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Critical role of TLR4/FAK signaling pathway in sepsis

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To the Editor:

Han Y et al, wrote an interesting article regarding the crosstalk TLR4/FAK with myocardial suppression after endotoxemia. Despite advances in critical care medicine and use of anti-sepsis therapy, the mortality remains high and the long term outcome is poor for patients that survive sepsis. The severe reality suggests a need for additional therapies to the conventional approach to sepsis, thus, there is an urgent need for effective and safe drugs for the treatment of myocardial sepsis. Toll-like receptor 4 (TLR4) contributes to sepsis pathogenesis and cardiac dysfunction with high mortality in animal model of experimental sepsis. However, the mechanism of TLR4 in sepsis-induced myocardial dysfunction remains unclear. This article will highlight the critical TLR4-mediated sepsis via modulate FAK signaling pathway that lead to pro-inflammatory responses consequences in the myocardial tissue damage.

Keywords: TLR4; FAK; Myocardial dysfunction; Sepsis

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To the Editor:

Sepsis, a serious medical condition that is characterized by an overwhelming systemic response to bacterial infection, can lead to multiple organ failure, shock, and death [1]. Severe sepsis, complicated by acute organ dys-function, is recorded in 10% of all intensive care unit (ICU) admissions and represents the most common cause of death among hospitalized patients in the USA [2]. Heart is one of the most frequently affected organs in complication of sepsis during the sequential development of multiple organ dysfunction [4]. Approximately 50% of the patients who are diagnosed with sepsis exhibit signs of myocardial dysfunction [3, 4]. Although, the molecular and cellular mechanisms that mediate the pathogenesis of septic cardiomyopathy are still unclear, several lines of evidence suggest that myocardial TLR4 plays a major role in myocardial dysfunction [5, 6]. Further, Focal adhesion kinase (FAK) is a potential mediator of cardiomyocyte responses to oxidative and mechanical stress and collagen deposition can affect cardiac compliance and contractility [7]. In this review, we will investigate the evidence that points to a role for TLR4 signaling in the pathogenesis of myocardial sepsis, through its ability to

promote myocardial dysfunction and FAK crosstalk. Activation of TLRs and downstream signaling has important physiological, immunological and pathological significance. Indeed, TLR4 is activated by many different LPS molecules expressed on various Gram-negative bacteria [8]. It is well known that cardiac contractile dysfunction caused by bacterial endotoxin is associated with the production of pro-inflammatory mediators [9]. TLR4 plays a central role in the regulation of endotoxin signaling and endotoxin-induced production of multiple pro-inflammatory mediators [10]. Scientists have observed that endotoxin induces cardiac contractile depression through upregulation of myocardial production of pro-inflammatory cytokines, such as TNF-α and IL-1β. In the previous studies [13], have demonstrated that the activation of TLR4 in IEC-6 cells by LPS inhibits enterocyte migration in a dose-dependent manner leading to the activation of FAK and a subsequent increase in the formation of FAK. Moreover, the finding that human ischemic cardiomyopathy was associated with down-regulation of the muscle selective β1D-integrin and the integrin-activated kinase, FAK supports the possibility that targeting this pathway may be beneficial in the prevention of ischemic human heart failure. Previously demonstrated that cardiac-restricted deletion of FAK exacerbates myocardial injury induced apoptosis and leads to enhanced cardiac decom-pensation following cardiac injury [15, 16]. The fact that FAK silencing was protective against heart collagen deposition underscores the therapeutic potential of FAK targeting by small interfering RNA. Furthermore, several recently developed chemo-therapeutic agents that target receptor tyrosine kinases upstream of FAK, including sunitinib and imatinib, induce myocyte apoptosis and cardiomyopathy [17, 18], it will be of future importance to evaluate whether enhancing FAK activation might also be an effective strategy to preserve myocardial function in this setting. identify a novel TLR4-FAK association in regulating enterocyte migration, and suggest TLR4/FAK as a therapeutic target in this disease.

Competing interests

Authors declare that we have no competing interests.

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