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Review

Sex differences and estrogen modulation of the cellular immune response after injury

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Abstract

Cell-mediated immunity is extremely important for resolution of infection and for proper healing from injury. However, the cellular immune response is dysregulated following injuries such as burn and hemorrhage. Sex hormones are known to regulate immunity, and a well-documented dichotomy exists in the immune response to injury between the sexes. This disparity is caused by differences in immune cell activation, infiltration, and cytokine production during and after injury. Estrogen and testosterone can positively or negatively regulate the cellular immune response either by aiding in resolution or by compounding the morbidity and mortality. It is apparent that the hormonal dysregulation is dependent not only on the type of injury sustained but also the amount of circulating hormones. Therefore, it may be possible to design sex-specific therapies to improve immunological function and patient outcome.

Keywords: Estrogen; Testosterone; Macrophage; Neutrophil; T cell; Injury; Burn; Trauma–hemorrhage; Cytokines; Immunity; Inflammation

1. Introduction

There is extensive evidence in the literature for a sexual dimorphism in the immune response leading to differences in a wide array of disorders ranging from susceptibility to autoimmune disorders to mortality following injury or infection [1–8]. During the reproductive years, females have a more robust humoral and cellular immune response compared to males [2]. This is reflected in observations showing that females possess a more developed thymus, higher antibody concentrations, and a greater capability to reject tumors [9]. Physiologic levels of estrogen, like those seen during the estrus/menstrual cycle, stimulate the immune response, whereas high levels of estrogen such as those found during pregnancy are suggested to down-regulate cell-mediated immune responses [9]. Estrogen receptors are found in reproductive tissue, as well as certain immune cells including T cells, monocytes, and macrophages [10–16]. Direct estrogen-mediated modulation of immune cell activity includes changes in cytokine production, as well as cell activation and proliferation. Following trauma, including burn and hemorrhage, significant differences have been observed in clinical and animal studies which are thought to be due to estrogen's ability to influence the immune response following injury.

2. Changes in the immune response following trauma

Burn and hemorrhagic shock are two major insults that result in immune dysregulation, which can be affected by gonadal hormones. The immune response to injury has

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been described as biphasic and can result in either resolution or death. Early events result in a systemic inflammatory response (SIRS), which is mainly mediated by innate immune cells and the production of pro-inflammatory cytokines. In many patients, a compensatory anti-inflammatory response syndrome (CARS) can develop, which is associated with immune suppression and anti-inflammatory cytokine production [17,18]. This combination of responses can also be complicated with the introduction of an opportunistic infection, described as the two-hit response hypothesis or model [19,20]. The second hit can then increase the risk for multiple organ dysfunction syndrome (MODS) and multiple organ failure (MOF) (Fig. 1). Clinical evidence shows that patients usually succumb to secondary infections rather than their primary injury; this infers that immune function after injury involves biological processes that are highly inefficient [21,22].

Both clinical and animal model studies demonstrate that burn injury leads to an enhanced systemic inflammatory response leading to MODS and MOF. This dysregulated immune response in humans and mice can be characterized by higher levels of interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), prostaglandin E2 (PGE-2), and lower delayed-type hypersensitivity (DTH) response and lymphocyte proliferation [23–25]. A retrospective study in burn patients demonstrated higher mortality in females when compared to males sustaining a similar sized burn injury [26–29]. Consistent with these observations, lower survival rates in female mice compared to males with 15% total body surface area (TBSA) were obtained [30]. Estrogen levels are significantly higher (10-to15-fold over baseline) in females following burn injury [31], whereas concentrations of circulating testosterone are decreased [32,33]. These observations suggest that significantly higher levels of estrogen may lead to improper cell-mediated immune response. This effect is also compounded with the addition of other co-morbidity factors such as alcohol use and age as discussed below.

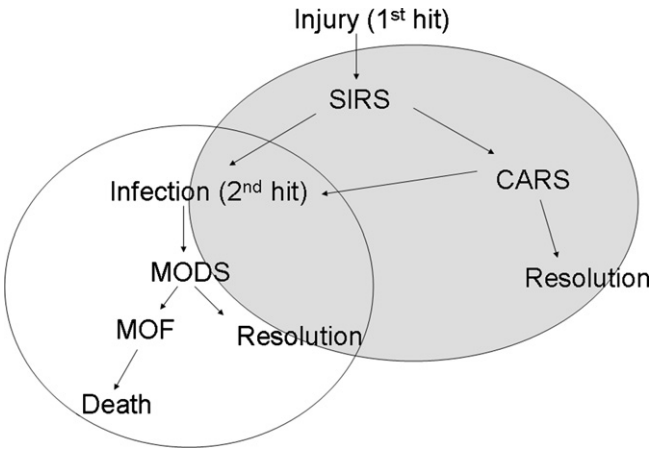

Fig. 1. Schematic of events following injury, with the circles representing innate (filled) and adaptive (open) immune responses. SIRS, systemic inflammatory response syndrome; CARS, compensatory anti-inflammatory response syndrome; MODS, multiple organ dysfunction syndrome; MOF, multiple organ failure.

Hemorrhagic shock is also characterized by an overabundant production of pro-inflammatory mediators which can lead to MODS and death [34]. Estrogen and testosterone can influence immune and cardiac function following trauma–hemorrhage and shock. Immunosuppression following trauma–hemorrhage is observed in males, however, unlike in burn injury, female mice demonstrate an enhanced immune response compared to their male counterparts [35,36] and to ovariectomized (OVX) females, suggesting a protective role of estrogen in this particular injury [37]. Differences in immune function were observed in humans and mice in cases of trauma–hemorrhage with increased incidences of MODS and sepsis occurring in males [38]. In addition, following trauma female patients are less susceptible to sepsis and subsequent multiple organ disorder than males [39]. In a recent clinical study evaluating patients with multiple injuries, it was observed that female patients had a lower incidence of MODS and sepsis. Additionally, the females in this study cohort showed significantly lower levels of IL-6 and interleukin-8 (IL-8) in serum at early time points and lower serum levels of IL-10 at late time points than age-matched male patients [40]. Consistent with these data, animal models show male mice were immunosuppressed, while female mice maintained a functional immune response following sepsis. Not surprisingly, female mice also have a significantly higher survival rate than males after sepsis [41]. Although both injuries display sex differences, the sex with the better outcome is not the same. Interestingly, following trauma–hemorrhage, females fair better than males, while in burn the opposite is true. This disparity in outcome is most likely due to changes in circulating hormones present after injury. Consistent with these observations, treatment of injured mice with the addition or removal of sex hormones affects the morbidity and mortality after injury. These outcomes are summarized in Table 1 and discussed in more detail in the text that follows. While other

Table 1
Effects on Morbidity and Mortality in Different Hormonal Treatment Groups

	Treatment	Burn injury	Trauma–hemorrhage
Male	Intact[@]	Beneficial	Detrimental
	GDX[*,#]	Detrimental	Beneficial
	Estrogen	Beneficial	Beneficial
Female	Intact[@]	Detrimental	Beneficial
	OVX[#]	Beneficial	Detrimental
	OVX + Estrogen	Detrimental	Beneficial

Effects are listed as beneficial or detrimental when compared to the outcome in the opposite sex (@) or compared to the outcome in the intact same sex(#). Male mice depleted of testosterone either by gonadectomy (GDX) or treatment with flutamide are marked with *. Ovariectomized female mice are listed as OVX. Estrogen treatment effects were compared to similarly treated mice given vehicle.