Biological Differences Between the Sexes and Susceptibility to Tuberculosis

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Globally, far more men than women have tuberculosis. Although the cause of this bias is uncertain, epidemiological factors have historically been considered the driving force. Here, we discuss evidence that biological differences between the sexes may also be important and can affect susceptibility to mycobacterial infection. We discuss the possible underlying mechanisms, with particular focus on how sex hormones modulate the immune responses necessary for resistance to tuberculosis. Studying these differences may provide valuable insight into the components that constitute an effective immune response to this deadly pathogen.

Keywords. tuberculosis; gender; male-bias; sex hormones; immunity.

Tuberculosis, caused by *Mycobacterium tuberculosis*, is among the leading causes of death from infectious disease. In 2012, approximately 8.6 million people were infected with *M. tuberculosis,* and 1.3 million died from tuberculosis, including 320 000 coinfected with human immunodeficiency virus (HIV). An estimated one third of the world's population has latent *M. tuberculosis* infection (LTBI), and approximately 10% of those will develop active disease in their lifetime. The spread of tuberculosis requires the tubercle bacillus, a susceptible host, and an environment that facilitates transmission. Therefore, any risk factor for tuberculosis must increase exposure, susceptibility, or both. HIV infection is a major risk factor, increasing an individual's risk of active tuberculosis to 10% per year, due to the increased host susceptibility resulting from the virus's impact on both innate and adaptive immunity. Other risk factors for tuberculosis include malnutrition, smoking, alcoholism, overcrowding, silicosis, diabetes, poverty, and male sex [1]. While the mechanism behind the association between HIV infection and tuberculosis risk has been well studied, the relationship between male sex and tuberculosis risk is less clear and is likely to involve a highly complex network of factors, as discussed below.

GENDER BIAS IN TUBERCULOSIS

Infectious diseases rarely affect males and females equally [2], and tuberculosis is no exception. Worldwide tuberculosis notification data for 2012 show a male-to-female ratio of 1.9:1. This is not a new phenomenon, having first been observed during the turn of the 20th century in New York, where the ratio of male-to-female mortality due to tuberculosis approached 2:1 [3], and during the 1950's in rural Wales, where radiographic surveys showed a male-to-female disease ratio of 2.1:1 [4]. The degree of male bias varies by geographic location and by year, but the overall trend is clear, and of the 20 high-burden countries for which data are available, the median male-to-female ratio is 1.8:1, with only Afghanistan reporting a ratio of <1:1 (WHO report 2013; http://www.who.int/tb/publications/global_report/en/.).

EPIDEMIOLOGICAL EFFECT OR ARTIFACT?

It is often suggested that male bias in tuberculosis is an artifact of systematic underreporting and underdiagnosis of tuberculosis in women. However, a meta-analysis of 29 surveys conducted in 14 countries found a concordant strong male bias in both notification rates and prevalence rates, strongly suggesting that access to healthcare is not a confounding factor [5]. In addition,

DOI: 10.1093/infdis/jiu147

male bias exists in countries without apparent differences in health-seeking behavior between the sexes [6].

Reporting bias can also be addressed by tuberculosis surveys. A multicenter case-control study in West Africa found male-to-female ratios of 2.03:1 among cases, compared with roughly even sex ratios among both household contacts and community controls, showing sex-related underdiagnosis to be unlikely [7]. A randomized household prevalence survey of >260 000 individuals in Bangladesh found a male bias (male-to-female ratio, 3:1), despite equal participation of women [8]. Finally, while studies have shown that women may be more difficult to diagnose because of factors such as poorer-quality sputum samples [9], male bias is retained in studies that rely on radiographic diagnosis [4, 10], a technique exempt from such confounding factors [9]. Taken together this suggests that, while differences in reporting and diagnosis may affect the data in some settings, they are unlikely to explain the consistent global trend for male bias in tuberculosis. The next question then is why are men more likely to get tuberculosis then women?

BEHAVIOR AND PHYSIOLOGY

Two major, but not mutually exclusive hypothesis have been put forward to explain sex bias in infectious diseases, the behavioral and the physiological. [2]. The behavioral hypothesis relates primarily to sex-specific exposure to infection, while the physiological hypothesis posits that biological differences between the sexes render one more susceptible to a given disease. What is the evidence for each hypothesis in the case of tuberculosis?

Behavior
Gender can affect *M. tuberculosis* exposure because of differences in social roles, risk behaviors, and activities. Males may travel more frequently; have more social contacts; spend more time in settings that may be conducive to transmission, such as bars; and engage in professions associated with a higher risk for tuberculosis, such as mining [1, 11]. On the other hand, household contact with an infected individual is a strong tuberculosis risk factor [7] in both high and low-middle income countries [12]. Despite spending less time in the home, men remain at higher risk than women of acquiring tuberculosis from a household contact [13].

Gender differences in other risk factors may indirectly influence the male-to-female ratio of tuberculosis. In high-burden countries, smoking is much more frequent in men than in women, and a correlative analysis of cigarette smoking, sex, and tuberculosis suggests that smoking might explain up to one-third of the gender bias observed in this setting [14]. Alcohol consumption is also a risk factor for tuberculosis, and the prevalence in low-income countries among men is much higher than that among women. However, other risk factors show opposite trends. The strongest risk factor for tuberculosis is concurrent HIV infection, and while approximately half of HIV-infected people globally are women, in sub-Saharan Africa 60% are women, and in South Africa >70% aged 20–30 years are women. Despite the high prevalence of HIV infection among South African women in this age group, however, incidence of tuberculosis remains higher in men.

In summary, it is highly likely that behavioral or epidemiologic factors play a significant role in tuberculosis acquisition, and some of these, such as smoking, alcohol consumption, and mine-related silicosis, have a strong male bias. However, other risk factors, such as shared household contact and HIV infection, are not male biased. Therefore, although these epidemiological factors are of vital importance, the overall contribution to the gender bias in tuberculosis is difficult to assess. An alternative way to address this issue is to determine whether there is evidence that physiology can contribute to the increased risk of tuberculosis in men.

Physiology
Animal models, which are largely free of confounders related to exposure and diagnosis, have been used to address the contribution of physiological factors to sex bias in tuberculosis. Historical data are somewhat conflicting. In the 1940s, Izzo and Circado found that castration of both male and female guinea pigs enhanced tuberculosis survival and reduced caseation [15]. However, other experimentalists at the time reported no effect of sex on resistance to tuberculosis in either rabbits or guinea pigs [16]. More recently, male mice were shown to be more susceptible to infection with *Mycobacterium intracellulare* and *Mycobacterium marinum* and developed more-severe disease, with the severity reduced among those that were castrated [17]. Conversely, female mice were more resistant to infection, and treatment of females or castrated males with testosterone increased their susceptibility. In addition, mice that have undergone ovariectomy are more susceptible to *Mycobacterium avium*, but the susceptibility is mitigated by estradiol therapy [18]. Finally, the progesterone contraceptive Depo-Provera impairs control of *M. tuberculosis* in mice [19]. In a more natural setting, it was found that rates of bovine tuberculosis in brushtail possums were an order of magnitude higher in males than females [20] and that castration reduced tuberculosis rates among males by half but doubled tuberculosis rates among females. Clearly, one has to be cautious when extrapolating any of these findings to human tuberculosis, but they suggest that gonads may influence mycobacterial disease in mammals.

Limited but nonetheless interesting parallels can be found in humans. A unique study of patients in an American institution for the mentally ill found that only 8.1% of medically castrated men (297) died from tuberculosis, compared with 20.6% of intact males (735) and 15.8% of intact female inmates (883) [21]. Conversely, a study of 142 young Swedish women who underwent medical oophorectomy because of advanced salpingitis found that 7% died of tuberculosis, compared with a

tuberculosis mortality rate of 0.7% for the country as a whole [22]. Additionally, pulmonary disease due to *M. avium* complex is most commonly observed in postmenopausal women [18].

A recent Brazilian study examining sex bias in 10 major pathogens observed not only the characteristic male bias in tuberculosis (1.9:1), but also that, although tuberculoid leprosy is slightly more common in females (0.85:1), the severe lepromatous form is heavily male biased (2.94:1) [2]. The immune response to leprosy is very similar to that to tuberculosis, with lepromatous disease being analogous to active tuberculosis and tuberculoid leprosy representing cured or contained disease [23]. Crucially, both diseases are caused by the same pathogen, and thus male bias for the tuberculosis-like lepromatous disease is highly unlikely to result from differences in exposure. Taken together, these data support the hypothesis that physiological differences between males and females can influence the susceptibility to tuberculosis.

PHYSIOLOGICAL MECHANISMS

Physiological explanations for the male bias in tuberculosis susceptibility include X-linked genetics and differences in the immune response, in anatomy, and in nutrition. Anatomy and nutrition have been reviewed elsewhere [24] and will not be discussed here.

X-Marks the Spot

Nine genes are known to be associated with Mendelian susceptibility to mycobacteria disease (MSMD), of which 2, IKBKB and CYBB, are X-linked and thus essentially only observed in males. Although these polymorphisms are rare and unlikely to underlie general male susceptibility in tuberculosis, they highlight the abundance of immune-related genes on the X chromosome and their potential impact on tuberculosis immunity. The X chromosome contains approximately 1100 genes, the majority of which are immunomodulatory [25], compared with only 100 or so on the Y chromosome. In females, 1 X chromosome in each cell is randomly inactivated to prevent gene-dosing effects, and females are thus chimeras of both the maternal and paternal X chromosomes they inherit. As a result, females always express the beneficial X-linked polymorphisms inherited and are less vulnerable to deleterious mutations. Males, on the other hand, are at the mercy of the X chromosome inherited from their mother. This is exemplified by X-linked Toll-like receptor 8 (TLR8) gene polymorphisms, which have been linked with susceptibility to tuberculosis [24, 26], particularly in male children [26]. In addition, females can benefit from gene-dosing effects, as approximately 15% of X-linked genes escape silencing, resulting in the increased expression of certain gene products [27]. This, in fact, goes beyond genes, as the X chromosome is now known to be particularly rich in micro-RNAs (miRNAs) as well, containing 112, compared with 2 on the Y chromosome.

These can also escape silencing, and many of them are immunomodulatory [28]. The importance of skewed expression of X-linked genes and miRNAs in tuberculosis is a largely undefined but nonetheless exciting area for further research.

Immune Responses

As a general rule, females exhibit more-robust immune responses to antigenic challenges, such as infection and vaccination, than males [25]. This is mediated to a large extent by sex hormones, the role of which in tuberculosis is supported by the fact that the male bias does not arise until puberty [10]. Sex hormones have diverse effects on many immune cell types, including B cells, T cells, neutrophils, dendritic cells, macrophages, and natural killer cells [25]. Although there are no direct studies, many of the key aspects of the tuberculosis immune response are modified by both male and female sex hormones. The cells types thought to be important in tuberculosis are shown in Figure 1, along with a summary of published data indicating how male and female sex hormones can influence the function of these immune cells in ways that may have relevance to mycobacterial control.

T-helper Type 1 (Th1) Immune Response

A robust Th1 immune response, characterized by production of interferon γ (IFN-γ) and tumor necrosis factor α (TNF-α), is vital to the control of tuberculosis, whereas a Th2 profile, as driven by helminthic infections, is detrimental [29]. In general, testosterone is thought to downregulate the Th1 response, whereas estrogen is believed to enhance it. In reality, the effects of sex hormones on the Th1/Th2 balance are more nuanced. Low levels of 17B-estradiol, for example, promote Th1 differentiation and production of cytokines such as TNF-α, while high levels promote Th2 polarization, with a consequent effect on cytokines [25]. Regulatory $CD4^+$ T cells (Tregs) are also known to fluctuate significantly with changing hormone levels during the menstrual cycle [25]. An excess Treg response may prevent effective clearance of the bacilli [30] but may also play a role in limiting tissue damage [29].

The importance of the Th1 cytokines IFN-γ, interleukin 12 (IL-12), and TNF-α in tuberculosis is clear from animal models and, in humans, from both the existence of MSMD-susceptibility polymorphisms in these loci and the detrimental effect of anti–TNF-α therapy on tuberculosis progression [29]. It is also highlighted by recent work on leprosy, showing that susceptibility to the tuberculosis-like lepromatous disease is a result of interleukin 10 (IL-10)–mediated inhibition of the protective IFN-γ–driven macrophage vitamin D antimicrobial response [23]. Estrogen is known to stimulate secretion of INF-γ (plus TNF-α and IL-12) and inhibit production of IL-10 [31], while testosterone increases IL-10 secretion and reduces IFN-γ secretion [32]. Vitamin D levels themselves have been directly correlated with tuberculosis resistance in humans [29], and estrogen
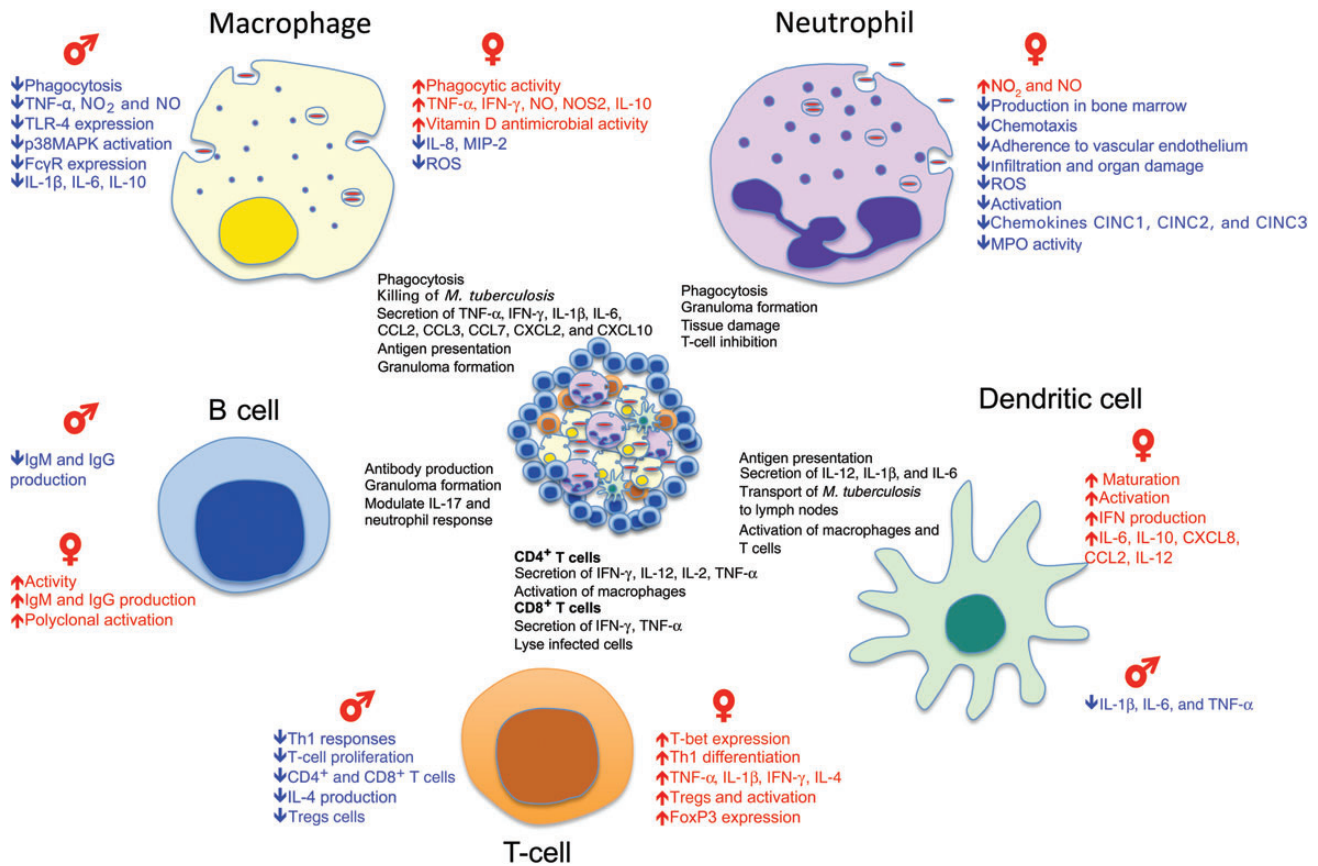
Figure 1. How sex hormones might modulate the immune response to *Mycobacterium tuberculosis*. Most, if not all, immune cells express specific receptors for sex hormones and are responsive to changes in hormone levels [25]. Included are the main cell types thought to contribute to the immune control of *M. tuberculosis*, here depicted by a stereotypical tuberculosis granuloma. The role of each cell type is highlighted, along with how these functions may be modulated by sex hormones, indicated here by male and female symbols, but typically referring to either estrogen and progesterone (for females) or testosterone (for males). Abbreviations: CINC, cytokine-induced neutrophil chemoattractant; IFN-γ, interferon γ; IgG, immunoglobulin G; IgM, immunoglobulin M; IL-1β, interleukin 1β; IL-2, interleukin 2; IL-4, interleukin 4; IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; IL-12, interleukin 12; IL-17, interleukin 17; MIP-2, macrophage inflammatory protein 2; MPO, myeloperoxidase; NO, nitric oxide; NOS, nitric oxide synthase; ROS, reactive oxygen species; Th, T helper cell; TLR, Toll-like receptor; TNF-α, tumor necrosis α; Treg, regulatory CD4+ T cell.

is known to directly modulate the immunological effects of vitamin D [33]. What effect this has on the antituberculosis activity of vitamin D is unknown.

Macrophages

Macrophages are central to the control of tuberculosis, not least through the direct killing of *M. tuberculosis* bacilli by activated macrophages. At a simple level, estradiol is thought to enhance macrophage activation [24], while testosterone downregulates it by reducing TLR4 expression [25]. However, as with the Th1/Th2 balance, the effects of sex hormones on macrophages are probably more nuanced. Apoptotic death of *M. tuberculosis*–infected macrophages is important for control of the infection. Where necrotic cell death promotes bacterial growth, apoptotic cell death limits bacterial growth and enhances the generation of a protective Th1 response [29, 34]. The balance between

apoptotic and necrotic cell death is regulated by the activity of prostaglandin (PGE2; proapoptotic) and lipoxin A4 (LXA4; pronecrotic) [29]. Sex hormones may influence this balance, as progesterone increases PGE2 production by monocytes, while testosterone inhibits it [35]. On the other hand, testosterone can also limit the synthesis of LXA4 through downregulation of arachidonate 5-lipoxygenase, the master enzyme involved in all leukotriene synthesis [36]. The role of sex hormones in regulating the overall balance of PGE2 and LXA4 and the effect of this on *M. tuberculosis*–induced apoptosis/necrosis remains to be investigated. In addition to modulating cell death, *M. tuberculosis* appears to avoid macrophage killing by inducing a shift toward a nonbactericidal M2 phenotype [37]. In wound healing, estrogen actually seems to promote an M2 phenotype [38], while progesterone appears to inhibit some M2 pathways and augment others [39]. However, the effect of sex hormones

on alveolar macrophage polarization at the site of *M. tuberculosis* infection is unknown. Recent elegant work shows a complex and sex-specific link between gut microbiota, testosterone, and M2 polarization [40]. With growing understanding of the lung microbiome, it will be fascinating to see if there is a sex-specific interaction between lung microbiota and the immune system that could modulate tuberculosis control, possibly by skewing macrophage polarization.

Neutrophils

There is growing interest in the role of neutrophils in the pathology of tuberculosis. Neutrophils rather than macrophages are thought to be the dominant infected cell type in pulmonary tuberculosis [41], and microarray profiling of subjects with active tuberculosis reveals a neutrophil-driven type I IFN signature [42]. Additionally, mice lacking IFN-γ or its receptor show heightened susceptibility to *M. tuberculosis* infection due to pathogenic accumulation of neutrophils in the lung [43]. The finding that tuberculosis risk is inversely correlated with neutrophil count [44], however, suggests that neutrophils are not all bad, and in vivo studies in Zebra fish show that neutrophils reduce the *M. tuberculosis* burden through phagocytosis of infected macrophages and subsequent killing of *M. tuberculosis* via NADPH oxidase-dependent mechanisms [45]. Neutrophils are thus a good example of a growing concept in tuberculosis immunology, the so-called goldilocks effect, in which protection derives from just the right level of a given immune response, with both too much and too little being detrimental.

Do sex hormones modulate neutrophils? Infection of mice with *Streptococcus pneumoniae* has a strong gender bias, with males showing substantially reduced survival and greater pathology due to excessive neutrophil accumulation in the lung [46]. In addition, neutrophil recruitment into the lung and subsequent inflammation in response to lipopolysaccharide is higher in males and in female mice that underwent ovariectomy, and reduced in males to the levels seen in female mice by administration of estradoil [47]. The mechanisms behind these observations are unclear but may involve the inhibitory effect of high levels of estradiol on production of CXCL-8, CXCL10, and CCL2 [48]. Neutrophil recruitment can also be modified by miRNAs. Recent work shows that miRNA-223 downregulates CXCL2 and CCL3 in neutrophils and thus limits their recruitment. Deletion of miRNA-223 renders resistant mice highly susceptible to *M. tuberculosis* infection because of excessive neutrophil accumulation in the lung and subsequent tissue damage [49]. As miRNA-223 is located on the X chromosome, females may therefore have higher levels due to incomplete gene silencing, which could reduce the pathological accumulation of neutrophils. Aside from recruitment, neutrophil activation (at least in response to trauma) also appears to be greater in males and is potentiated by testosterone and limited by estrogen

[50]. In females, the action of progesterone and estrogen causes decreased spontaneous neutrophil apoptosis ex vivo, compared with males [51].

Finally, In addition to these direct effects, recent human and mouse data suggest that neutrophil-derived suppressor cells are present in the tuberculosis granuloma and exacerbate disease by inhibiting T-cell responses [52, 53]. Although not directly analogous, an increased risk of skin cancer in males is linked to greater accumulation of similar GR1, CD11b double positive suppressor cells in the skin of male mice and may be influenced by estrogen [54]. What effect, if any, sex hormones may play in the development and recruitment of this suppressive neutrophil subset to the lung in tuberculosis is unknown.

SUMMARY

It is clear that much work remains to be done to understand the relationship between sex and tuberculosis. The difference between the immune response of men and women is not black and white. However, it is also increasingly clear that neither is immunity to tuberculosis. If the secret to successful immune control of this deadly pathogen lies in hitting the goldilocks zone of not too little and not too much, then the often subtle influence of sex hormones could well play a key role of determining this. Taking gender and the influence of sex hormones into account may help us gain a better understanding of the immune response required to keep tuberculosis at bay. This knowledge will aid the development of future therapies and may be important when evaluating the effectiveness of vaccines and other immunological interventions.

Notes

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