-1 production, which provides anti-apoptotic signals. It may also act directly on thymic stromal cells to increase the production of growth factors such as SCF and IL-7 [108].

GH and IGF-1 have already been administered to AIDS patients with mixed results. The growth factors were well tolerated and increased thymic volume in children, but only a modest increase in T cell function was observed.

OP9-DL1 Generated T Cell Precursors

Studies by Zuniga-Pflucker and Bernstein demonstrated that normal T cell development from HSCs can be achieved *in vitro*, using activation of Notch-1 in the presence of growth factors (especially IL-7). This is due to the development of an *in vitro* culture system which takes advantage of the requirement of Notch-Notch ligand interaction for normal T cell development [121,122]. *In vivo* proliferation, survival, lineage commitment and tissue architecture are all dependent on Notch signaling to varying degrees (reviewed in [123]). It is, however, the interaction between Notch1 and its ligand Delta-like 1 or 4 (DL1 or DL4) that is essential for T lineage commitment and differentiation.

When cultured in an *in vitro* system in the presence of Notch1, both murine and human hematopoietic and embryonic stem cells develop into T cells or their precursors [122,124–126]. To date, two Notch1-based culture systems have been developed: a. coculture of seeded cells with OP9 bone marrow-derived stromal cells expressing DL1 (OP9-DL1 cells) [122], and b. culture of precursor cells in the presence of immobilized DL1-hIgG fusion protein ($DL1^{ext\text{-}IgG}$) [121].

Using the OP9-DL1 stromal cells, the culture of murine LSKs ($Lineage^{-}Sca\text{-}1^{+}c\text{-}kit^{+}$ HSC containing population) in the presence of IL-7 and FLT3L can result in large numbers of T/NK cell precursors. These cells can then be adoptively transferred with either T cell-depleted (TCD) BM or purified LSKs to enhance T cell reconstitution [127]. Recipients of OP9-DL1-derived T cell precursors showed increased thymic cellularity and significantly improved donor T-cell chimerism. Combination of T cell precursor administration and treatment with KGF had additive effects on thymic reconstitution. In thymectomized recipients, adoptively transferred T cell precursors enhanced extrathymic T cell development. OP9-DL1-derived T cell precursors gave rise to host-tolerant $CD4^{+}$ and $CD8^{+}$ populations with normal T cell receptor repertoires, cytokine secretion, and proliferative responses to antigen. Administration of OP9-DL1 derived T-cell precursors increased resistance to *L. monocytogenes* infection after HSCT and mediated significant GVT in the absence of GVHD [127]. This novel method can be modified to generate high numbers of human T cell precursors from human $CD34^{+}$ cells [125,126], indicating the feasibility of using this approach to improve immune response and anti-tumor activity in patients with T cell deficiencies including recipients of high-dose chemotherapy, or autologous and allogeneic HSCT.

In addition to high-dose chemotherapy and autologous and allogeneic HSCT, adoptive T cell precursor therapies could present a new approach for the treatment of T cell deficiencies such as SCID and AIDS, as well as the management of hematopoietic failure due to radiation damage. Bernstein and coworkers developed an animal product-free Notch1 based culture system using $DL1^{ext\text{-}IgG}$ to generate clinical grade heterogenous populations of human hematopoietic progenitor cells. They are currently conducting a clinical trial at Fred Hutchinson Cancer Research Center to study the effect of adoptively transferred progenitor cells, originating from cord blood-derived $CD34^{+}$ HSCs expanded with $DL1^{ext\text{-}IgG}$, on immune reconstitution after HSCT.

In conclusion, although a true T cell growth factor, similar to G-CSF or GM-CSF for myeloid lineage and erythropoietin for the erythroid lineage, has not been developed, several candidate strategies, including IL-7, KGF, Lupron and T/NK cell precursors are now in clinical development. The potential use of these strategies for immunotherapies holds great promise for the future.

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