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Sex steroid ablation: an immuno-regenerative strategy for immunocompromised patients

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Abstract

Age related decline in thymic function is a well-described process that results in reduced T cell development and thymic output of new naïve T cells. Thymic involution leads to reduced response to vaccines and new pathogens in otherwise healthy individuals; however, reduced thymic function is particularly detrimental in clinical scenarios where the immune system is profoundly depleted such as after chemotherapy, radiotherapy, infection and shock. Poor thymic function and restoration of immune competence has been correlated with increased risk of opportunistic infections, tumor relapse and autoimmunity. Apart from their primary role in sex dimorphism, sex steroid levels profoundly affect the immune system in general and, in fact, age-related thymic involution has been at least partially attributed to the increase of sex steroids at puberty. Subsequently it has been demonstrated that removal of sex steroids, or sex steroid ablation (SSA), triggers physiologic changes that ultimately led to thymic re-growth and improved T cell reconstitution in settings of hematopoietic stem cell transplant (HSCT). Although the cellular and molecular process underlying these regenerative effects are still poorly understood, SSA clearly represents an attractive therapeutic approach to enhance thymic function and restore immune competence in immunodeficient individuals.

Keywords

sex steroid ablation; immune reconstitution; thymus

Introduction

One of the best described consequences of aging is the progressive decline in immunocompetence (1, 2). This deleterious phenomenon involves both quantitative and

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qualitative changes, including loss of bone marrow and thymic output, reduced proliferation of lymphoid progenitors, and diminished function of mature lymphocytes in the periphery. Consequently, older individuals are more susceptible to microbial infections, have decreased immune surveillance against malignant cells and, almost paradoxically, are more susceptible to certain autoimmune diseases (3-7).

The thymus is the principal organ responsible for the generation and development of naïve T cells that circulate in the periphery (8). Thymopoiesis, that is the process of T cell development, is tightly regulated by the bidirectional crosstalk between developing thymocytes and the thymic stromal compartment; which is composed of non–hematopoietic thymic epithelial cells (TECs), endothelium and fibroblasts, as well as the hematopoietic components such as macrophages and dendritic cells (9). T cell development initiates when circulating bone marrow-derived T-lineage progenitors (CTPs) migrate to the thymus and undergo a series of well-defined developmental steps that ultimately lead to the formation of naïve $CD4^+$ and $CD8^+$singlepositive T cells ready to enter into the circulation and encounter antigens (9-11).

Paradoxical to its critical function in maintaining a functional and effective T cell pool to mediate immunity to new pathogens, the thymus undergoes profound age-related degeneration (12-15). This process starts early in life, but becomes more prominent from the onset of puberty. Although in humans the physical size of the thymus remains unchanged, thymic spaces are progressively replaced by adipose tissue during aging that occurs extensively after the age of 15 (16, 17). This process leads to a dramatic decrease in thymic output that is estimated to have plummeted to approximately 90% of its original function by the age of 30 (18).

Age-related thymic involution is problematic for the aged response to new pathogens and in vaccinations. For example, only approximately 30-40% of people over the age of 65 are capable of responding to the influenza vaccine (19-22). Thymic involution also limits thymic regeneration resulting in prolonged time of recovery following immune suppression such as common cancer cytoreductive therapies like chemotherapy or radiation therapy (23-25). Reduced thymic function is particularly critical for older recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT), who experience a prolonged period of post-transplant T cell deficiency after thymic damage due to cytoreductive conditioning (26-30). Insufficient recovery of thymopoiesis has been intrinsically linked to an increased risk of opportunistic infections and adverse clinical outcome (31, 32). Although young recipients can recover thymic function within months, old patients, whose thymic function is already impaired by the immune senescence, exhibit a long period of T cell deficiency; with an inverse correlation between T cell recovery and age in cancer patients after chemotherapy (28, 33, 34).

Restoration of immune competence, and in particular T cell recovery, is critically dependent on residual thymic function. Therefore, understanding the processes that trigger the decline in thymic function during aging, and developing strategies that can reverse these effects, represent a clinical challenge with the potential to generate therapeutic strategies to

rejuvenate the immune system and improve overall outcome in immune compromised patients.

Although several promising strategies to rebuild the thymus and immune recovery have been proposed, including Keratinocyte Growth Factor (KGF), IL-7, IL-12, IL-22, FMS-Related Tyrosine Kinase 3 Ligand (Flt3L), Leptin, Ghrelin, Insulin-Like Growth Factor-1 (IGF-1), Op9-DL1 cultured Pre T cells and Growth Hormone (GH) (35-43); one of the most widely studied has been sex steroid ablation (SSA). Here we provide a brief overview on the effects of sex steroids on immune system and on SSA as a therapeutic tool to enhance thymic function and immune recovery in immunodeficient recipients.

Effect of sex steroids on thymic function

The age-related decline in thymic function is a well-known process conserved in all vertebrates. However, although it has been the topic of intensive research for many years, the mechanisms driving this phenomenon are still poorly understood. Several possible mechanisms have been proposed, including aging of the BM and the depletion in the supply of T-cell progenitors, reduced expression from the supporting micro-environment of thymopoietic cytokines (i.e.IL-7, KGF), increase in TGF-beta, down regulation of the critical TEC factor FoxN1, block in TCR rearrangement and decreased proliferation and increased apoptosis of early thymic progenitors (ETPs) (44-50). It is increasingly evident that thymic involution is a complex process involving the interplay of many mechanisms, however, it is also becoming increasingly apparent that the thymic stromal cell compartment, and in particular the TECs, are believed to represent one of the most sensitive compartments in the process of thymic aging (51).

Although there is evidence to suggest that thymic involution begins immediately after birth, the rate of decline in size and function is more pronounced from the onset of puberty; fitting the increase in circulating sex steroids at that time. Due to this temporal connection, the increase in sex steroids during puberty has been proposed to contribute to the process of thymic involution. This model of thymic involution has been further validated by several studies demonstrating that administration of sex steroids (androgens or estrogens) in young pre-pubertal mice promotes thymic involution (52-58).

All steroid hormones mediate their biological effects through the interaction with specific receptors. Androgen receptors (AR) and estrogen receptor (ER) are expressed in male and female thymii in both the hematopoietic and stromal compartments (56, 59-61). In most instances, after binding their respective sex steroid, the receptor translocates to the nucleus where it directly mediates changes in the expression of target genes. A direct effect of sex steroids on thymocytes has been proposed where testosterone can induce apoptosis of CD4+CD8+ double positive thymocytes though the up regulation of TNF-alpha; and estrogens can induce thymic atrophy by eliminating ETPs and inhibiting proliferation of beta selected thymocytes (62, 63). However, despite this direct negative regulation of the thymocyte compartment by sex steroids, studies using transgenic mice defective in AR function on either the hematopoietic compartment or the stromal compartment, suggested that the presence of a functional of AR within the thymic stromal components but not on the

thymocytes is required for sex-steroid mediated thymic atrophy (58, 64). Although the possibility that some of the effects of androgens resides in the hematopoietic cells cannot be excluded, these studies highlight thymic stromal cells, and in particular TECs, as principal targets of the negative actions of sex steroids.

While there is still some debate over the role of sex steroids in the initiation of thymic involution as well as their effects on thymic function (Table 1), SSA represents a rational strategy to boost thymic function and promote its rejuvenation in young and adult mice in steady state condition as well as following immune insults (Figure 1).

Sex steroid ablation as a therapeutic tool to rejuvenate the thymus

Studies published as early as the beginning of the twentieth century reported that the removal of gonads in cattle and guinea pigs sustained thymic size and architecture in adult animals, providing the first evidence that SSA have positive effect on thymic growth (65, 66). Subsequently, several studies have shown that surgical SSA increases thymic cellularity, restores thymic architecture and organization and enhances thymopoiesis in young and adult animals (67-70). Castration of 9 month old mice rapidly reverses thymic atrophy, restoring the level of $CD4^+$ $CD8^+$ SP, DP and all developing thymocytes starting form the more immature $CD25^+CD44^+CD117^+$ ETPs, to the same level of thymocytes from 2-month old mice (71). Moreover, Heng and colleagues demonstrated that surgical SSA provided functional benefits in old mice, increasing T cell responsiveness to tumor antigens and enhancing viral clearance (72). Importantly, the T cell repertoire of young mice after surgically castration was similar to that of sham-castrated controls, suggesting that thymic regeneration after SSA does not lead to the peripheral expansion of particular T cell clones (73, 74). In addition to its potential for improving thymopoiesis in aged animals, several studies have also found that immune recovery was accelerating after SSA in recipients of autologous and allogeneic HSCT, and after chemotherapy (75-77). In particular, removal of sex steroids led to an increase in LSKs, common lymphoid progenitors (CLPs), pro-B, pre-B and immature B cells in castrated mice (78).Enhanced immune recovery was also observed in all thymocytes subsets and in peripheral T and B cells following HSCT. In models of allo-HSCT,T cell function and GVL effects were intact while GVHD was not exacerbated (76, 79).

Therapeutically, castrate levels of sex steroids can be achieved in a transient and reversible manner using compounds originally developed for prostate cancer and breast cancer patients. These include targeting upstream signaling events such as luteinizing hormone releasing hormone (LHRH), or directly blocking sex steroid receptors. Previous studies have reported that mice treated with the LHRH-agonist Lupron, or ASC-J9® (an anti-AR), showed increased number of lymphoid and myeloid progenitors in the bone marrow and increased thymic and splenic recovery after allo-HSCT (64, 79).

Although most studies examining SSA have focused on male mice, primarily due to the ease of surgical castration versus ovariectomy, previous reports have shown that both surgical and chemical SSA can also positively impact thymic function in female mice (70, 80-82). However, the specific mechanisms of thymic regeneration after SSA in female mice in

comparison to male mice has not been extensively studied; in particular, the relative contributions of estrogen and androgens in male versus female mice are currently unclear.

Clinical trials of SSA have shown that an LHRH-agonist in a small cohort of prostate cancer patients between 60 and 77 years enhances thymic function (75).A significant increase was observed in naïve $CD4^+$ and $CD8^+$ T cells and NK counts 4 months after treatment. Analysis of thymic function by measuring recent thymic emigrants by T-cell receptor excision circles (TRECs) revealed that 8 of the 10 patients showed increase in total $TREC^+$cells/milliliter blood compared with pretreatment conditions. A nonrandomized pilot study involving patients with allogeneic or autologous HSCT showed significant enhancement of naïve ($TREC^+$) T cell regeneration after transplant when the LHRH-Agonist Goserelin, which was administered 21 days prior transplant. Moreover, analysis of V-beta CD3 regions by spectra typing on FACS purified $CD4^+$ and $CD8^+$ T cells showed a significant increase in diversity in LHRH-agonist treated patients in the allogeneic transplant setting (83).

These clinical studies demonstrated that agonists for the LHRH-receptor represent a valid and rational strategy to enhance thymic function, not just in immune compromised patients, but also during normal aging. The continued interest in developing more potent sex steroid blockers for cancer patients, such as the most recent AR inhibitors and LHRH-Antagonists (that have the advantage of bypassing the surge in sex steroids observed with LHRH-Agonists (84)), may provide additional therapeutic tools to reverse sex steroid action and rapidly trigger the recovery of the thymic function (figure 1). Moreover, as our understanding of the molecular regulators of SSA-mediated regeneration, new targets open up for sustained thymic regeneration without the systemic effects of SSA.

Conclusions

Sustained thymopoiesis is a critical process that allows for the recovery of immune competence after thymic injury. This is particular critical for older allo-HSCT recipients whose thymus and immune function are already profoundly impaired due immune senescence. The clinical and preclinical studies highlighted in this review promote SSA as a valid approach to boost thymic regeneration and enhance immune recovery, providing the bases for novel immune regenerative therapies.

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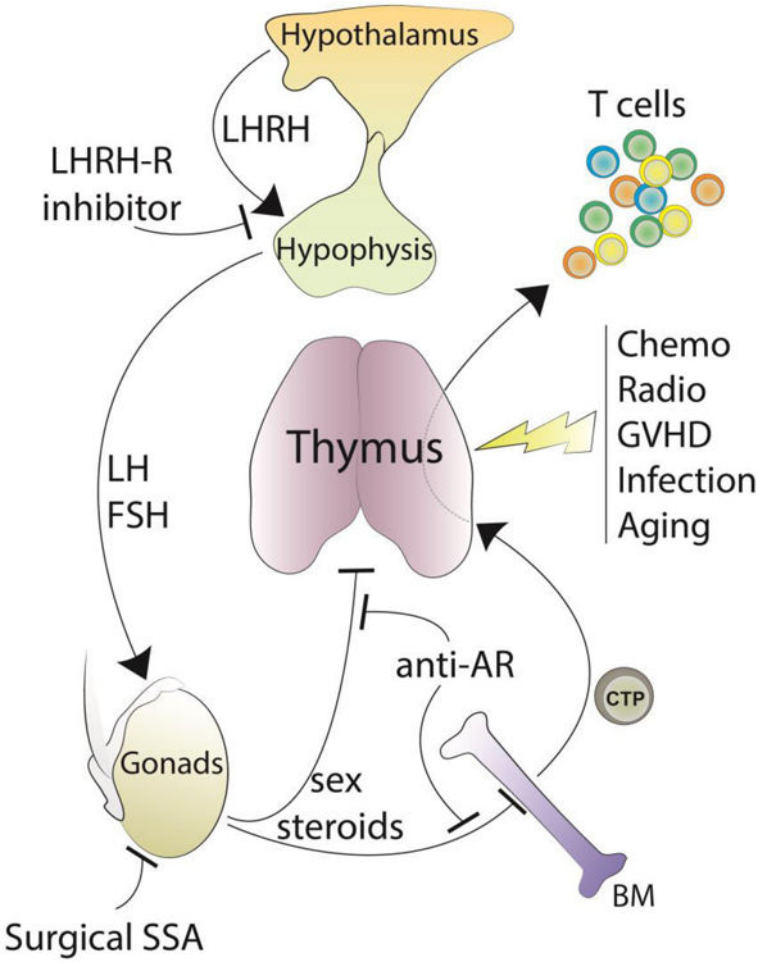

Figure 1.

Overview of the hypothalamic–pituitary–gonadal axis and its implication in regulating thymic function. SSA using LHRH-R inhibitors or anti-AR, blocks the negative effects of sex steroids on BM and thymus and promotes their rejuvenation in steady-state conditions as well as following immune insults.

Table 1

Major questions still open for the biological effects of sex steroids and SSA on thymic function:
What is the role of sex steroids in the initiation and progression of age-related thymic involution?
What are the physiological targets of sex steroids (and SSA) within the thymus?
How durable is sex steroid ablation-mediated thymic regeneration? What causes the normalization of the thymus after SSA?