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Sex Hormones and Bacterial Infections

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1. Introduction

Epidemiological and experimental data suggest the association of gender and sex with susceptibility and severity of infectious diseases (Moss, 2005). Gender and sex likely affect viral and parasitic infectious diseases (Morales-Montor *et al.*, 2004; Fish, 2008; Snider *et al.*, 2009). Here we will review the effect of gender and sex on bacterial infectious diseases (sepsis, mycobacterial diseases and Q fever). We will differentiate gender and sex by considering that gender refers to differences determined by cultural and societal factors and sex refers to the biological differences between males and females (Fish, 2008). Indeed, variables such as poverty, occupational status and marital status affect differently men and women in different countries (Theobald *et al.*, 2006), leading to different risks of exposition to infectious pathogens and accesses to efficient treatment. This is illustrated by the decreased prevalence of tuberculosis in industrialized countries associated with socio-economic changes including reduced malnutrition and overcrowding, improved sanitary conditions in the workplaces before the use of chemotherapy (Davies *et al.*, 1999). Sex-based differences in the susceptibility to pathogens include what is due to chromosome effect and sex hormones. Thus, it is critical to delineate the respective roles of gender and sex on bacterial infections. The present review focuses on four features of the association between sex and bacterial infections with a special attention for bacterial sepsis, mycobacterial infections and *Coxiella burnetii* infection.

2. Epidemiological approach of susceptibility to bacterial infections

Epidemiological data show that the susceptibility to bacterial infectious diseases is unequally distributed in men and women. In sepsis, an infectious process associated with systemic inflammatory response syndrome, large-scale studies reported higher incidence in men than in women (Angus *et al.*, 2001; Martin *et al.*, 2003; Pietropaoli *et al.*, 2010). Men also develop more frequently sepsis episodes among patients with trauma (Osborn *et al.*, 2004; Wafaisade *et al.*, 2011) or acute kidney injury (Lopes *et al.*, 2010). In addition, men are over-

represented among patients with respiratory infections (Esper *et al.*, 2006) or bloodstream infections (Laupland *et al.*, 2004) (Table 1).

Reference	**Number of patients**	**Patient selection**	**Sepsis incidence**	**Sepsis: Sex effect**	**Mortality: Sex effect**
Angus *et al*. 2001	6,621,559	All	3/1000	Men *vs.* Women 2.83 vs. 2.87 /1000	Men *vs.* Women 29.3 vs. 27.9%
Martin *et al*. 2003	750 million hospital admissions	All	1.3%	Men 1.28 [1.24 to 1.32]	Men *vs.* Women 22.0 vs. 21.8%
Osborn *et al*. 2004	30,303	Trauma	2%	Women 0.65 [0.49 to 0.86]	Women 0.76 [0.66 to 0.88]
Laupland *et al*. 2004	9,266	Positive blood culture	15.7/100,000 /year	Men *vs.* Women 17.7 vs. 13.5 / 100,000/year	No listed as independent risk factor
Esper *et al*. 2006	930 million hospitalizations	All	1.3% of all hospitalizations	Men 1.27 [1.24 to 1.30]	Men *vs.* Women 20.1 vs. 21.0%
Pietropaoli *et al*. 2010	Unknown	All	Unknown	Men *vs.* Women 54 vs. 46%	Men *vs.* Women 33 vs. 35% (p = 0.01)
Lopes *et al*. 2010	Unknown	Acute kidney injury	Unknown	Men *vs.* Women 72.5 vs. 27.5%	Men 1.1 [0.5-2.3]
Wafaisade *et al*. 2011	29,829	Trauma	10.2%	Men 1.81 [1.61 to 2.03]	Unknown

Table 1. Gender effect in epidemiological studies (Result are expressed as either absolute number, percentage, or relative risk and 95% confident interval as required (and available in the original study))

In the context of infectious diseases due to intracellular bacteria, such as tuberculosis (*Mycobacterium tuberculosis*) (Che & Antoine, 2011), Q fever (*C. burnetii*) (Tissot Dupont *et al.*, 1992; Anderson *et al.*, 2009) and Legionnaires' disease (*Legionella pneumophila)* (Campese *et al.*, 2011), men represent the majority of patients (Table 2).

Infection due to intracellular bacteria	**Sex ratio**	**Reference**
Tuberculosis	1.4	Che & Antoine, 2011
Q fever	2.4	Tissot-Dupont, 1992
Legionnaires' disease	2.9	Campese, 2011

Table 2. Epidemiological data show that males and females are differently affected by bacterial infections. The reasons that explain this difference in susceptibility to and/or severity of the disease may be multiple. They include different risks of pathogen exposure, social behavior associated with gender such as smoking or drinking and biological parameters such as sex hormones.

With respect to Q fever, the male-to-female ratio of patients admitted to hospital is 2.45 in adults (Tissot Dupont *et al.*, 1992). The rate of Q fever-related complications is higher in males than in females (Raoult *et al.*, 2000). Men represent 75% patients diagnosed as having *C. burnetii* endocarditis (Houpikian & Raoult, 2005), the most severe manifestation of chronic Q fever. Note that females have fewer symptoms during pregnancy (Tissot-Dupont *et al.*, 2007).

In contrast to susceptibility to bacterial infections, studying the role of sex in the mortality provided contrasting evidence. Some epidemiological studies did not report any gender differences in sepsis-related death (Crabtree *et al.*, 1999; Martin *et al.*, 2003; Laupland *et al.*, 2004; Esper *et al.*, 2006) whereas other found either increased mortality in men (Osborn *et al.*, 2004; Melamed & Sorvillo, 2009; Wafaisade *et al.*, 2011) or women (Combes *et al.*, 2009; Pietropaoli *et al.*, 2010; Nachtigall *et al.*, 2011). As men are also at increased risk of death due to trauma, cancer and cardiovascular diseases as compared with women, the analysis of epidemiological data should integrate these potential biases (Micheli *et al.*, 2009; Pinkhasov *et al.*, 2010; Coronado *et al.*, 2011).

The literature provides evidence that sex hormones may account for the differences of susceptibility to bacterial infections and their prognosis between men and women. The production of sex hormones evolves with aging, suggesting that susceptibility to infection will change along the life. In adults, the widest difference in sepsis incidence occurs between 25-30 years of age when sex hormones play a key role in the sexual dimorphism (Angus *et al.*, 2001). In elderly patients, sepsis tends to occur later in women than in men (Martin *et al.*, 2003). Most studies show that the infection distribution is similar in children independently of sex (Tissot Dupont *et al.*, 1992; Rose *et al.*, 2001; Odetola *et al.*, 2007). No difference is found in young boys and girls with Q fever (Maltezou & Raoult, 2002) or with tuberculosis (Che & Antoine, 2011).

Whether sex hormones govern the susceptibility to and the severity of bacterial infections, infection modulates the amounts of sex hormones. In patients with sepsis (Christeff *et al.*, 1988; Fourrier *et al.*, 1994; Majetschak *et al.*, 2000) or tuberculosis (Bottasso *et al.*, 2007; Rey *et al.*, 2007) circulating levels of estrogens are increased whereas those of testosterone dramatically fall. It has been also found that increased levels of estrogens are especially marked in males with sepsis (Fourrier *et al.*, 1994; Majetschak *et al.*, 2000). In addition, high circulating levels of estrogens seem efficient predictors of death in sepsis (Christeff *et al.*, 1988; Dossett *et al.*, 2008; May *et al.*, 2008). The mortality of elderly patients with severe infections is related to increased estradiol levels in both men and women, whereas increased testosterone levels are found in females who do not survive (Angstwurm *et al.*, 2005).

Pregnancy represents a remarkable model for investigating the effect of sex hormones on the development of infectious diseases. Indeed, the developing placenta produces human chorionic gonadotrophin that stimulates the ovaries to supply higher levels of estrogen and progesterone. It is well known that pregnancy is associated with listeriosis. Pregnant women with listeriosis account for 27% of all listeriosis cases and 60% of listeriosis cases among 10-40 years old persons (Lorber, 1997). Less spectacular is the case of Q fever. The primo-infection to *C. burnetii* during pregnancy increases the risk to develop a chronic evolution of the disease with potential fatal evolution (Carcopino *et al.*, 2009). The true incidence of sepsis or severe sepsis in parturient women is difficult to assess in part because the standard criteria used for sepsis identification are not effective to predict sepsis during pregnancy (Lappen *et al.*, 2010).

The analysis of epidemiological data indicates that male gender predisposes to develop sepsis and chronic bacterial infectious diseases whereas women are relatively protected. Although sex hormones seem to be critical in the sex dimorphism, we have to integrate other variables related to the host such as chromosomal factors and exposure to bacterial pathogens.

3. Sex hormones and experimental models of bacterial infection

The use of experimental models of infection was the easiest approach to study the role of sex hormones in bacterial infections; the availability of castrated animals with or without hormonal substitution has been largely contributive.

3.1 Experimental endotoxemia

Endotoxemia may be experimentally reproduced by the administration of lipopolysaccharide (LPS) to animals or human volunteers. LPS are present in the outer membrane of Gram-negative bacteria and act as endotoxins inducing strong inflammatory response in animals. Females produce a more vigorous pro-inflammatory response than males as demonstrated by higher circulating levels of Tumor Necrosis Factor (TNF) (Trentzsch *et al.*, 2003). The effect of sexual dimorphism in the outcome of endotoxemia depends on LPS dose. The intraperitoneal administration of low doses of LPS (5 mg/kg) to C57BL/6 mice leads to a lower survival of males compared to females (Laubach *et al.*, 1998) whereas the administration of higher doses (12.5 mg/kg) leads to similar mortality in males and females.

The study of the role of sex hormones in this dimorphism has benefited from the modulation of hormonal context. First, the circulating levels of TNF are higher in castrated C57BL/6 male mice than in intact males treated with LPS (Trentzsch *et al.*, 2003), suggesting that testosterone may reduce TNF production. Reinforcing this hypothesis, the LPS-induced response observed in castrated mice is reduced after testosterone treatment, regardless of sex (Spinedi *et al.*, 1992; Torres *et al.*, 2005). Second, the intraperitoneal injection of LPS in ovariectomized females is associated with reduced levels of TNF, interleukin (IL)-6, and IL-10 as compared with intact females. This is accompanied by the reduced macrophage expression of Toll-like receptor (TLR)-4, a pattern recognition receptor interacting with LPS (Rettew *et al.*, 2009). The role of estrogens in LPS response has been shown by complementation of castrated mice with sex hormones. Indeed, ovariectomized animals receiving exogenous 17β-estradiol showed higher TNF levels after endotoxin challenge than untreated gonadectomized or intact animals. In addition, peritoneal macrophages isolated from ovariectomized mice receiving 17β-estradiol replacement bind LPS more efficiently than untreated animals because of upregulated expression of CD14 and TLR-4 (Rettew *et al.*, 2009). Finally, the administration of 17β-estradiol to castrated C57BL/6J male mice increases the circulating levels of LPS-induced TNF production, as compared with control male or female mice (Trentzsch *et al.*, 2003). These findings should be analyzed according to the genetic background of the animals. Castrated males react differently according to the mouse strain (A/J, DBA/2J, AKR/J, BALB/cJ) (Trentzsch *et al.*, 2003; Torres *et al.*, 2005) after LPS challenge.

In contrast to estrogen treatment, the exogenous treatment of mice with progesterone-containing implants fails to increase circulating levels of LPS-binding protein, cell surface levels of CD14 on peritoneal macrophages or total TLR-4 content in macrophages (Rettew *et*

al., 2009). The role of testosterone appears variable according to the experimental conditions. Orchiectomy does not alter the mortality of wild-type male mice but, after orchiectomy, increased mortality is observed in knockout (KO) male mice that are phenotypically normal but lack the ability to produce increased nitric oxide during endotoxemia. This increased mortality in orchiectomized KO males is prevented by the administration of exogenous testosterone (Laubach *et al.*, 1998), demonstrating that exogenous testosterone is potentially protective for the host when nitric oxide production is deficient. This experiment also suggests that testosterone may play a different role in healthy individuals and patients in severe conditions.

In humans, 30 young volunteers including 15 males and 15 females received 2 ng/kg LPS. The females were studied in the follicular phase and nine of them used oral contraceptives. During endotoxemia, the decrease in blood pressure is more pronounced in females than in males. Norepinephrine sensitivity remains unchanged in females but decreases in males, suggesting that the clinical picture is more evident and the response to treatment is more effective in females than in males. The administration of LPS results in increased circulating levels of TNF, IL-6, interferon (IFN)-gamma and IL-10 in males and females, but TNF and IFN-gamma levels are significantly higher in females than in males (van Eijk *et al.*, 2007). This study suggests that the hypotension that likely occurs earlier in females than in males may be related to a more marked immune response to LPS administration.

Taken together, murine models of LPS-mediated inflammation and endotoxemia in humans highlight the role of estrogens, and testosterone to a lesser extent, in host responses to LPS and TLR-4 activation.

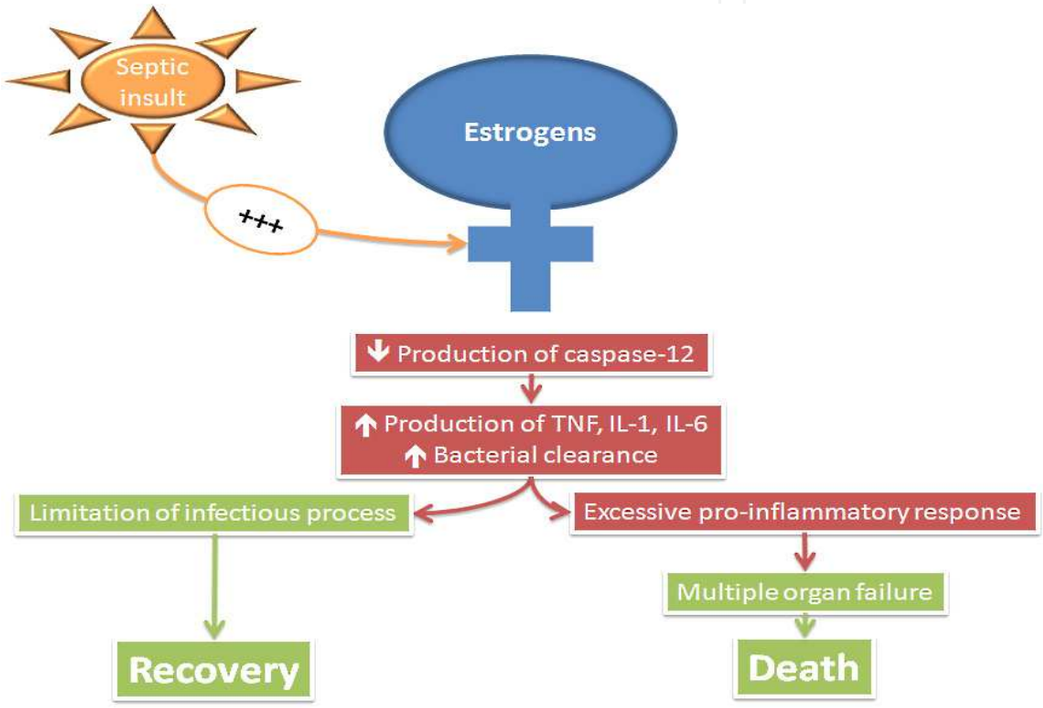
3.2 Mouse model of sepsis

The models of sepsis using cecal ligation and puncture (CLP) seem to be more accurate than those using LPS injection (Dyson & Singer, 2009). The most frequent scenario used to evaluate the effect of sex is a two-hit model consisting of hemorrhages followed by sepsis. Male and proestrus female C3H/HeN mice are subjected to hemorrhage or sham operation and to polymicrobial sepsis by CLP twenty-four hours after. Animals subjected to hemorrhage followed by CLP show depressed splenocyte and macrophage functions as compared with sham animals (Angele *et al.*, 1997). After CLP, females have lower mortality than males, irrespective of prior hemorrhage or sham operation. Unlike males, hemorrhages do not increase the mortality rate in females (Diodato *et al.*, 2001).

Female sex hormones likely play a major role in protection against CLP sepsis. Indeed, after CLP, the mortality of ovariectomized CBA/J mice is significantly higher than in intact mice. Ovariectomy results in a decreased production of IL-1 and IL-6 by splenic and peritoneal macrophages, but the production of IL-1 and IL-6 by macrophages from intact female mice is maintained after trauma-hemorrhage (Knöferl *et al.*, 2002). Thus, in septic conditions, female sex hormones protect female mice by producing increased levels of pro-inflammatory cytokines.

The modulation of estrogen receptors is a convenient way to study the role of estrogens in sepsis models. In a CLP model, multiple oral doses of a nonsteroidal selective estrogen receptor-beta agonist increase survival of mice, decrease systemic bacteremia, reduce peritoneal IL-6 and TNF levels. Interestingly, the estrogen receptor-beta agonist provides a comparable level of protection in both males and females (Cristofaro *et al.*, 2006). On another

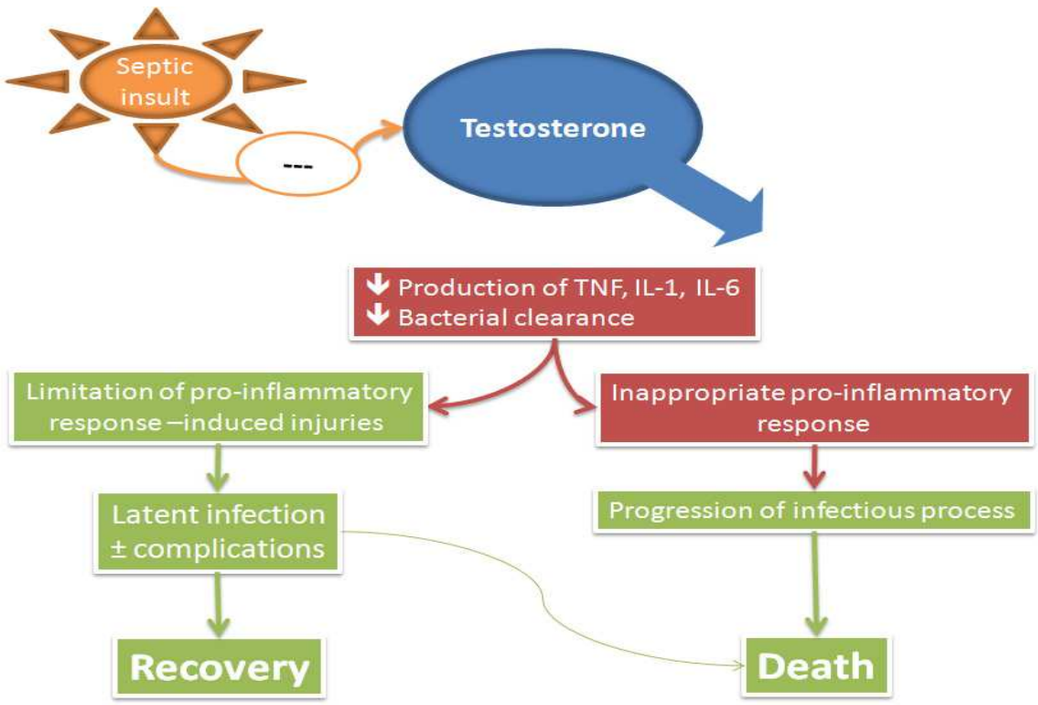
hand, the administration of an estrogen receptor alpha agonist entirely prevents the rise in plasma IL-6 and IL-10 levels induced by a sequence of trauma-hemorrhage whereas the administration of an estrogen receptor beta agonist is only in part effective. Similar conclusions can be drawn from experiments at the cell level. The effects of an estrogen receptor beta agonist on Kupffer cells, splenic macrophages, alveolar macrophages and peripheral blood mononuclear cells following trauma-hemorrhage are less pronounced than that of an estrogen receptor alpha agonist (Dienstknecht *et al.*, 2004). In all cases, the beneficial effects of 17β-estradiol are limited to tissue-fixed macrophages, suggesting the compartmentalization of host response (Suzuki *et al.*, 2007). In figure 1, we hypothesized possible mechanisms for explaining the dual role of estrogens in sepsis.



Estrogens reduce the production of caspase-12 and then increase that of pro-inflammatory mediators. This is associated either with a rapid limitation of the infectious process leading to fast recovery or with the occurrence of multiple organ failure related to an excessive pro-inflammatory response leading to death. Note that sepsis induces a positive feedback on estrogen production. (IL: interleukin, TNF: tumor necrosis factor).

Fig. 1. Interaction between estrogens and host response

Testosterone has detrimental effect on survival of male mice by attenuating immune response. Indeed, after CLP, the survival rate of male mice treated with flutamide, an androgen receptor blocker, is higher than that of vehicle-treated mice. Flutamide treatment also restores splenocyte proliferation and IL-2 release as well as the release of IL-1 by splenic macrophages (Angele *et al.*, 1997). The effect of testosterone on experimental sepsis may be controlled by IL-10. Indeed, after CLP early IL-10 treatment is associated with increased survival of males, but not of females (Kahlke *et al.*, 2000). In figure 2, we hypothesized possible mechanisms for explaining the role of testosterone in sepsis.



Testosterone decreases the intensity of the pro-inflammatory response, resulting in an inappropriate response to septic insult, progression of the infectious process and death. In some cases, the limitation of an excessive pro-inflammatory response may appear beneficial by limiting the occurrence of multiple organ failure. This can lead to a latent infection with infectious complications, resulting in either death or recovery. Note that sepsis induces a negative feedback on testosterone production. (IL: interleukin, TNF: tumor necrosis factor).

Fig. 2. Interaction between testosterone and host response

3.3 Infection by extracellular bacteria

Pseudomonas aeruginosa is one of the predominant Gram negative bacteria responsible for pulmonary infection in intensive care units (Leone *et al.*, 2007). The role of gender is not specifically reported in epidemiological studies although men are more prone to develop lung infection than women (Leone *et al.*, 2007). The importance of sex hormones has been assessed in a model of C57BL/6 mice challenged to pulmonary infection with *P. aeruginosa*. At variance with other models, the weight loss, bacterial load and inflammatory mediators in the lungs are higher in females than in males. The number of bacteria found in the lungs of IL-10-deficient males is higher than that observed in wild type males. These findings clearly show that female mice are more susceptible to *P. aeruginosa* lung infection than males and that IL-10 modulates host response to infection as described above in sepsis models (Guilbault *et al.*, 2002).

On the other hand, *P. aeruginosa* is the predominant bacterium found in the course of cystic fibrosis. Importantly, the outcomes are worse for cystic fibrosis women infected with *P. aeruginosa* as compared with men (Demko *et al.*, 1995). A mouse model has been dedicated to investigate the effect of gender on cystic fibrosis. The administration of exogenous estrogen to adult cystic fibrosis males with *P. aeruginosa* pneumonia leads to more severe manifestations of inflammation in both lung tissue and bronchial alveolar lavage fluid.

Inflammatory infiltrates are increased as determined by histological studies. The inflammatory response is accompanied by an increased lung tissue expression of both IL-23 and IL-17 (Wang *et al.*, 2010). Thus, sex hormones modulate *P. aeruginosa* infection with a marked inflammatory effect of estrogens.

3.4 Infections by intracellular bacteria

3.4.1 Mycobacterial infections

As tuberculosis occurs more frequently in males than in females, the effect of sex should be a common feature of mycobacterial infections. Male mice infected by *Mycobacterium marinum* are more susceptible than female mice in terms of mortality, incidence of gross skin lesions and bacterial load in lungs and spleen. The castration of males improves their resistance to infection and this effect is substantially reversed by continuous testosterone treatment. The testosterone treatment also increases the susceptibility of females to *M. marinum* infection, demonstrating that testosterone is partly responsible for the increased susceptibility of mice to *M. marinum* infection (Yamamoto *et al.*, 1991). In DBA/2 female mice infected with *Mycobacterium avium*, the number of bacilli in the lungs of infected mice increased after ovariectomy, suggesting a protective effect of female sex hormones. The treatment of ovariectomized mice with exogenous 17β-estradiol reduces the burden of bacilli to the level found in sham-operated mice. Estrogens enhance the bacteriostatic activity of IFN-gamma against *M. avium* via increased nitrite production by macrophages (Tsuyuguchi *et al.*, 2001). These findings show that estrogens enhance the host protection against mycobacterial infections but testosterone is detrimental.

3.4.2 *C. burnetii* infection

From the epidemiological data in which mature adult men are more at risk to develop Q fever than women (Tissot-Dupont *et al.*, 2007), we showed that sex hormones play a role in the occurrence and the severity of *C. burnetii* infection. In C57BL/6 mice infected with *C. burnetii*, bacterial load and granuloma numbers are lower in females than in males and are increased in ovariectomized females to levels similar to those found in males. The treatment of ovariectomized mice with 17β-estradiol reduces both bacterial loads and granuloma numbers (Leone *et al.*, 2004), demonstrating that estrogens control *C. burnetii* infection. To analyze the differences between males and females, intact and castrated mice have been infected with *C. burnetii* for 24 hours, and gene expression has been measured in liver cells using whole-genome microarrays. The expression of a total of 2,777 probes is specifically modulated by *C. burnetti* infection. Surprisingly, 86% of them are differentially expressed in males and females. Castration of males and females shows that sex hormones are responsible for more than 60% of the observed gene modulation, and this effect of sex hormones is most pronounced in males. Using functional annotation of modulated genes, four clusters have been identified as enriched in males. These clusters are related to cell-cell adhesion, signal transduction, defensins and cytokine/Jak-Stat pathways (Textoris *et al.*, 2010). A major cluster of modulated genes has been identified in females consisting of the circadian rhythm pathway with positive (Clock, Arntl) and negative (Per) limbs of a feedback loop. Clock and Arntl are down-modulated whereas Per is up-regulated. These changes may be associated with efficient bacterial elimination in females but not in males, in which the immune response would be inefficient.

4. Infectious diseases associated with pregnancy

The pregnancy is characterized by dramatic changes in sex hormones with decreased estrogen and increased progesterone levels. Estrogens and progesterone are known to affect the susceptibility to pathogens likely through the modulation of the immune responses. Indeed, pregnancy is a transient period of tolerance in which the prevention of fetus rejection increases the susceptibility to intracellular bacteria (Munoz-Suano *et al.*, 2011). Several examples of infectious diseases will illustrate this statement.

In humans, Q fever is frequently asymptomatic in pregnant women but it may result in increased risk to develop a chronic form of the disease (Carcopino *et al.*, 2009). Female BALB/c mice have been infected with *C. burnetii* through the intraperitoneal route before repeated pregnancies over a 2-year period. Persistent infection associated with abortion and perinatal death is observed in these mice. The occurrence of endocarditis on native valves, which characterize chronic Q fever following *C. burnetii* infection during pregnancy, has been observed in some infected pregnant mice (Stein *et al.*, 2000).

Pregnancy is a risk factor for typhoid infection (Olubuyide, 1992). After an infection challenge with *Salmonella enterica* serovar Typhimurium, the splenic bacterial load is markedly increased in pregnant mice compared with non-pregnant mice (Pejcic-Karapetrovic *et al.*, 2007). The increased bacterial load is related to sex hormones since a three-day treatment of virgin mice with 1 mg/day of estrogen increases their susceptibility to an intraperitoneal bacterial challenge as compared with control mice. In contrast, a three-day treatment of virgin mice with 1 mg/day of progesterone is associated with increased survival time (Kita *et al.*, 1989). It is likely that progesterone improves the resistance of mice by increasing the influx of peritoneal cells after infection whereas estrogen affects the acute inflammatory responses (Kita *et al.*, 1989).

Listeriosis is an infection that occurs in about 30% of cases in pregnant women (Lorber, 1997). The impact of sex hormones on the course of the disease has been especially well described. Exposure to diethylstilbestrol, a synthetic nonsteroidal estrogen, precipitates a dramatic increase in *Listeria* susceptibility. To assess the interplay between diethylstilbestrol, sex hormones and immune response, *L. monocytogenes* has been intravenously administered to C3H/HeSlc female and male mice treated with diethylstilbestrol. The delayed-type hypersensitivity response is suppressed in females treated with diethylstilbestrol but not in males. After castration, a diethylstilbestrol-induced suppression is also observed in males. Testosterone inhibits this diethylstilbestrol-induced suppression (Kato *et al.*, 1988). Another report shows that the administration of estradiol or diethylstilbestrol is associated with an increased mortality of female B6C3F1 mice infected with *L. monocytogenes*. This effect of estradiol or diethylstilbestrol is due to their estrogenic activity since compounds such as 5α-dihydrotestosterone or progesterone with little or no estrogenic activity do not affect the mortality of infected mice (Pung *et al.*, 1984). Female C3H/He mice treated with exogenous doses of estrogen have been inoculated with *L. monocytogenes* by the intraperitoneal route. On days 3, 5 and 7 after infection, the bacterial load in spleen and liver is higher in estrogen-treated mice than in control mice (Salem *et al.*, 1999). Note that the sensitivity of mice to infection is highly dependent on the genetic background since the C57BL/6 mice are 100 times more resistant to intravenously injected *L. monocytogenes* than BALB/c mice, due to the action of a single gene, Lr (Mandel & Cheers, 1980). Taken together, these experimental studies demonstrate the role of sex hormones in the context of materno-fetal tolerance and susceptibility to intracellular bacteria.

5. How sex hormones affect bacterial infection?

Although epidemiological analysis and experimental models of infection provide convincing evidence of the role of sex hormones in host susceptibility to bacterial pathogens, the mechanisms used by sex hormones to modulate the susceptibility of hosts to pathogens are poorly understood. It is likely that sex hormones target immune cells according to their critical role in host defense (Fish, 2008). It is known that estrogens, androgens and glucocorticoids influence a large proportion of cell transcriptome (Duma *et al.*, 2010) and interact with specific receptors on immune cells. Cell-mediated and humoral immune responses represent the adaptive part of the immunity and are usually associated with the clearance of intracellular pathogens. Females exhibit robust cell-mediated and humoral immune responses after infectious challenge or vaccination as compared with males (Bouman *et al.*, 2005). This is partly related to changes in T cell distribution. Women have higher $CD4^+$ T cells number than men, which accounts for the robustness of adaptive immune responses. In addition, the numbers of regulatory T cells (Treg) that shape immune responses vary during the ovarian cycle: the Treg number increases during the follicular phase of menstrual cycle when estrogens are high and decreases during the luteal phase when estrogens are low (Arruvito *et al.*, 2007). The increase in Treg number during the pregnancy is essential for materno-fetal tolerance but favors the occurrence of infectious diseases due to intracellular pathogens (Belkaid & Tarbell, 2009). Hence, estrogens appear as regulators of $CD4^+$ T cell subsets; they also affect the Th1/Th2 equilibrium known to be essential in the control of bacterial infections. Indeed, it is clearly demonstrated that estrogens and progesterone favor Th2 cell responses during the third trimester of pregnancy (Munoz-Suano *et al.*, 2011). Low doses of estrogens are associated with Th1 cell responses that support microbicidal responses via IFN-gamma production; the effect of estrogens seems to be related to increased expression of t-bet, a master regulator of Th1 differentiation. In contrast, high doses of estrogens promote Th2-cell responses known to interfere with antibacterial immunity (Fish, 2008). Estrogens affect antibody production via their action on B cells; they decrease the negative selection of immature B cells and increase the survival of autoreactive B cells and polyclonal activation of B cells (Grimaldi *et al.*, 2002; Verthelyi, 2001). This is consistent with increased levels of autoimmune diseases in women (McCombe *et al.*, 2009), but it is not demonstrated that estrogen-mediated increased humoral response to pathogens is due to a direct effect on B cells. In contrast to estrogens, the effects of androgens such as testosterone on adaptive immune response are suppressive, which accounts for decreased T- and B-cell proliferation, immunoglobulin and cytokine production (Fish, 2008). This may explain why men are more susceptible than women to infectious agents because of the inability to mount efficient adaptive immune response.

Sex hormones may also affect the innate immune response that is the first line of defense against pathogens and that is necessary to shape adaptive immune response. Monocytes and macrophages are cell effectors of innate anti-infectious immunity and support inflammatory responses. The number of circulating monocytes is higher in men and women after the menopause than in fertile women (Bouman *et al.*, 2004). The effects of estrogens on monocytes and macrophages are suppressive but have to be analyzed according to the context. They likely act on CD16 promoter, leading to downmodulated CD16 expression and decreased production of proinflammatory cytokines (Kramer *et al.*, 2004). Inflammatory cytokines such as TNF and IL-1 are modulated during the ovarian cycle: low doses of estrogens are associated with increased production of TNF and IL-1 as compared with high

doses of estrogens (Bouman *et al.*, 2005). The role of estrogens in inflammation has been assessed in sensitized mice with LPS. LPS elicits transcriptional activation of inflammatory genes in microglial cells. Their expression is inhibited in the brain from ovariectomized mice (Soucy *et al.*, 2005). On another hand, testosterone exerts a suppressive effect on monocytes and macrophages likely by decreasing the expression of TLR-4 (Rettew *et al.*, 2008). This is more ambiguous in vivo. Castration of male mice strikingly accelerates wound healing and dampens associated inflammatory response. Similarly, systemic treatment with flutamide depresses inflammatory response (Ashcroft & Mills, 2002). Other cells involved in the innate immune response are likely targeted by sex hormones. Indeed, the activity of neutrophils and natural killer cells is suppressed by estrogens (Fish, 2008). Estrogens regulate the differentiation of dendritic cells from bone marrow precursors to conventional dendritic cells producing IL-12. The treatment of mature splenic dendritic cells with estrogens leads to the expansion of IFN-gamma-producing dendritic cells (Bengtsson *et al.*, 2004).

The impact of sex hormones on adaptive immunity may explain the generally superior ability of females to deal with and to be protected from infections, but their effect on innate immunity clearly depends on hormone doses, explaining the differences between in vitro and in vivo data. This is related to the stress system that has potent action on inflammatory and immune responses (Chrousos, 2010).

6. Conclusion

Although it is difficult to separate biological factors from social and economic factors, the epidemiological studies have shown that the sexual dimorphism may explain the differences in the susceptibility to and/or the severity of bacterial infections between men and women. The use of experimental models of infection demonstrates the role of sex hormones in this sexual dimorphism. Sex hormones target the immune system known to be essential in the host response to infection and, in turn, can be modulated by infection. While estrogens induce efficient cell-mediated and humoral immune responses necessary to bacterial clearance, androgens are rather suppressive. The pregnancy is an excellent model of the interplay between hormonal and immune systems and it teaches us that hormonal control of immune responses varies with time. It would be essential in the future to examine the sex-based differences in immune responses in humans likely by using tissue bio-banks and high throughput methods.

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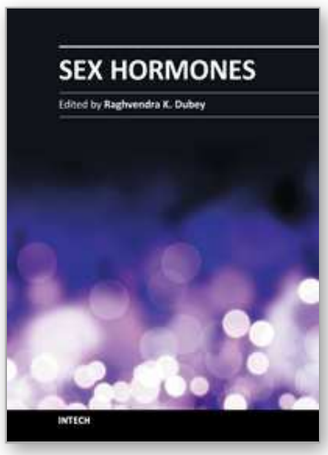
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Sex Hormones not only regulate reproductive function, but they also play a prominent role in the biology and physiology of several organs/tissues and in the pathophysiology of several diseases. During the last two decades, the information on the mechanisms of action of sex hormones, such as estrogens and androgens, has rapidly evolved from the conventional nuclear receptor dependent mechanisms to include additional non-nuclear, non-genomic and receptor-independent mechanisms. This highlights the need to update the current knowledge on sex hormones and their mode of action. Increasing evidence that exogenous/epigenetic factors can influence sex hormone production and action highlights the need to update our knowledge on the mechanisms involved. This book provides a systematic and updated overview of the male/female sex-hormones and their impact in the biology and physiology of various organs. Additionally, the book discusses their positive and negative association with the pathophysiology of various diseases (e.g. osteoporosis, cardiovascular-disease, hypogonadism, reproduction, cancer) and their therapeutic potential.

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