Commentary

Immunomodulatory role of sex steroids in tuberculosis disease

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Abstract

Tuberculosis is more prevalent in males than in females. This Sex difference is majorly seen in adults, which indicates involvement of sex steroids in immunity. Despite the presence of other factors for the presence of this sex difference evidences showed that sex hormones play important role in modulating immune response through manipulating expression of inflammatory and anti-inflammatory cytokines. Thus, understanding immunomodulatory role of sex steroids in tuberculosis disease could provide important insight for developing new treatments, biomarkers and finding vaccine targets..

Keywords: Sex steroid; Tuberculosis; Immunity

Description

Tuberculosis (TB) is a global health care problem caused by Mycobacterium tuberculosis (MTB).There are more cases of TB in males as compared to females with 2:1 ratio. Majority of individuals infected with TB develop latent infection which is characterized by absences of clinical sign and symptoms and only 5-10 % of those with latent infection will develop a disease.

Immune response to against bacterial, viral, and parasitic infections is accompanied by altered hormonal response. TB is associated with different type of altered endocrine hormones. Interaction between endocrine and immune system affects the outcome of immune response against infectious diseases like TB in which there is a prolonged interaction between the immune system and the pathogen. Evidences showed that in response to an infection, cytokines produced by immune cells, can activate endocrine hormones which in turn affects the inflammatory process. This interaction is due to the presence of common receptors on hormone producing and cytokine producing cells.

TB exhibits a strong male-bias, with a sex ratio of two males to every female. This Sex difference is majorly seen in adults. Although definitive cause of this bias is unknown biological differences between the sexes are shown to affect susceptibility to mycobacterial infection. Sex hormones such as testosterone and estradiol may play a role for sex bias in TB. Testosterone has been shown to impair production of proinflammatory cytokines, on the other hand production this cytokines is induced by estrogen. Therefore, this review assessed immunomodulatory role of sex steroids in tuberculosis disease.

Sex hormones and Immunity

In addition to their role in reproduction and sexual differentiation sex hormones has role in immune system. Evidences showed that sex hormones play important role in modulating immune response through manipulating expression of inflammatory and anti-inflammatory cytokines, including toll-like receptors (TLRs) expression and antibody production. Sex hormones exert their function by binding to either specific intracellular receptors that act as ligand-dependent transcription factors (classical mechanism) or membrane receptors that stimulate several signal transduction pathways (non-classical mechanism).

Different animal and human studies showed immune response modulation by sex hormones both physiologically and pathologically. Experimental study done in mice showed that testosterone reduce the activity of natural killer (NK) cells. Testosterone has been shown to decrease macrophage and monocyte Toll-like receptor 4 (TLR4) expressions which is important in innate immune responses. Additionally, its effect in inhibiting synthesis of proinflammatory cytokines and promoting synthesis of anti-inflammatory cytokines as interleukin (IL)-10 shows its role in decreased immune response seen in males as compared to females.

On the other hand presence of estrogen receptors in different immune cells enables estrogens interact with immune cells and modulate target genes expression in immune cells. In opposite to testosterone function estradiol enhances NK cell cytotoxicity and promotes proinflammatory cytokines such as IL-1, IL- 6, and tumor necrosis factor alpha (TNF-α) synthesis. Estradiol

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also inhibits IL-4, IL-10 production.

Sex hormones and TB disease

Experimental studies suggested that androgen deprivation due to the castration of male mice leads to an increase in the absolute number of T lymphocytes in the peripheral lymph nodes and an increase in the proliferation of these cells following antigen recognition. On the other hand Invariant natural killer T-cells (iNKT) from female mice produce more IFN-y than to cells from male mice in response to in vivo challenge with iNKT cell li- gand α-Galcer.

In humans proinflammatory cytokines produced during infections affects the hypothalamic pituitary gonadal axis. Even though there are limited studies done on the role of sex hormones in TB disease there are some studies that try to assess profile of sex hormones in TB patients. In experimental study done in Mexico in 2015 which aimed to investigate how pro-inflammatory cytokines affect production of gonadal androgens in TB patients showed that Patients has decreased levels of testosterone in presence of high amounts of Luteinizing hormone, together with augmented IFN-y, IL-6 and Transforming growth factor beta (TGF-β) levels. In addition in this study in vitro treatment of Leydig cells with these cytokines led to a remarkable reduction of testosterone production.

On the other hand in a comparative study done in Turkey in 2016 on 68 subjects (38 TB patients and 30 healthy controls) to determine interaction between TB and female hormone levels in post-menopausal women revealed increased level of estrogen in TB patients (n=38) as compared to Healthy controls. Another study done in 2017 in South Africa by Kleynhans and his colleagues on 37 TB patients also shows increased estradiol concentration and decreased testosterone level in TB patients. Del Rey et al also showed reduced amounts of testoster- one and modest increases in the concentration of estradiol accompanied by increased levels of IFN-Υ, IL-10, IL-6 in TB patients as compared to healthy controls. This alteration of sex hormones during TB disease suggests that sex hormones might involve in immune response to MTB and therefore the course of the disease.

Conclusion

Global control of TB can only be achieved through the development of effective vaccines, improved diagnostics, and novel and shortened therapeutic regimens. This is achieved through understanding of role different biological factors like sex steroids in tuberculosis immunology. Evidences of hormones role as immunomodulators could be a factor for sex difference in TB, however there are only few studies done in this area, Therefore large scale longitudinal study of immuno-endocrine interaction is required to have full picture on the role of sex hormones in TB immunology.

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Conflict of Interest

We have no conflict of interests to disclose and the manuscript has been read and approved by all named authors.