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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