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Suppressive effects of androgens on the immune system

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ABSTRACT

Sex-based disparities in immune responses are well known phenomena. The two most important factors accounting for the sex-bias in immunity are genetics and sex hormones. Effects of female sex hormones, estrogen and progesterone are well established, however the role of testosterone is not completely understood. Evidence from unrelated studies points to an immunosuppressive role of testosterone on different components of the immune system, but the underlying molecular mechanisms remains unknown. In this review we evaluate the effect of testosterone on key cellular components of innate and adaptive immunity. Specifically, we highlight the importance of testosterone in down-regulating the systemic immune response by cell type specific effects in the context of immunological disorders. Further studies are required to elucidate the molecular mechanisms of testosterone-induced immunosuppression, leading the way to the identification of novel therapeutic targets for immune disorders.

1. Introduction

The most common type of normal immune challenges that we face are invasions by pathogens (infections) and vaccination against such pathogenic infections. Sex based disparity in immune responses is well documented and the interplay of sex hormones and immunity is a well-studied phenomenon. Such sex disparity may be explained by intrinsic genetic differences between males and female (XX versus XY) and/or the differential levels of specific sex hormones produced by males and females. Evidence pointing towards a significant role for sex hormones has come from human and animal studies of hormone-manipulation. It has been shown on several occasions that females are more susceptible to autoimmunity and respond better to pathogenic infections and vaccination programs both in mouse models and clinical studies [1–3]. In fact studies have shown that of all the autoimmune-disease affected individuals, more than 75% are females (Reviewed in detail in [4,5]). Additionally, androgen ablation boosts the immune response and increases the efficacy of vaccination in a mouse model of prostate cancer [6]. In a study addressing the susceptibility of human infants to infections, males were found to be significantly more susceptible to infections as compared to females; a trait attributed to an early androgen surge experienced by male infants at birth [7]. Likewise, testosterone-replacement therapy of Klinefelter's Syndrome patients led to decreased serum antibody and cytokine levels and decreased T and B cell levels [8]. Similar studies in avian model systems further support the immune-suppressive role of testosterone on both adaptive and innate immune responses [9–12]. Experimental increase in *in ovo* testosterone levels were shown to suppress both innate and adaptive immune response in House wrens (*Troglodytes aedon)* and leads to a decreased anti-bacterial response in the nestlings hatching from testosterone treated eggs [13]. It is evident that the immune-suppressive role of testosterone is not restricted to certain species but can be viewed as a widely distributed phenomenon across species, and we can speculate that it is a part of the evolutionary program. There are also intrinsic/genetic attributes of the immune system, but nonetheless data indicate that there is a significant role played by sex hormones in modulating the immune response to both induced (immunization) and spontaneous (autoimmune) reactions.

Owing to the fact that the majority of autoimmune affected individuals are females, a lot of emphasis has been placed on the role of female sex hormones in driving and exacerbating autoimmunity and the effect of female sex hormones on different immune cell subsets. The above-mentioned studies indicate that androgens may play an immunosuppressive role in normal immune responses against pathogens and after vaccination, however the underlying

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cellular and molecular effector mechanisms of testosterone on the immune system are not very well understood. In this review we discuss the effect of testosterone on regulatory and effector immune cell subsets that play key roles in shaping immune responses.

2. Androgens and immune dysregulation

In the case of autoimmunity the immune system is generally believed to be hyper-activated, while in cancer the immune system fails to mount the required immune response to combat cancerous cells. Thus, autoimmunity and cancer can be viewed as polar opposites when it comes to the need for immune activation.

2.1. Autoimmunity

Systemic lupus erythematosus (SLE), a hallmark systemic autoimmune disease, has a female to male ratio of 9:1. There are various mouse models to study SLE, the F1 hybrid of NZB and NZW (BWF1) is a spontaneous model of lupus in which disease symptoms and the sex-bias closely resemble the human disease [14]. Some of the earliest studies focusing on the role of androgen in autoimmunity were done on BWF1 mice in the early 1970's and demonstrated a significant protective role of testosterone during lupus like disease development [15,16]. For example, male lupus-prone BWF1 mice were protected from disease development by the presence of testosterone as castration resulted in the development of lupus-like disease symptoms similar to those observed in female age-matched BWF1 mice. Even more interesting, female BWF1 mice with severe disease showed reduced disease severity and prolonged survival upon treatment with testosterone.

The protective role of testosterone is not only limited to SLE but it has been shown to play a protective role in other autoimmune diseases as well. In experimental autoimmune encephalitis (EAE), a mouse model of multiple sclerosis, testosterone has been suggested as a viable therapeutic treatment option capable of restoring both hippocampal function and disease-associated pathology [17]. Rheumatoid arthritis (RA) is also more prevalent in women as compared to men, however lower levels of testosterone may be predictive of RA in men [18]. Similarly, in SKG mice (a mouse model of RA) testosterone was shown to be protective against arthritis, autoantibody production, and RA associated lung disease [19]. In studies conducted with autoimmune patients, treatment with androgens results in more inconspicuous effects. Male patients with relapsing-remitting MS treated with testosterone for 12 months showed improved cognitive performance and a slowing of brain atrophy, however no change was observed in the number or volume of relapsing lesions [20]. Likewise treatment of female SLE patients resulted in changes only in the SLAM-R score, but did not significantly affect disease activity [21]. Further studies investigating the effect of androgens as a therapeutic agent are required. Based on the above-mentioned studies, testosterone appears to have a suppressive effect on the immune system and play a critical role in protection from autoimmunity.

2.2. Cancer

It has been reported that males are more prone to develop cancer as compared to females [22–25]. In addition, there is poor prognosis of cancer and higher risk of secondary malignancies in both juvenile and adult males [26–28]. A recent study based on cancer patient data in the United States from 2004–2008 shows an incidence rate ratio of 1.33 (male:female) [29]. Surprisingly, this ratio was true even after the exclusion of sex-specific cancers. These data were supported by another study (2012) which found that the lifetime expectancy for developing cancer was 44.85% for males, and 38.08% for females [30]. In a recent study of follicular thyroid cancer, testosterone was shown to promote tumor progression by suppressing tumor immunity via inhibiting tumor infiltrating CD8+ T cells and M1 macrophage [31]. Similarly, in a model of early colonic cancer, castration significantly protected male rats from developing colonic adenomas [32]. The inability to mount adequate immune responses against cancerous cells due to a dampened immune system in men could explain the higher risk for cancers and poor survival. Thus, the role of testosterone in rendering males more susceptible to cancer cannot be overlooked. Androgen and androgen receptor (AR) based therapies in cancer have been well documented and recently the specific targeting of the androgen receptor as a therapy for prostate cancer has gained ground (reviewed in [33–36]). To summarize, testosterone appears to play a suppressive role in the immune response to cancer and thus may act as a potential promoter of tumor growth.

3. The effect of androgen on innate immune cells

The innate immune system develops in the bone marrow (BM) from common myeloid progenitors (CMPs). Due to the expression of AR in hematopoietic progenitors, there is reason to believe testosterone may play an important role in shaping the immune cell repertoire even prior to the cells leaving the BM.

3.1. Neutrophils and monocytes

Neutrophils and monocytes are cells of myeloid origin and are the first responders to pathogenic infections. Neutrophils/monocytes arise from CMPs in response to a number of stimuli including both cytokines and growth factors. Mature neutrophils and monocytes are released in the periphery where they circulate in the blood until being called to sites of infection or injury. Classically, these cells are considered to be inflammatory and are associated with the production of pro-inflammatory cytokines such as IL-6 and IL-1β.

Over the past decade, evidence has pointed to a new unexpected regulatory role for neutrophil/monocyte like cells. Such cells have been named myeloid derived suppressor cells or MDSCs. The regulatory functions of MDSCs and the identification of MDSCs as potent immunosuppressive cells were first established in cancer models, where the cells act to suppress T cell mediated anti-tumor responses (reviewed in detail in [37]). MDSC subsets isolated from tumors have been characterized as granulocytic and monocytic, and have been shown to use reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), and TGF-beta as their main mechanisms of T cell suppression [38–41]. Myeloid derived suppressor cells have also been identified in inflammatory mouse models such as EAE and type I Diabetes [42,43].

We have previously reported the existence of immunosuppressive neutrophils, resembling granulocytic MDSCs, in protected male lupus-prone BWF1 mice [44]. Our studies showed that not only did male BWF1 mice contain increased levels of these immunosuppressive regulatory neutrophils, but also the cells were regulated by testosterone and protected against the development of lupus-like disease [44]. Since lupus shows a strong female bias, we speculated that these MDSCs could represent the missing link between the well-known immunosuppressive effects of testosterone and the much-reduced incidence of autoimmunity in males. Analysis of multiple autoimmune and normal mouse strains identified significantly elevated levels of Gr1-expressing cells in males as compared with females in all strains, indicating that the male system in general supports higher numbers of Gr1-expressing cells, although the regulatory capacity of cells from non-autoimmune

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mice remains to be determined (unpublished observation). Additionally, MDSCs have been shown to accumulate in tumor condition and elevated levels of circulating MDSCs are observed in cancer patients [45,46], but comparisons of circulating MDSCs between healthy male and female human controls is lacking. In support of a connection between testosterone and neutrophils, granulopoiesis is significantly reduced in AR deficient non-autoimmune C57Bl/6 mice [47]. More specifically, neutrophils from AR deficient mice are less responsive to granulocyte-colony stimulating factor-induced proliferation, more susceptible to apoptosis, and defective in their response to migratory signals *in vitro* [47]. Thus, neutrophil homeostasis depends on functional AR expression. Interestingly, expression of the AR by myeloid progenitors is in itself regulated by testosterone [47], although whether this effect is direct or indirect is not well understood.

3.2. Macrophages

Macrophages constitute an important part of the innate immune system and are highly pleiotropic in function. Depending on the location and origin of the macrophages they can perform a variety of functions ranging from tissue homeostasis, remodeling, clearance of apoptotic bodies, capturing antigens, and secreting a variety of cytokines shaping the immune response [48,49]. Macrophages play an important role in disease conditions like arteriosclerosis and infections and the effect of androgen on macrophage function has been addressed in several studies over the years. For example, castrated (androgen deficient) male C57/BL/6 mice were found to be significantly more susceptible to endotoxic shock, possibly due to the significantly higher expression levels of surface TLR4 on macrophages [50]. Notably, the expression levels of TLR4, as well as the susceptibility to endotoxic shock, could be reversed when the castrated animals were treated with exogenous testosterone [50]. In a set of similar studies, Chaudry and coworkers have shown the immunosuppressive role of testosterone in septic shock and other organ injury models (reviewed in detail in [51]). Their studies have shown reduced splenic macrophage activity and cytokine production in major abdominal surgery and septic shock conditions leading to poor survival [52,53]. Testosterone has also been shown to directly suppress the expression of TNF-α and IL-lβ from oxidized low-density lipoprotein stimulated human macrophages [54].

Finally, chronic inflammation induced by macrophages is strongly associated with atherosclerosis and cardiovascular disease [55]. Castration of New Zealand white rabbits lead to aggravated aortic plaque area and foam cell (composed of macrophages) formation and higher LOX-1 (lectin-like oxidized low-density lipoprotein receptor-1) expression which was significantly attenuated by treatment with dihydotestosterone (DHT). Similarly, *in vitro* treatment of macrophages from wild type mice with DHT lead to decreased oxidized low-density lipoprotein induced foam cell formation, lower expression of LOX-1 and decreased pro-inflammatory cytokine production [56].

3.3. Dendritic cells

Dendritic cells (DCs) have been thoroughly studied as modulators of immune response since their discovery in 1970 by Steinman and Cohn [57,58]. DCs can be circulating or tissue specific residents, carrying out crucial immune functions such as immune surveillance, the gathering and presentation of antigen to naïve T cells and ultimate induction of protective immunity against pathogens (Reviewed in [59,60]). Besides playing a crucial role in the activation of T lymphocytes, DCs also play a significant role in inducing central T cell tolerance to self-antigens during T cell development in the thymus [61], and by promoting peripheral self-tolerance via the induction of regulatory T cells [62–65].

Two predominant subsets of DCs have been characterized based on cell surface marker expression and function: cDCs (conventional DCs) and pDCs (plasmacytoid DCs). The role of estrogen in controlling and regulating the immune response of DCs is well studied, and is reviewed elsewhere in this *Special Issue*. Below, we will therefore solely review the literature for androgen-dependent effects on DC development and function.

3.3.1. cDCs

Conventional DCs (cDCs) were defined by Steinman and Cohn as either lymphoid DCs ($CD8^+CD11b^-$ $CD11c^+$) or non-lymphoid DCs ($CD8^-CD11b^+$ $CD11c^+$) [59]. The main functions of cDCs are immune surveillance, antigen capture, and antigen processing and presentation to T cells in secondary lymphoid organs. Recent castration studies examined the effect of androgen on cDC function and activation and found that removal of testosterone resulted in significantly elevated expression of MHC class II and co-stimulatory molecules by cDCs in lymph nodes [6]. Removal of testosterone also prolonged the survival of prostate cancer patients [66], although whether this effect is via increased DC activation and better immune mediated tumor eradication or via a direct effect on androgen-dependent prostate cancer cells remains unclear.

Hypogonadism in men is strongly correlated with an increased incidence of autoimmunity indicating an immune-suppressive role of androgen [67,68]. Interestingly, $CD16^+$ DCs from peripheral blood of hypogonadal men showed significantly enhanced immune response to TLR9 ligand (CpG ODN) resulting in increased expression of the DC activation marker CD107b [69]. Furthermore, a clinical study of type 2 diabetic men showed the immune-suppressive effect of testosterone on pro-inflammatory cytokine production (IL-1β, IL-6 and TNF-α) by DCs, which persisted long after the termination of testosterone treatment [70]. Taken together all these studies indicate a strong immune-suppressive role of testosterone on cDC activation, cytokine production and subsequently their ability to mount an immune response.

3.3.2. pDCs

Plasmacytoid DCs (pDCs) were first identified as $CD11c^-$ immature DCs in human peripheral blood [71]. As compared with cDCs, pDCs express lower levels of MHCII, lower levels of co-stimulatory molecules and a reduced ability to stimulate T cells [71]. In contrast, pDCs are the dominant interferon-producing cells in response to most viral infections. In fact pDCs have been shown to produce 200–1000 times more type I interferon, in response to microbial challenge, compared to any other cell type, conferring these cells an important role in anti-viral and anti-tumor immune responses [72,73]. There is a clear sex-bias in the production of type I interferon by pDCs and despite new evidence that estrogens are involved in this capacity [74], the role of androgens cannot be overlooked. For example, male pDCs produced significantly less type I interferon in response to HIV-1 infection and mounted a weaker $CD8^+$ T cell response against the virus resulting in higher viral loads in male than female patients [75]. Also, human male infant pDCs were shown to respond significantly less to TLR7/8 crosslinking as compared to pDCs from age-matched females [7]. Whether the sex-bias in pDC response can be attributed to the androgen surge that happens early in infancy, reduced estrogen levels, or differential expression/function of X-linked TLR7/8 expression remains to be fully addressed.

4. The effect of androgen on adaptive immune cells

4.1. The effect of androgen on T lymphocyte development

Due to the onset of thymic involution following puberty, and the effect of castration on thymic size, the role of androgens on

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the thymus and development of T cells has been investigated. Several early studies showed that androgen deprivation in males is associated with enlargement of the thymus, and this has been confirmed numerous times [76–82]. Ablation of androgen through castration of male animals, as well as a defect in androgen signaling, results in reversion and re-expansion of the involuted thymus, accompanied with increased cellularity due to more proliferating and fewer apoptotic thymocytes [77,79,83]. Additionally, androgen ablation accompanied by hematopoietic stem cell transplantation results in increased lymphoid recovery and cellularity, revealing a negative role of androgens in immune reconstitution [84,85]. The reversal of thymic atrophy post castration is age independent and can be reversed with administration of testosterone or DHT, leading to the inhibition of thymic rejuvenation, decreased proliferation and increased apoptosis of thymic T cells [78,86]. Olsen and Kovacs confirmed these results in humans by showing that restoration of testosterone in androgen-deficient men resulted in decreased thymic output of T cells [87]. Additionally, castration of aged male mice resulted in the return of thymic output to levels comparable with that of younger mice [77]. These results taken together indicate a suppressive effect of androgens on the development of the thymus and the regulation of thymocytes. The response of the thymus to changes in androgen levels suggested that the effects were exerted through AR mediated mechanisms. Ligand binding assays, immunoblotting, and flow cytometry revealed the expression of AR by $CD3^+$, $CD4^+$, and $CD8^+$ thymocytes, with the highest expression on $CD3^{low}CD8^+$ thymocytes [78,88–90]. Since other studies have shown by quantitative RT-PCR analyses, a higher amount of AR mRNA in thymic epithelial cells, as opposed to thymocytes, Olsen and colleagues developed bone marrow chimeras in which AR expression was restricted either to thymocytes or thymic epithelium and compared thymus size and cellularity with that of normal C57BL/6 mice and androgen insensitive X-linked testicular feminized (Tfm/Y) mice [78,91,92]. Lack of AR expression on thymic epithelial cells rendered the thymus unable to respond to androgens, highlighting the necessity of AR expression on thymic epithelium, rather than on thymocytes themselves, for androgen-induced thymic involution.

4.2. The effect of androgen on the peripheral T cell population

Thymic involution results in the reduced export of T cells into the periphery, and as a result, a reduced peripheral T cell receptor (TCR) repertoire and function [93–95]. Castration studies of male mice show a significant increase in recent thymic emigrants, specifically $CD44^{low}$ naïve $CD4^+$ and $CD8^+$ T cells, replenishing the peripheral T cell pool [77,80,87]. In addition to increased thymic output described above, Sutherland et al. showed that the TCRVβ repertoire of aged mice was normalized post castration [77]. This is in contrast to another study, which showed that androgen deprivation failed to alter TCR diversity [80]. These studies show that androgens act to inhibit the number, and perhaps the repertoire, of recent thymic emigrants entering the periphery. Finally, proliferation of splenocytes in response to TCR stimulation increased after castration of male mice independent of age, suggesting that androgens may affect the magnitude of T cell responses after immunization [77,80]. Whether this effect is direct or indirect, however, remains unclear. As described above, we have previously reported the inhibition of T cell proliferation by testosterone-regulated neutrophils [3], and thus effects on total T cells *in vivo* could be mediated via a decrease in regulatory neutrophils. Additional studies are needed to determine if androgens directly affect the numbers of peripheral T cells.

4.3. The effect of androgen on the differentiation of T helper cells

4.3.1. Th1 differentiation

Testosterone has shown to have an overall suppressive effect on the immune system, in particular to viral and host antigens [96–99]. In addition, it is known that women are more responsive towards viral vaccines, including influenza [100–102]. T_H1 cells play a pivotal role in protecting an individual from infections by bacteria, fungi, and viruses [103–108]. The pro-inflammatory cytokines produced by these cells, IFNγ and TNFα/β, stimulate innate and cell-mediated responses, resulting in the clearance of pathogen as well as anti-tumor effects [109–112]. T_H1 cells however, can also elicit negative effects including inflammatory bowel disease (IBD), graft rejections in transplantation, and autoimmune diseases such as type 1 diabetes and rheumatoid arthritis [113–116]. The lower prevalence of these diseases in men would lead one to speculate about an effect of androgens on T_H1 cell differentiation. Conversely, the higher incidence of cancer in men may be associated with inhibition of T_H1 pro-inflammatory cytokines, and as a result a weakened anti-tumor response [25,117,118]. EAE, a mouse model of multiple sclerosis, is associated with T_H1 responses to myelin-like autoantigens and shows a female bias [119,120]. Splenocytes from male SJL mice stimulated with anti-CD3 were shown to have significantly lower expression of IL-12 as compared to female mice, indicating that induction of T_H1 cells in male SJL mice is reduced [89]. This may explain why male SJL mice do not develop as severe EAE as female mice. In a direct comparison, T cells from male mice with EAE were less able to transfer disease than female T cells [90,121]. Treatment with androgens *in vitro* resulted in inhibition of T_H1 differentiation, less IFNγ production, and decreased IL-12-dependent induction of the T_H1 phenotype [122]. Similarly, androgen ablation following bone marrow transplantation (BMT) was shown to ameliorate signs of EAE and reduce demyelination and lymphocyte infiltration within the CNS [84]. Importantly, these studies also showed that castration of C57Bl/6 mice does not increase susceptibility to EAE, indicating that the castration-dependent induction of EAE relies also on the genetic background of the mouse model used. Studies addressing in more detail the effect of testosterone have revealed that testosterone stimulation results in the up-regulation of the phosphatase Ptpn1 in an AR dependent manner [122]. Ptpn1 is known to inactivate Jak2, and Tyk2 kinases responsible for IL-12 induced STAT 4 phosphorylation needed for the induction of T_H1 differentiation [123]. T cells from patients with prostate cancer undergoing androgen deprivation therapy were also shown to have a decreased expression of Ptpn1 as compared to control patients [122]. It is interesting to note that Ptpn1 also regulates insulin-like growth factor (IGF) signaling, and decreased IGF-induced signaling have been suggested to lower influenza vaccine efficacy in males by altering lipid metabolism [101,124]. It is apparent through these studies that androgens exert an overall inhibitory effect on T_H1 differentiation, and this inhibition may explain the lower incidence of autoimmune disease and the heightened susceptibility to viral infections in males.

4.3.2. Th2 differentiation

The function of T_H2 cells is associated with activating humoral immunity and promoting IgG1 and IgE class switching, and thus T_H2 cells are important in protecting against extracellular pathogens such as helminthes [107,125]. T_H2 cells are known to secrete IL-4, IL-5, IL-6 as well as the pleiotropic cytokine IL-10. Interleukin-10 is best known for its anti-inflammatory effects; inhibiting the activation of dendritic cells, and its capacity to enhance the survival and differentiation of B cells [126–129]. There is some evidence that testosterone may directly induce the production of IL-10 by Th2 cells in the EAE model both *in vivo* and *in vitro*.

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Splenocytes from female SJL mice treated with DHT secrete significantly greater amounts of IL-10 *in vitro*, and the addition of DHT to $CD4^+$ T cell cultures leads to more IL-10 production. Subsequently, female SJL mice have been shown to have a lower prevalence of EAE after DHT treatment [89,90,121]. Further investigation is required to fully delineate the protective role of IL-10 in EAE. In studies of parasitic infections, androgens have been associated with suppression of T_H2 cell differentiation. For example, women have been shown to mount a better immune response toward parasitic infections than males by generating a greater T_H2 response, which is crucial for expulsion of the parasite [125,130]. Studies of IL-4 deficient Balb/c mice infected with the parasitic helminth *Trichuris muris* show that female mice are able to generate a delayed IL-13 mediated T_H2 response and expel the parasite, whereas male mice cannot. Castration of male mice however renders them able to clear the helminth infection and was shown to be dependent on a reduction of IL-18 expression. Ovariectomised female mice on the other hand were still able to generate a T_H2 response and clear the parasite. These results indicate that testosterone acts to inhibit helminth expulsion by suppressing T_H2 driven immunity, predominantly through the up-regulation of IL-18 [125]. Thus, in general, an overall dampening of the immune response by androgens can be observed. In the case of EAE, androgens promote T_H2 differentiation in order to suppress the overactive T_H1 response associated with this disease, and in the case of helminth infections, androgens inhibit the necessary T_H2 response required to clear the infection.

4.4. The effect of androgen on other T cell subsets

As mentioned above, testosterone has been shown to induce IL-10 production by T cells [64,65]. The prototypic IL-10 producing cell is the induced regulatory T cell (iTreg). The effect of androgens on regulatory T cell (Treg) development has therefore been investigated in several mouse disease models. The conclusions, however, are far from clear. On one hand administration of testosterone was shown to increase the number of immunosuppressive Tregs, derived from splenic $CD4^+$ cells in a model of experimental autoimmune orchitis [131], while on the other hand a study using prostate-specific Pten−/− mice showed an expansion of Tregs after castration [132]. In the latter example, Treg expansion only occurred after an increase in $CD8^+$ T cells was observed, and depletion of Tregs restored $CD8^+$ function in castrated mice. Thus, androgens may induce Treg expansions, hereby suppressing general immune functions.

One consequence of thymic atrophy is the diminished ability to generate T dependent antibodies [133]. Owing to the fact that androgens are associated with thymic involution, and males show a weaker response to vaccination, it can be inferred that male mice may not respond as well to T-dependent immunizations as females. Studies by our lab confirmed this by showing that female autoimmune BWF1 mice generate a greater antibody response to a T dependent immunization than male mice [3]. Interestingly, this response was inhibited by testosterone-dependent immunosuppressive $Gr1^+$ cells in male, but not female, BWF1 mice via inhibition of T follicular helper cell (T_{FH}) differentiation [3]. In summary, androgens can affect T cells both directly and indirectly via control of T helper cell differentiation, induction of iTregs, and through regulation of T-dependent antibody responses.

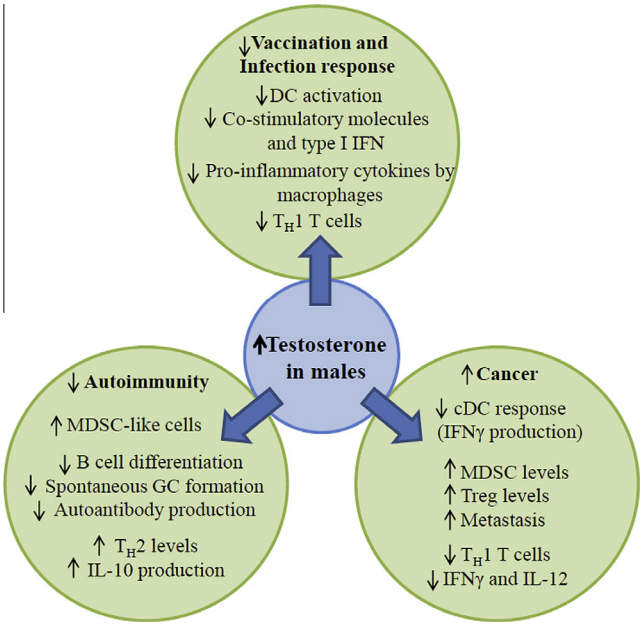

Fig. 1. Regulation of immune responses by testosterone in males. Testosterone acts on various cell types involved in immune response to vaccinations and pathogenic infections, autoimmunity, and cancer. Testosterone has a suppressive effect on key cellular components responsible for mounting immune responses against different stimuli.

4.5. The effect of androgen on B lymphocyte development

As described above, sex hormones induce regulatory effects on BM lymphopoiesis [82,134,135]. For example, while castration of male mice results in increased lymphopoiesis and thus more B cells and B cell precursors (early pro-B cell (Fraction B) and the late pro-B cell (Fraction C)), androgen replacement therapy of castrated mice replenishes the numbers of B cells back to normal levels [82,135,136]. Likewise, Tfm mice, that are insensitive to androgens, show increased percentages and total numbers of IL-7-responsive B cell precursors (similar to Fractions B and C) within the BM [82,137]. IL-7 is produced by stromal cells within the BM and is required for B cell proliferation and differentiation, thus the effects of androgen on B cell lymphopoiesis may be mediated by bone marrow stromal cells [138]. Since both bone marrow stromal cells and B cell progenitors express AR, chimeric mice in which AR expression was restricted to either stromal cells or lymphoid cells within the BM were generated to identify the primary cellular target of androgens in the BM [136,137,139]. These studies elegantly showed that AR expression in stromal cells, but not lymphoid cells, was necessary for testosterone's negative effect on B cell lymphopoiesis [139]. Interestingly, the inhibitory effect of testosterone was not directly due to reduced IL-7 production by stromal cells, but rather via the induction of TGF-β secretion by BM stromal cells subsequently leading to reduced IL-7 levels [139,140]. Reduced levels of androgen or abnormally low AR expression correlates with an increased susceptibility to RA, which is present in males with low levels of androgens as well as patients with prostate cancer undergoing androgen deprivation therapy [141]. This was in part due to increased proliferation and decreased apoptosis of B lymphocytes, allowing autoreactive B cells to expand into the periphery [141]. Ultimately, these studies suggest a crucial role of androgens in regulating the development of B cells as well inhibiting the expansion of potentially autoreactive B cells in the periphery, leading to autoimmune disease. Finally, although castration of normal male mice also results in expansion of newly emigrated immature B cells within the periphery [82,136,137,141], it is important to note that B cells within the spleen do not express AR and thus, that effects exerted by androgens are likely directed towards B cell lymphopoiesis [91]. Whether AR-independent effects play a role in regulating peripheral B cell levels has not been extensively investigated.

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5. Concluding remarks

Male and female sex hormones seem to have very distinctive and exclusive roles in shaping the immune system and immune responses, however the role of androgens has not been well examined. In this review, we explored the effects of testosterone regulation of the immune system. In summary, there is little doubt that androgens play a very important role in modulating the immune system by affecting the innate as well as the adaptive immune system, both at the developmental and functional levels. Androgens are generally immunosuppressive targeting many arms of the immune system and act to dampen the immune response. This effect may partly explain the sex-bias witnessed in various immune related disorders (Fig. 1). The emerging body of literature shedding light on the cellular and molecular targets of androgen-mediated immune-suppression has opened numerous therapeutic and interventional approaches to manage conditions like – autoimmunity, cancer and cardiovascular diseases.

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