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Rejuvenation of the aging T cell compartment

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Summary of Recent Advances

The elderly face significant risk for susceptibility to infection and cancer due to declining immune function. Various agents used in the setting of bone marrow transplantation and aging studies represent promising approaches to combating T cell defects in the aging population. Preclinical and clinical studies on the T cell reconstitution effects of sex steroid ablation, keratinocyte growth factor, the growth hormone pathway, and the cytokines interleukin-7, interleukin-12, and interleukin-15 indicate that these strategies may be used to alleviate the effects of T cell deficiencies in the elderly.

Introduction

Immune function decreases with age, due to quantitative and qualitative changes in the cells of the immune system and their niches. The deleterious effects of aging on the T cell compartment are well-studied as they lead to increased susceptibility to infection, decreased immunosurveillance of malignant cells, and difficulty in establishing protective immunity via vaccination. Aging reduces the number and T cell potential of hematopoietic precursors, and involution of the thymus renders it less capable of supporting de novo T cell development. Consequently, aging compromises the functional capacity of lymphocytes, resulting in a T cell pool with restricted receptor specificity and fewer naïve T cells [1,2]. These effects are reviewed in depth elsewhere in this issue, and we will concentrate instead on strategies to boost T cell function in aging individuals.

The conditioning regimens for hematopoietic stem cell transplantation (HSCT) cause significant damage to recipient thymi, resulting in prolonged post-transplant T cell deficiency [3]. Studies in experimental mouse models of HSCT have identified agents that are relevant for boosting T cell reconstitution not only after transplant, but also potentially in aging recipients.

Reviewed below are studies in older and transplanted mice, which elucidate mechanisms for improving T cell development.

Sex steroid ablation

Sex steroids are known to negatively regulate development of immune cells. The increase in sex steroids at puberty corresponds to the dramatic involution of the thymus at this time. Accordingly, prepubescent castration to reduce sex steroid levels prevents thymic atrophy and post-pubescent castration reverses thymic atrophy while enhancing T cell numbers in the periphery [4-9]. Murine models of autologous and allogeneic HSCT have indicated that surgical castration of recipients increases T cell reconstitution following transplantation [10, 11].

Luteinizing Hormone-Releasing Hormone (LHRH) modulates testicular steroidogenesis, and LHRH agonist treatment results in chemical castration. Administration of the LHRH agonist Leuprolide to aging recipients leads to larger thymus size and improved thymic architecture [4-7]. Administration of Leuprolide following allogeneic HSCT significantly improves thymocyte and T cell reconstitution [12]. In addition to increased T cell numbers, Leuprolide also enhanced T cell function after allogeneic transplant in vitro and in vivo [12]. Leuprolide treatment following allogeneic HSCT leads to enhanced hematopoietic stem cells (lineage-Sca-1+c-kit+) and common lymphoid progenitors (lineage-ckit^{lo}IL-7Ra+) in the bone marrow, which may result from blocking deleterious effects of sex steroids on the bone marrow stromal cell compartment [12]. The increase in lymphoid progenitors likely contributes to enhanced T cell reconstitution.

Clinical trials using chemical castration with the LHRH agonist goserelin following autologous and allogeneic HSCT resulted in greater CD4 T cell regeneration, broad TCR repertoire, and enhanced peripheral T cell function [13].

Keratinocyte Growth Factor (KGF)

KGF, also called Fibroblast Growth Factor 7, mediates the proliferation and differentiation of epithelial cells, including thymic epithelial cells (TECs), which express the KGF receptor FGFR2IIIb [14]. Thymic fibroblasts, mesenchymal cells, and thymocytes can produce KGF [15-17]. KGF administration can protect the thymus from damage, and enhance T lymphopoiesis in young and old mice [18].

KGF^{-/-} mice do not have thymic defects, but display impaired T cell reconstitution following sublethal irradiation and/or allogeneic and syngeneic BMT [19-21]. Administration of exogenous KGF results in enhanced thymic reconstitution following HSCT and can augment post-transplant T cell responses to DNA plasmid tumor vaccination [19,22]. HSCT recipients treated with KGF had (a) more T cells before vaccination, (b) greater numbers of tumor-specific T cells following vaccination, (c) a higher T effector-to-regulatory T cell ratio, (d) a larger proportion of memory T cells with central memory phenotype, and (e) effector T cells with a broader T cell receptor repertoire [22]. Pretransplant and peritransplant KGF treatment in rhesus macaques resulted in preservation of thymic architecture, increased thymic output and naïve T cell numbers, and enhanced T cell function [23].

KGF treatment in aged mice leads to improved thymocyte numbers, improved thymic architecture, and enhanced peripheral T cell function [19]. Middle-aged recipients of BMT treated with posttransplant KGF had increased thymopoiesis and peripheral T cell numbers [19].

In addition, KGF treatment can also be combined with sex steroid blockade resulting in preservation of thymic architecture, enhanced thymopoiesis and peripheral T cell reconstitution, and improved T cell repertoire and function [24].

KGF is FDA-approved for the prevention of mucositis in patients receiving high dose therapy (especially HSCT recipients). The proven safety of KGF and the extensive preclinical data regarding its effects on thymopoiesis make KGF a promising strategy to enhance thymopoiesis in the elderly. Clinical trials are on-going to determine if KGF administration to patients undergoing T cell-depleted allogeneic HSCT will enhance T cell reconstitution.

Growth hormone (GH), Insulin Growth Factor-1 (IGF-1), and ghrelin

GH is produced primarily by the pituitary, but it can also be produced by hematopoietic cells [25-28]. GH receptor is expressed on thymocytes, peripheral T cells, and various other cells of hematopoietic origin [29-32]. Aging humans have lower serum levels of GH, as well as IGF-1, a downstream target of GH signaling [33]. GH effects are mediated in large part via IGF-1 induction, although GH may also act directly to improve immune reconstitution [33]. The IGF-1 receptor is expressed on thymocytes and T cells, and may act directly on these cells to stimulate lymphopoiesis by modulating homing receptors on progenitors, or induce IL-7 or stem cell factor production by thymic epithelial cells [33-37]. Administration of GH or IGF-1 can enhance T cell recovery in (a) syngeneic HSCT recipients, (b) allogeneic HSCT recipients, (c) aging mice, and (d) aging BMT recipients [38,39].

Ghrelin is a peptide hormone that can (a) promote the secretion of GH through activation of the growth hormone secretagogue receptor (GHS-R) and (b) exert anti-inflammatory effects by blocking the NF κ B pathway, and cytokine secretion in Th1 and Th17 cells [40-43]. Ghrelin is expressed in the thymus and spleen of young mice, and decreases with age [43,44]. Administration of ghrelin can improve thymic organization and thymocyte numbers in aging mice resulting in increased recent thymic emigrants, peripheral T cell populations, and an improved T cell repertoire [44]. Both ghrelin- and GHS-R-deficient mice demonstrate accelerated thymic involution associated with increased adipocyte formation in the thymus [44,45]. Ghrelin affects not only the development of T cells, but also their function in the periphery. Recently, Dixit et al demonstrated that T cell-derived ghrelin is responsible for controlling proinflammatory cytokine expression in aging mice and in humans [43]. Treatment with exogenous ghrelin corrected age-related inflammation [43], which could further contribute to the improved T cell reconstitution in older mice.

Interleukin (IL)-7, IL-12, IL-15

IL-7 and IL-15 are common cytokine γ chain receptor cytokines, with various stimulatory effects on lymphocytes. IL-7 is produced by stromal cells throughout the body, including thymic stroma [46]. Signaling induced by IL-7 supports thymocyte development, and peripheral T cell survival and proliferation [47-51]. The administration of IL-7 to aging individuals and individuals with thymic damage caused by chemotherapeutic or radiation-based conditioning for bone marrow transplantation has been shown to increase thymopoiesis, T cell maturation and function [52-56]. These findings extend to clinical trials, where human IL-7 administration has proven safe and effective in increasing T cell immunity [57]. Administration of recombinant human IL-7 (rhIL-7) to a cohort of metastatic melanoma and metastatic sarcoma patients led to expansion of CD4 and CD8 T cells, with a reduction in the percentage of regulatory T cells [58]. Another clinical study found that patients with nonhematologic, nonlymphoid cancers who received a course of IL-7 treatment had increased circulating CD4 and CD8 T cell numbers [59]. In addition, the T cells in these patients (a) were cycling, (b) up-regulated the anti-apoptotic factor Bcl-2, (c) had a broad TCR repertoire, and (d) had naïve and central memory phenotypes, with lower proportions of regulatory T cells and senescent CD8 effector cells [59]. Treatment with IL-7 also increased numbers of naïve and central memory phenotype cells from CD4 and CD8 lineages in HIV-infected patients, and expanded T cells produced IFN γ and/or IL-2 in response to HIV antigens [60].

IL-15 is secreted by many cell types in the body, ranging from fibroblasts to epithelial cells to immune cells. It signals through the IL-15R α , IL-2R β , and common cytokine receptor γ chain to stimulate proliferation in lymphocytes. Administration of IL-15 following bone marrow transplantation improves peripheral memory CD8 T cell expansion by promoting proliferation and decreasing apoptosis by increasing intracellular Bcl-2 levels [61,62]. IL-15, which is less toxic than IL-2, may also be combined with other treatments such as immunotherapy and tumor vaccination in order to augment their effects on T cell reconstitution [63-65].

IL-12 has been reported to act as an accessory cytokine to IL-7 and IL-2 to support thymocyte proliferation and development [66]. Although IL-12 levels are not decreased in aging wildtype animals, thymic involution was accelerated in aging IL-12b^{-/-} mice, and *in vitro* stimulation of thymocytes with IL-7 or IL-2 in combination with IL-12 led to synergistic enhancement of proliferation [66]. Additionally, Chen et al recently demonstrated that adenoviral administration of IL-12 (AdIL-12) to aging mice followed by wildtype adenoviral treatment resulted in enhanced cytotoxic lymphocyte (CTL) responses measured *in vitro* and *in vivo* [67]. The aging mice (18 months old) treated with AdIL-12 secreted greater levels of IFN γ , showed comparable T cell proliferative responses to those in young mice, and demonstrated efficient antigen-specific killing *in vitro*. These results indicate that administration of IL-12 to aging individuals may slow or reverse thymic involution by augmenting thymocyte proliferation, which would lead in turn to regenerative crosstalk between thymocytes and the thymic stroma.

Conclusion

Recent mechanistic and clinical studies have defined strategies that could enhance T cell immunity in aging individuals (summarized in Figure 1). These approaches enhance the number of T cell precursors (sex steroid ablation), promote thymopoiesis (sex steroid ablation, KGF, GH, IGF-1, ghrelin, IL-7, IL-15, and IL-12), and peripheral T cell numbers (sex steroid ablation, KGF, GH, IGF-1, ghrelin, IL-7, IL-15), survival (GH, IGF-1, ghrelin, IL-7, IL-15), repertoire (sex steroid ablation, KGF, ghrelin, IL-7), and function (sex steroid ablation, KGF, GH, IGF-1, ghrelin, IL-7, IL-15, IL-12).

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Figure 1. Strategies to enhance immune function in the elderly improve the development, expansion, and function of T cells
Sex steroid modulation via surgical or chemical castration in aging and transplanted mice or humans enhances lymphoid progenitor generation, thymopoiesis, and peripheral T cell function. Keratinocyte growth factor acts directly on thymic epithelial cells to promote proliferation and differentiation, leading to greater capacity for T cell development and function in the periphery. Members of the growth hormone signaling pathway act on lymphocytes to enhance thymic and T cell function. The cytokines IL-7, IL-12, and IL-15 exert their effects on thymocytes and mature T cells to enhance numbers and function.