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ITCH puts the brakes on septic cardiomyopathy

Sepsis is a life-threatening condition defined by organ dysfunction that is caused by a dysregulated host response to infection. Septic cardiomyopathy occurs in 10–70 % of patients with sepsis, and is a key contributor to organ dysfunction, further complicating the therapeutic management of sepsis. The molecular mechanisms underlying septic cardiomyopathy remain incompletely understood. Several mechanisms have been proposed, including excessive production of cytokines, reactive oxygen species (ROS), nitric oxide (NO), mitochondria dysfunction, and calcium dysregulation.

Bacterial endotoxins, also known as lipopolysaccharides (LPS), are a major trigger of sepsis that can activate nuclear factor-κB (NFκB)-mediated inflammatory responses. Previous studies have demonstrated that NFκB plays a central role in the development of septic cardiomyopathy through enhanced production of proinflammatory mediators such as TNFα, Interleukin (IL)-1β, IL-6, and iNOS. This notion is supported by the beneficial effects of NFκB inactivation in cardiomyocytes in the setting of LPS-induced cardiac dysfunction [1].

In this issue of *Journal of Molecular and Cellular Cardiology Plus*, Saito et al. described a new mechanism underlying NFκB activation in septic cardiomyopathy, which is linked to the downregulation of ITCH, a HECT domain E3 ubiquitin ligase, in the myocardium [2]. Importantly, ITCH deficiency in immune cells has been associated with persistent activation of NFκB signaling, resulting in augmented inflammation [3]. However, the role of ITCH in cardiomyocytes had not been examined. Here Saito et al. found that ITCH acts as a negative regulator of NFκB in cardiomyocytes in vitro and in vivo. It is postulated that insufficient inhibition of the NFκB pathway due to ITCH downregulation may contribute to the development of septic cardiomyopathy.

Mechanistically, Saito et al. showed that ITCH inhibits NFκB signaling by interacting with TNF receptor associated factor 6 (TRAF6) and TGF-β-activated kinase 1 (TAK1), key components of the NFκB signaling pathway. Upon LPS binding with Toll-like receptor 4 (TLR4), a complex consisting of MyD88 and IL-1 receptor associated kinases (IRAKs) assembles on the cytoplasmic domain of TLR4, which recruits and activates TRAF6 (Fig. 1). TRAF6 functions as an E3 ubiquitin ligase that conjugates K63-linked ubiquitin chains onto itself as well as to other proteins, such as IRAK1. TRAF6 then recruits the downstream kinases TAK1 and IκB kinase (IKK) via K63-linked ubiquitin chains to assemble a signaling complex that facilitates TAK1 and IKK activation. This process requires the TAK1 regulatory subunit TAB2 (or TAB3) and IKK regulatory subunit NFκB essential modulator (NEMO), both of which have ubiquitin-binding functions. Activation of this complex results in the phosphorylation and degradation of IκB and subsequent release of NFκB. NFκB then translocates into the nucleus and induces inflammatory gene expression. Intriguingly, both TRAF6 and TAK1 were markedly downregulated by ITCH in cardiomyocytes, which represents an important mechanism underlying the inhibitory effects of ITCH on NFκB signaling (Fig. 1). However, the detailed mechanism underlying ITCH-mediated downregulation of TRAF6 and TAK1 in cardiomyocytes remains unclear. Moreover, Saito et al. showed that ITCH interacts with other ubiquitin modifying enzymes including A20 and cylindromatosis (CYLD) in cardiomyocytes. Such interactions have also been observed in other cell types such as immune cells. For example, it has been shown that ITCH coordinates with CYLD, a K63-linked deubiquitinase, to promote TAK1 degradation in bone marrow-derived macrophages [4]. Several questions arise from this observation that are open for further investigation. Is A20 or CYLD required for ITCH mediated NFκB inactivation? How do these interactions alter the ubiquitination status and protein turnover of TRAF6 and TAK1? Does the cardioprotective effect of ITCH involve other signaling pathways? Finally, the mechanism underlying ITCH downregulation by LPS in cardiomyocytes needs to be further delineated. Of note, it has been shown that ITCH was downregulated in response to enhanced oxidative stress through auto-ubiquitination mediated protein degradation [5].

An important finding from the study of Saito et al. is that cardiomyocyte-specific overexpression of ITCH improved cardiac function and survival rate in septic cardiomyopathy. This observation suggests that ITCH may represent a potential therapeutic target for septic cardiomyopathy. Given that ITCH downregulation appears to be a key contributor to disease pathogenesis, strategies that promote ITCH activity and/or prevent its degradation may provide cardioprotective effects. Overexpression of ITCH may preserve cardiac function through the inhibition of NFκB activity and subsequent reduced production of inflammatory cytokines such as IL-6. Indeed, it has been shown that systolic dysfunction, inflammation, and apoptosis in septic mice were attenuated by genetic knockout of IL-6. As a limitation of this study, only acute effects were assessed, which showed no significant difference in myocardial macrophage infiltration or cardiac fibrosis between ITCH transgenic and wild-type mice after acute LPS administration (6 h). However, it is possible that ITCH overexpression may limit cardiac inflammation and maladaptive remodeling after prolonged LPS stimulation, which warrants further investigation. Moreover, it is important to further determine whether ITCH exerts its protective effects by targeting additional mechanisms associated with septic cardiomyopathy, such as calcium dysregulation, ROS accumulation, mitochondrial dysfunction, and metabolic changes. Another important question is whether loss of ITCH in cardiomyocytes directly contributes to the pathogenesis of septic cardiomyopathy, which needs to be further examined using ITCH knockout models. As a future direction, it would be important to elucidate the role of ITCH in other cell types such as immune cells, as well as in the setting of different models of heart disease.

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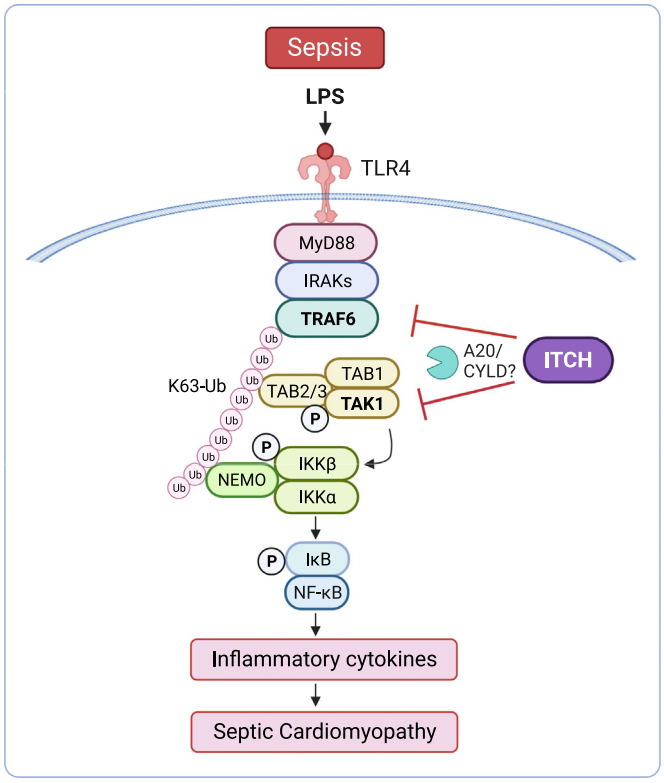

Fig. 1. ITCH attenuates septic cardiomyopathy by inhibiting NFκB signaling. Upon LPS stimulation, TLR4 recruits MyD88, IRAKs, and TRAF6 to assemble a signaling complex, where TRAF6 undergoes K63-linked auto-ubiquitination to recruit and activate downstream kinases TAK1 and IKKs. This process requires the TAK1 regulatory subunit TAB2 (or TAB3) and IKK regulatory subunit NEMO, both of which have ubiquitin-binding functions. Activation of this complex results in phosphorylation of IκB and subsequent activation of NFκB, which promotes the production of inflammatory cytokines, leading to septic cardiomyopathy. ITCH negatively regulates NFκB signaling by targeting TRAF6 and TAK1, possibly in coordination with A20 or CYLD. Myocardial ITCH is downregulated in sepsis though an undefined mechanism, which contributes to an enhanced inflammatory response and septic cardiomyopathy. Created with BioRender.

Overall, key findings made by Saito et al. contribute to our understanding of ITCH-mediated inactivation of NFκB in cardiomyocytes and its functional implications in attenuating septic cardiomyopathy. The finding that the E3 ubiquitin ligase ITCH controls key components of NFκB signaling highlights the importance of ubiquitin signaling in the pathogenesis of heart disease such as septic cardiomyopathy. Whether therapeutic modulation of this ubiquitin dependent signaling pathway provides cardioprotection in heart disease is an exciting avenue for future research.

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