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REVIEW

Androgen-dependent immune modulation in parasitic infection

Julie Sellau[1] · Marie Groneberg[1] · Hannelore Lotter[1]

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Abstract

Parasitic infections modulate the immune system of the host, resulting in either immune tolerance or the induction of pro-inflammatory defense mechanisms against the pathogen. In both cases, sex hormones are involved in the regulation of the immune response, as they are present in the systemic circulation and can act on a wide variety of cell types, including immune cells. Men and women have a different milieu of sex hormones, and these hormones play a role in determining immune responses to parasitic infections. Men, who have higher plasma levels of androgens than women, are generally more susceptible to parasitic infections. Many immune cells express the androgen receptor (AR), and the immunologic functions of these cells can be modulated by androgens. In this review, we will highlight the immune cell types that are sensitive to male steroid hormones and describe their roles during three parasitic diseases, amebiasis, leishmaniasis, and helminthiasis.

Keywords Sex hormones · Androgens · Sex difference · Parasitic infections

Introduction

Infectious diseases occur widely around the world. All human beings will likely experience several infections in their lifetime. Parasitic infections are more common in developing countries, especially in tropical regions, due to the higher temperatures and lower hygienic standards. The human body has distinct mechanisms to combat infections, but not every individual responds in the same way. Well-known factors such as age and environmental circumstances are considered to be crucial in determining how a host responds to infections. Furthermore, recent studies have focused more and more on the differences between men and women with respect to their ability to combat infections [1, 2]. Parasitic diseases in particular show sex differences in the host immune response. There are also differences in the prevalence of parasitic diseases between men and women; in rural areas, this disparity is partially due to traditional roles of men and women in society. Differences in the distribution of household duties can affect access and exposure to sources of infection, which therefore might falsely create a sex bias concerning infection and disease outcome.

Nevertheless, there is an increasing body of evidence that immune responses to parasitic infections differ between men and women [3–5]. Sex differences in the immune response may originate from the direct influence of hormones or via chromosomal effects. Notably, the Y chromosome contains the *SRY* gene, which is responsible for the development of the gonads and is therefore essential for the production of male steroid hormones [6–8]. However, the X chromosome carries approximately 10-fold more genes than the Y chromosome, and among these are genes of crucial importance for the immune response, including Toll-like receptor *(TLR)7* and *IL2RG* [9, 10]. Female cells harbor two copies of these X-linked genes, whereas male cells only contain one copy. The resulting imbalance in the gene dosage can lead to impaired immune responses. One example is the well-studied imbalance of TLR7 activity in women and its link to the autoimmune disorder systemic lupus erythematosus (SLE) [9]. However, it is generally accepted that sex hormones also shape the immune response to infectious diseases differently in men and women. Sex hormones are able to regulate immune cells directly and indirectly, via modulation of hormone-sensitive surrounding tissues. This regulation of the immune response by sex hormones is possible because circulating as well as tissue-resident immune cells express steroid hormone receptors [11].

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✉ Julie Sellau
sellau@bnitm.de

[1] Department of Molecular Biology and Immunology, Molecular Infection Immunology, Bernhard Nocht Institute for Tropical Medicine, Bernhard-Nocht-Straße 74, 20359 Hamburg, Germany

During immune responses against parasitic infections, the innate and adaptive immune system engage defense mechanisms in which specific immune cell types are known to play a crucial role. Nevertheless, the response to each infection remains unique. Here, we will highlight established immune responses to parasitic infections that are influenced by steroid hormones, especially androgens.

A brief overview of sex hormones and their function

Steroid hormones are essential for the development of the reproductive systems of men and women. During the co-evolution of hosts and parasites, genes for health and balanced immunity were favored by the host, whereas in the evolution of parasites, genes were favored that improved their synergy with the host. The role of steroid hormones in the immune response was underestimated for a long time, and recent findings have shed light on important mechanisms to combat infections. Simple experiments such as the removal of steroid hormone-producing organs showed that these hormones directly influence immune responses and therefore the outcome of parasitic infection [1, 12].

Steroid hormones are a group of small lipophilic molecules. They are able to cross the plasma membrane without any secondary messenger. All sex hormones are synthesized from cholesterol through a defined enzymatic cascade in the gonads as well as the adrenal glands [13] (Fig. 1). The active products are classified into three types of molecules, androgens (19 carbons), estrogens (18 carbons), and progesterone (21 carbons). Progesterone can be further processed into mineralocorticoids or glucocorticoids. What makes this biochemical pathway of particular interest is the plasticity of these three groups of sex hormones, as progesterone can be enzymatically converted to testosterone and testosterone can be aromatized by the enzyme aromatase to estradiol, a molecule of the estrogen family [14]. Androgens, the predominant sex hormones in men, are mainly produced by the gonads and the adrenal glands. Androgens include testosterone, dihydrotestosterone (DHT), androstenedione, androstenediol, and dehydroepiandrosterone (DHEA), with DHT being the most potent [15]. In the plasma, androgens are mostly bound to sex hormone-binding globulin (SHBG) and albumin, and only 1–3% of the testosterone is not bound to plasma proteins. Albumin-bound testosterone and unbound testosterone are both considered to be bioavailable [16]. These steroid hormones signal either through the classical androgen receptor (AR), which is located intracellularly, or the non-classical AR, which is located in the plasma membrane. ARs are expressed on a variety of different cells and tissues, which makes androgens potent modulators of many biological functions outside of the reproductive system, including the cardiovascular, neural, and hematopoietic system [17]. The plasma concentration of androgens is about seven times higher in men than in women and ranges from approximately 2.64 to 9.16 ng/mL after puberty, depending on age [18–20]. By contrast, in women, the concentration of 17ß-estradiol, the predominant form of estrogen, depends on the menstrual cycle. During the midfollicular phase, the concentration averages 20–80 pg/mL, and it peaks at 200–500 pg/mL during the pre-ovulatory phase [21]. The general function of estradiol is the maintenance and regulation of female estrus. As with androgens, the estrogen receptor is expressed on many different cell types and tissues, and is involved in several non-reproductive functions, such as the stabilization of bone resorption [22].

Besides androgens and estrogens, progesterone is another steroid hormone of the reproductive system, and it is predominantly produced during pregnancy (200 ng/mL) by the placenta [23], but also in the secondary phase of the menstrual cycle by the corpus luteum in the ovary. During the postmenopausal phase, women have similar amounts of progesterone as men (ranging from 0.3–2.54 ng/mL in women to 0.6–4.45 ng/mL in men). The levels of progesterone in women fluctuate according to the menstrual phase, ranging from 0.64–4.77 ng/mL during the follicular phase to 2.54–9.54 ng/mL during the ovulatory phase, and 5.41–85.86 ng/mL during the luteal phase [24]. In both sexes, progesterone is also produced by the adrenal glands, even though the function differs. One of the main functions of progesterone in females is to induce the growth of the endometrium for embedding the fertilized ovum. In males, progesterone has an impact on spermatogenesis, and it also interacts with the central nervous system, by regulating the susceptibility of seizure, stress, and anxiety, giving this hormone and its derivatives (e.g., allopregnanolone) the name neurosteroids [25, 26]. Progesterone acts via the progesterone receptor and, to a lesser extent, the glucocorticoid and mineralocorticoid receptors. Progesterone-sensitive cells of the immune system include macrophages, dendritic cells (DCs), T cells, and natural killer (NK) cells [27, 28]. Even though for the latter, it is not fully elucidated if this is due to a direct or indirect (over secondary, progesterone-sensitive cells) interaction of progesterone with NK cells. Overall, steroid hormones are not necessarily related to one sex, since both men and women are able to produce them. Even though the estradiol concentrations are low in men, the role of this hormone is often underestimated. Spermatogenesis as well as libido is affected by estradiol in men [29]. In women, testosterone is positively associated with sexual functions [30, 31], and it is thought to play an additional role in non-reproductive tissues such as the brain, the lung, and the colon, all of which express the AR [32, 33]. In women, androgens are mainly produced by the ovaries and by the peripheral conversion of androstenedione and dehydroepiandrosterone. These pre-androgens are produced by the ovaries

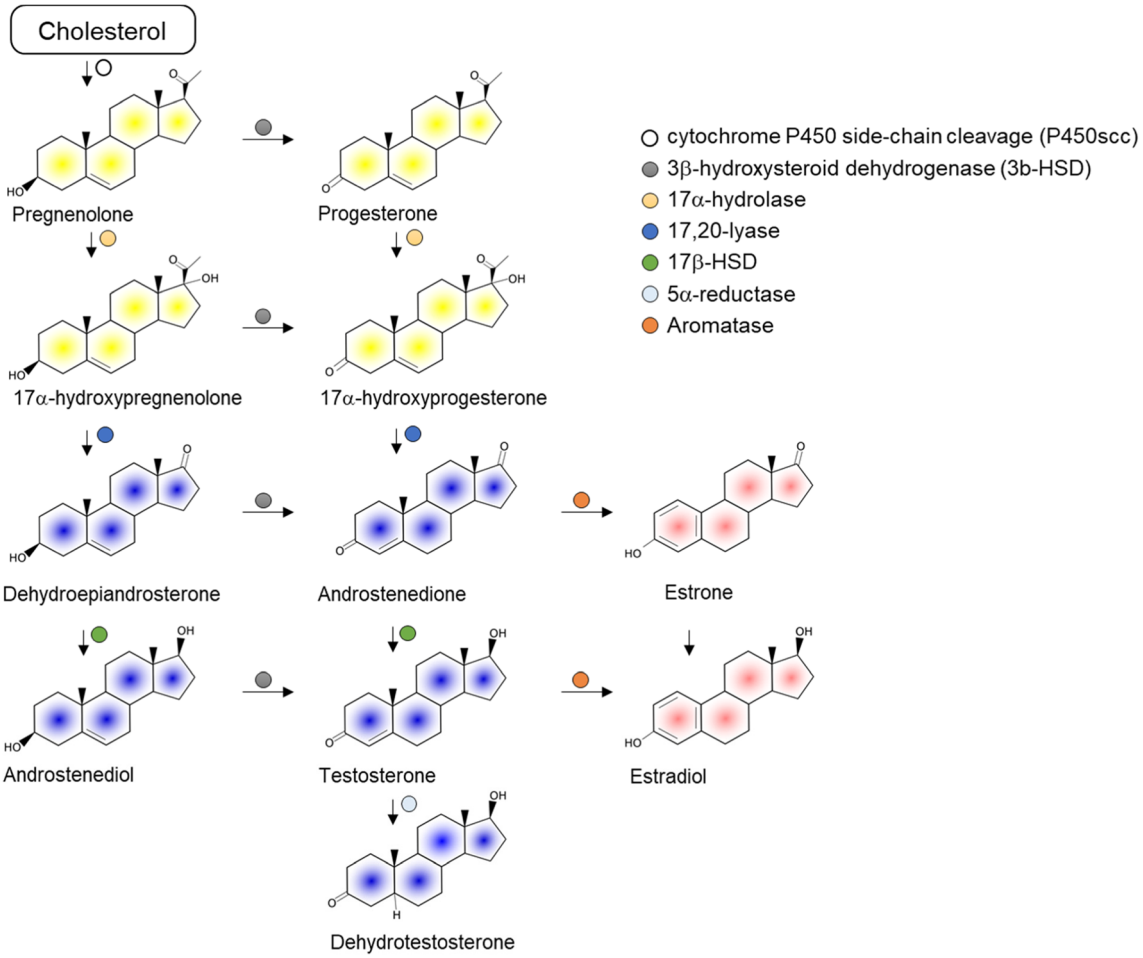

Fig. 1 Biosynthetic pathway of steroid hormones: The three major groups of sex steroid hormones, progesterones (yellow) androgens (blue), and estrogens (red) originate from cholesterol via a cascade of enzyme-mediated reaction steps (colored circles)

as well as the adrenal glands [34]. Although in women androgens circulate at even higher levels than estrogens, it has been a challenge to precisely measure these low levels of androgens due to assay inaccuracy. Liquid chromatography-tandem mass spectrometry (LC-MS) is currently considered the most sensitive method for measuring hormone levels [35, 36].

The impact of estrogen-related hormones on the immune system has been investigated in various settings [37–39], but the precise role of androgens during immune responses still needs to be further elucidated. Moreover, in many parasitic diseases, the presence of androgens clearly correlates with increased susceptibility and a worse outcome.

Androgen receptors and their impact on the immune system

The androgens testosterone and DHT regulate immune cells by binding to ARs. A large variety of hematopoietic cells express ARs. Among these are a variety of stem cells and progenitor cells, including both myeloid and lymphoid progenitors [40]. Accordingly, myeloid-derived cells also express ARs and may therefore respond in a sex-dependent manner to an infectious challenge. Interestingly, monocytes, macrophages, and neutrophils, but not myeloid-derived dendritic cells, express ARs. While only mature mast cells express ARs, eosinophils do not express ARs at all. With respect to lymphoid cells, ARs are expressed in T cells and B cells, but in the latter, only during development [40, 41]. However, AR expression on other immune cell types remains to be characterized.

One characteristic of steroid hormones is their lipophilic nature, which allows them to easily diffuse across cell membranes. Classical hormone receptors are expressed intracellularly and are bound to chaperones in the cytoplasm until ligand binding occurs [42, 43]. After the formation of the ligand:receptor complex and the exchange of chaperones through cofactors, the complex translocates into the nucleus where it interacts with DNA regulatory sequences known as androgen response elements (AREs), consequently leading to the transcription of target genes [44]. Notably, the binding affinity of AR:DHT complexes is higher than that of AR:testosterone complexes. Hence, studies using DHT rather

than testosterone might lead to a more conclusive evidence regarding the role of androgens in immune responses. Moreover, DHT cannot be converted into estradiol by aromatases [14, 15]. In addition to the classical AR, androgens can signal through the non-classical AR. The non-classical AR can be activated by the direct binding of androgens or indirectly via SHBG [45, 46]. The activation of the non-classical AR leads to the recruitment of downstream transcription factors, as well as the release of intracellular calcium and inositol 1,4,5-trisphosphate, which in turn leads to cell activation [47]. Some transcription factors and signaling proteins are known to regulate the activation of the AR. NF-κB is an important transcription factor in the development and maintenance of inflammation and has been shown to increase the nuclear translocation and transactivation of AR, and to increase the expression of AR [48–51]. Other immune factors such as Janus kinase (JAK)-signal transducers and activators of transcription (STAT) family members influence AR signaling by transactivating and stabilizing the AR complex [52, 53]. One particular transcription factor, Foxa1, not only induces AR transactivation but also controls its recruitment to the DNA [54, 55]. In addition to modulating the activity of the AR, Foxa1 is able to induce a suppressive phenotype in T cells [56, 57].

Taken together, androgens have direct and indirect effects on the immune response, and, vice versa, immune factors can also modulate AR signaling. These findings suggest that androgens may indeed play an important role during the immune response to parasitic infections, which is underlined by several studies showing an increased prevalence and intensity of parasitic infection in males [2, 58].

The role of androgens in the immune system

Immune cells can be divided into cells of the innate and adaptive immune system, and most are sensitive to androgens through their expression of the AR. However, the effects of androgens are complex and somewhat contradictory, and cannot be categorized simply as suppressive or activating.

Androgens trigger the differentiation of neutrophils [59], and mice lacking the AR exhibit neutropenia [60]. This androgen-dependent neutropenia can be reversed by anti-androgens such as flutamide [59]. However, androgens act immunosuppressive on mature neutrophils by reducing the production of superoxide and decreasing the microbicidal activity [61].

Other innate immune cells such as monocytes and macrophages react to androgens mostly via the rapid release of intracellular calcium and the phosphorylation of the transcription factor extracellular-related kinase (ERK), an important member of the mitogen-activated protein kinase (MAPK) pathway [46, 62]. Gonadectomy of male mice increased the expression of TLR4, leading to a more efficient response to pathogens. This finding was further supported by the observation that androgens downregulate TLR4 expression on macrophages in vitro [63], suggesting the overall conclusion that androgens have potent immunosuppressive effects on macrophages.

Furthermore, it is known that macrophages play a role during wound healing. In castrated animals, fewer macrophages were present at the site of injury, leading to reduced production of inflammatory cytokines and faster wound healing [64]. By contrast, the application of DHT in a diabetes model led to improved tissue regeneration due to the increased production of collagen fibers [65]. In conclusion, the modulatory effects of androgens during the process of wound healing are not sufficiently understood and seem to depend on the mode of administration, the cell type, and the animal model. Androgens also reduced the secretion of IL-6 by monocytes, which is notable since androgens did not alter interleukin (IL)-6 release from B cells or T cells [66]. However, the production of other potent immunomodulatory cytokines such as tumor necrosis factor (TNF)-α, IL-12, and IL-1β were increased in male-derived monocytes after endotoxin stimulation compared with female-derived monocytes [67, 68].

DCs are one essential bridge between the innate and the adaptive immune system. Androgens induce an inhibitory phenotype in these professional antigen-presenting cells. Even though the AR is not expressed on myeloid-derived DCs [69], treatment with DHT inhibited DC expression of major histocompatibility complex (MHC) and the ablation of androgen led to an increase of co-stimulatory molecules on DCs (70), and enhanced the secretion of pro-inflammatory cytokines [70, 71]. Given that these studies were conducted in vivo, it is still not clear whether DCs are directly responsive to androgens.

Lymphoid cells may also be sensitive to androgens, depending on their AR expression. The number of B cells is influenced by testosterone, in that low testosterone levels are correlated with elevated B cell numbers, high testosterone levels in men are correlated with poor vaccination efficacy [72, 73] and diminished production of IgG1 and IgM [66]. Since mature B cells do not express the AR, one can conclude that either the effect of testosterone on mature B cells is indirect or it occurs during B cell maturation [39]. In addition, the relationship between B cell numbers and testosterone levels was found to be due to the suppressive actions of testosterone on B cell activating factor (BAFF), a cytokine important for the activation, differentiation, and survival of B cells. Even though splenic stromal cells were found to be the source of the BAFF secreted in the absence of testosterone [74], immune cells, including monocytes, macrophages, and neutrophils, are known to be potent producers of BAFF as well [75].

In addition to developing B cells, T cells also express the AR [76, 77]. They mature in the thymus, an organ that is highly sensitive to androgen signaling, as loss of testosterone leads to significant thymus enlargement [78, 79]. Epithelial

cells in the thymus play an important role in inducing an androgen-dependent effect on T cell maturation through their expression of autoimmune regulator (Aire), a transcription factor crucial for the elimination of autoreactive T cells [80]. Another indirect effect on T cells in male mice is the enhanced transforming growth factor (TGF)-β production in the thymus due to high circulating androgen levels, which leads to increased T cell tolerance [81]. Furthermore, high levels of DHT as well as testosterone can non-selectively induce cell death in peripheral T cells [82].

Furthermore, adding DHT to T cell cultures leads to the upregulation of the T_H2 cytokine IL-10 [83]. Stimulation of $CD4^+$ T cells from male mice with autoimmune encephalomyelitis with a CD3 antibody predominantly resulted in the secretion of T_H2 cytokines, while T cells from female mice are more proned to produce T_H1 cytokines such as IL-12 [83]. Moreover, antigen-specific production of interferon (IFN)γ by T cells is suppressed by androgens, in line with a reduced IL-12 signaling [84–86], although the suppressive influence of androgens on the development of a T_H1 response is still considered controversial [87]. Furthermore, AR signaling in T cells promotes the conversion of peripheral T cells from women in their ovulatory phase into Foxp3-expressing regulatory T cells, but this response is not seen in T cells derived from men [88].

The effects of androgens on different immune cell types are summarized in Fig. 2. However, given the complexity of the interactions between immune cells and pathogens or parasites, our current knowledge on the role of sex hormones in infection is relatively poor, and continued efforts should be made to further characterize these responses. For this purpose, the implementation of representative animal models that reflect the same sex difference as observed in the corresponding human disease are necessary as well as the identification and characterization of hormone-sensitive cell types responsible for the sex difference in respective infections. For the detailed description of the role of steroid hormones in infectious diseases, it is of crucial importance to unravel molecular pathways of hormone and immune cell interactions.

The relevance of androgens on parasitic infections

Even though the increased susceptibility of men to infectious diseases has been linked to steroid hormones [72], the immune modulatory effects of androgens in parasitic diseases are insufficiently understood. Although it is well known that androgens primarily exert immunosuppressive effects, our understanding of the role of AR and its ligands in parasitic infections is lacking. In the following chapters, we highlight recent findings on the role of androgens in the immune response to selected parasitic infections that clearly present in the same sex-dependent manner in humans and animal models.

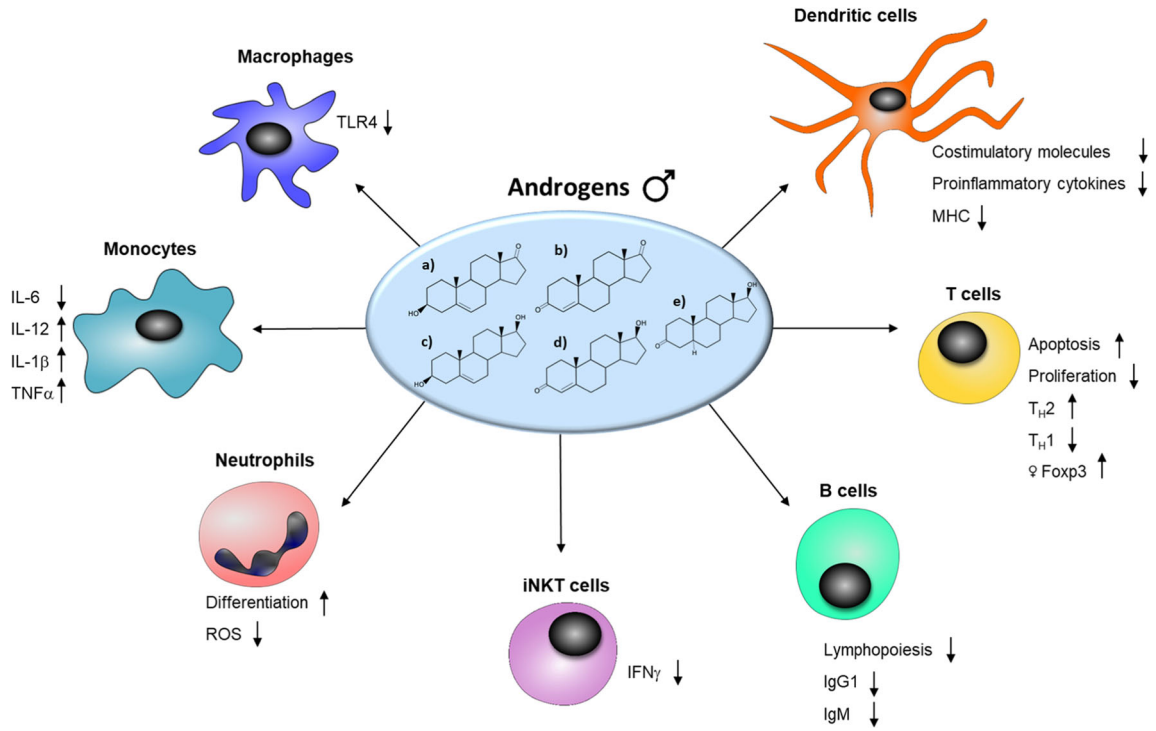

Fig. 2 Influence of androgens on immune cell subsets. (a) Dehydroepiandrosterone, (b) androstenedione, (c) androsteinidione, (d) testosterone, and (e) dihydrotestosterone, and their effects on dendritic cells, T cells, B cells, invariant natural killer T (iNKT) cells, neutrophils, monocytes, and macrophages. In general, androgens show direct or indirect suppressive effects on most immune cell types

Sex-dependent immune modulation in amebiasis

The causative agent of amebiasis is the protozoan *Entamoeba histolytica* (*E. histolytica*), a parasite that is widely distributed in tropical and subtropical areas [89]. *E. histolytica* begins its simple life cycle as an environment-resistant cyst that is ingested in contaminated water or food. If accidentally swallowed, *E. histolytica* cysts reach the gastrointestinal tract, where they develop into motile trophozoites. These trophozoites persist in the gut for several months or years without inducing any clinical symptoms. Under as-yet-unclarified circumstances, *E. histolytica* trophozoites penetrate the intestinal mucosa and reach the epithelial cell barrier, where they initiate necrosis and apoptosis via the activation of enzymes such as cysteine peptidases, which are normally involved in the digestion of bacteria in food vacuoles of the parasite. The induction of cell death causes tissue destruction and inflammation, leading to hemorrhagic, ulcerative colitis. Occasionally, the parasite spreads via the bloodstream to other organs including the lung, brain, and, most often, the liver, leading to the formation of amebic liver abscesses (ALA) [90]. Infection of the liver by *E. histolytica* occurs with a clear sex bias towards adult men [91]. This sex difference is not influenced by any cultural or social behavior, since men from different endemic regions as well as male travelers develop ALA more frequently than women [92–94]. Moreover, a study in Vietnam reported that the occurrence of ALA increases after puberty in men, reaching a male-to-female ratio of 7:1 in individuals between the ages of 36 and 40, even though there is a higher prevalence of the parasite in women [90]. A serological analysis of *E. histolytica* asymptomatic carriers revealed significantly lower titers of total immunoglobulin and the IgG1 subclass in men compared with women [4]. In addition, no significant differences in peripheral T_H1 or T_H2 cytokines or chemokines were observed between male and female ALA patients and asymptomatic carriers, with one exception: the C-C chemokine ligand (CCL)2, also known as monocyte chemotactic protein (MCP)-1, was significantly higher in the serum of asymptomatic male carriers than female carriers [4]. Using an immunocompetent mouse model for *E. histolytica* infection [95] that exhibits the same sex difference for ALA as observed in humans, recruitment of $Ly6C^{hi}$ inflammatory cells via CCL2 was found to be crucial in the development of liver destruction upon intrahepatic infection of male mice with amebic trophozoites [96]. Mice depleted of inflammatory monocytes or lacking the receptor for CCL2 (CCR2) on monocytic precursors showed significantly smaller liver lesions, suggesting a pathological role for these innate immune cells during tissue destruction. Consequently, adoptive transfer of inflammatory monocytes into CCR2 knock-out mice restored the phenotype [96]. Further investigation of the underlying mechanisms revealed a significant contribution of the IL-23/T_H17 immune axis, which precedes CCL2 production during ALA development in male mice [97]. Furthermore, the pro-inflammatory environment during intrahepatic infection with *E. histolytica* is shaped by TNFα, a cytokine produced by $Ly6C^{hi}$ monocytes and macrophages, and known to be upregulated in endotoxin-stimulated monocytes derived from men [39, 68]. Neutralization of TNFα during intrahepatic infection in male mice led to diminished abscess formation [96]. However, ALA development in female mice is mediated by IFNγ and natural killer T (NKT) cells [95, 98, 99]. Mice lacking all NKT cell subsets ($CD1d^{-/-}$) or mice lacking invariant (i) NKT cells ($J\alpha18^{-/-}$) were dramatically impaired in their ability to control abscess development and parasite load in the liver [99]. This NKT cell-dependent protection in female mice was further confirmed by treatment of infected mice using the potent NKT cell activator α-galactosylceramide (αGalCer) or native *E. histolytica*-derived lipopeptidephosphoglycan (EhLPPG), both of which resulted in a reduction of the liver damage [99]. Accordingly, supplementation of female mice with testosterone reduced the NKT cell-dependent production of IFNγ and decreased the ability of the mice to control abscess development [12]. Moreover, at the steady state, female mice have higher numbers of NKT cells than male mice. This, together with a stronger activation of NKT cells, leads to control of the parasitic infection. However, although the activating role of estradiol on NKT cells is well documented [38], it remains unknown whether these cells express the AR. In humans, iNKT cells from men and women differ in their cytokine profiles, depending on the stimulus. Stimulation with αGalCer led to a significant increase in TNFα and IL-17A production by peripheral NKT cells derived from women compared with men [100].

Taken together, data from the murine model and the correlative human data elucidate our understanding of the influence of androgens on immune cell subsets during parasitic infection. Interestingly, in the case of *E. histolytica* infection, androgens exert an immunosuppressive effect on NKT cells by inhibiting their production of IFNγ, which reduces the ability of the host to control the parasitic infection. However, androgens also exert an immune stimulatory effect on monocytes by increasing their release of TNFα, which exacerbates tissue destruction and abscess development [96].

The male bias in leishmaniasis

Similarly to amebiasis, leishmaniasis is induced by a protozoan parasite, but in contrast to *E. histolytica*, *Leishmania* species are obligate intracellular pathogens. Depending on the *Leishmania* species, the infection shows a wide range of clinical manifestations. Cutaneous leishmaniasis (CL) is characterized by large lesions of the skin that can leave disfiguring scars. This form of leishmaniasis is caused by *Leishmania (L.) major*, *L. braziliensis*, and *L. mexicana.* Visceral leishmaniasis (VL) is caused by *L. donovani* and causes splenomegaly,

hepatomegaly, progressive anemia, and prolonged fever [101]. Interestingly, *L. infantum* is able to cause both forms of leishmaniasis and appears in the Old World as well as in the New World [102]. Leishmaniasis is endemic in 97 countries that are mainly located in tropical and subtropical regions, with one billion people living at risk in these affected areas. More precisely, 65 countries are endemic for both CL and VL, ten countries are endemic for VL only, and 22 countries are endemic for CL only [103].

Leishmania species are naturally transmitted via the bite of sandflies of the genus *Phlebotomus* (Old World) or *Lutzomyia* (New World). As a result, the promastigote form is transmitted to the host, where it is phagocytosed by dendritic cells or macrophages. Here, the parasite differentiates into its amastigote stage and starts to multiply intracellularly until the infected cell bursts and the parasite is released, allowing new cells to be infected. The lifecycle of the parasite is completed when another sandfly bites an infected host and ingests *Leishmania*-infected blood [101].

The general consensus is that a T_H1 response, driven by IL-12 expression from macrophages and DCs, protects against *Leishmania* infection. IL-12 is a potent inducer of IFNγ from innate and adaptive immune cells. IFNγ enhances the activity of inducible nitric oxide synthase (iNOS), and NO production results in microbicidal action against this intracellular parasite [104]. Many studies in different geographical regions have shown that men are more frequently infected than women, independent of the parasite species [105–107]. In an animal model, the sex bias towards males for leishmaniasis could be reverted with the administration of testosterone to females; by contrast, administration of estradiol to males did not affect the sex bias. The same report showed significantly higher levels of typical T_H2 cytokines such as IL-4, IL-10, and TGFβ at the site of the lesion in male animals [108]. Furthermore, the fact that the sex difference in *Leishmania* infection appears after puberty [109] gives rise to the assumption that sex hormones may play a crucial role in modulating the immune response to *Leishmania* infection. Consistent with this hypothesis, androgens showed an effect on the development of leishmaniasis in murine models [2, 110]. Sanchez-Garcia and colleagues discovered that DHT directly influences *L. mexicana* promastigote development in bone marrow-derived macrophages (BMMs), leading to enhanced parasite replication and an increased infection rate, with increased parasitic survival [111]. Moreover, testosterone inhibits the apoptosis of *L. donovani*-infected BMMs [112]. However, the immune response of *L. donovani*-infected BMMs was affected by testosterone, which downregulated the p38 MAPK pathway, leading to increased survival of the parasite, even though testosterone did not inhibit the p38 MAPK pathway directly [113]. In conclusion, androgens seem to have an influence on *Leishmania* infection, but the exact mechanisms are not fully understood. Moreover, the fact that there are many different *Leishmania* species with different clinical manifestations that depend on both age and sex makes it especially difficult to generalize the role of steroid hormones during leishmaniasis.

Impact of androgens in helminthiasis

Infections with helminths do not necessarily cause clinical symptoms, but under circumstances not fully understood, the parasitic worm can lead to immunologic symptoms, malnutrition, and anemia. Due to the variety of helminth species, including cestodes (tapeworms), trematodes (flukes), and nematodes (roundworms), the manifestation of symptoms is highly diverse. This review will focus on nematode infections, as the role of androgens in parasitic worm infection has been well-studied in this helminth species. The basic life cycle of nematodes can be separated into two phases, the pre-parasitic phase and the parasitic phase. The pre-parasitic phase starts with the release of eggs from the infected host into the external environment. Outside of the host, the nematode passes through several larval stages until it matures into its infectious form. The pre-parasitic phase can occur in the external environment as well as in a secondary host, called an intermediate host, before the parasite re-infects its original host, in which it develops into its adult form, comprising separate male and female parasites. Sexual reproduction occurs in the infected host and finishes with the release of fertilized eggs [114].

Epidemiological studies have shown that men are more susceptible to infection with nematodes such as *Necator americanus* than women [115–117]. Even though it is widely believed that the sex bias in humans is due to sex-related differences in exposure rather than differences in susceptibility, several studies in rodents showed the same bias towards males [118–121]. Infection with nematodes leads to tissue damage, which in turn induces an immune reaction in the host. The first immune response to gastrointestinal nematodes is the degranulation of mast cells and the presentation of nematode antigens by antigen-presenting cells in the regional lymph nodes. In particular, a T_H2 response is induced during nematode infection, leading to secretion of the cytokines IL-4, IL-5, IL-10, and IL-13, which further enhances eosinophil degranulation and the development of antibody-producing plasma B cells [122]. A special feature of nematodes is the ability to actively modulate the immune response against the infection, including via the production of immunosuppressive proteins [123] or cysteine protease inhibitors called cystatins that inhibit the cell surface expression of peptide-presenting MHC II [124]. Nevertheless, androgens have an immune modulatory effect in nematode infection, as illustrated by a decreased *Strongyloides venezuelensis* load in gonadectomized male rats and an increased parasite load in testosterone-treated female rats [120]. Consistent with this, *Nippostrongylus brasiliensis*--infected male rats had a stronger prevalence of infection accompanied by more intense symptoms. Tiuria and colleagues

Table 1 Sex-biased parasitic infections and the effect of androgens on disease

Disease	Parasite	Sex bias	Sex-associated immune response	Androgen influence on disease
Amebiasis (ALA)	*Entamoeba histolytica*	M > F	↑ IFNγ in females[95] ↑ TNFα in males[96]	T: ↑ ALA in female mice[12] Castration: ↓ ALA[12]
Leishmaniasis	*Leishmania* species	M > F	↑ IL-4, IL-10, TGF-β in males[107]	T: ↑ lesions in female hamsters[108] T: ↑ survival of *L. donovani*[113] DHT: ↑ *L. mexicana* replication, infection rate, and survival[111]
Helminthiasis	i.a. Nematode species	M > F	NS	T: ↑ *S. ratti* recovery in females[119] Castration: ↓ *S. venezuelensis* parasite load[120] T: ↑ parasite load in female rats[120] T: ↓ goblet cell function and proliferation[118]

ALA amebic liver abscess, *BMMs* bone marrow-derived macrophages, *DHT* dihydrotestosterone, *T* testosterone, *NS* not studied

documented a negative effect of testosterone on goblet cell function and proliferation, which in turn led to delayed expulsion of the parasitic worm [118]. In a further study, treatment of female mice with testosterone during *Strongyloides ratti* (*S. ratti*) infection led to increased recovery of the parasite. Interestingly, blocking macrophages in the same setting led to the same result, suggesting a link between androgens and macrophages during *S. ratti* infection [119].

Conclusion

Parasitic infections are not only influenced by the age and health of the host but also by its sex. The different levels of steroid hormones in men and women modulate immune responses differently within the context of different infectious diseases. Since the immune reaction to each type of parasitic infection is unique, it is challenging to generalize the effect of steroid hormones on immune cells during infection. In this review, we have focused on the effects of androgens on different cells of the immune system (Fig. 2) and the known immunologic effects of androgens during three specific parasitic infections (Table 1).

The three parasitic infections discussed in this review show a clear male bias in humans that is independent of any cultural or social behavior. They exhibit the same sex bias in the respective animal model, in contrast to many other studies investigating sex differences in diseases. In particular, androgen treatment reverses the initial sex bias in these models. Monocytes and macrophages are major representatives of the innate immune system and play an important role in the defense mechanisms against invading pathogens. In amebiasis, leishmaniasis, and helminthiasis, these innate immune cells appear to be involved in the development of the male bias. In amebiasis, monocytes and macrophages contribute to *E. histolytica*-dependent destruction of the liver tissue via the induction of immunopathological processes. In leishmaniasis, macrophages are, among others, target cells for leishmania parasites. Furthermore, their ability to control intracellular parasite replication is influenced by androgens. In *S. ratti* infection, again, macrophages are fundamentally involved in the parasite control. Blockade of macrophages and simultaneous treatment with testosterone led to an additive increase of the parasite burden. However, the direct link between macrophages and androgen modulation needs further investigation in this infection model.

Given that monocytes and macrophages express both ARs, outline these cells as potent targets of androgen-dependent immune modulation and therefore they can be considered to be at least partially responsible for the sex bias in the discussed parasitic infections. For the identification and characterization of further hormone-sensitive cells, responsible for the development of the sex difference in respective diseases, the implementation of representative animal models will be of crucial benefit. Additionally, the elucidation of the molecular mechanisms in hormone and immune cell interaction, would give new insights for the understanding of the development of sex-differences in immune responses.

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