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GSK3β and its Role in Sepsis

Tomeka Subber and Yutong Zhao*

Department of Medicine, The University of Pittsburgh, Pittsburgh, Pennsylvania, USA

***Corresponding author:** Yutong Zhao, Department of Medicine, The Acute Lung Injury Center of Excellence, The University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA, Tel: 412-648-9488; E-mail: zhaoy3@upmc.edu

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Introduction

Sepsis is a leading cause of critical illness and death worldwide. The most recent consensus statement defines this complex clinical syndrome as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [1]. Despite clinical studies that have led to improved quality of care in the management of sepsis, mortality remains high [2]. An unmet need in the field is the development of pharmacologic interventions that target aberrant pathways that cause tissue injury in sepsis. Glycogen synthase kinase-3β (GSK3β), while initially identified in studies of glucose metabolism, has critical roles in apoptosis, cell proliferation, and inflammation (Figure 1). Over the past decade, studies have shown many inflammatory pathways to converge on GSK3β. In experimental models of sepsis, inhibition of GSK3β kinase activity decreases severity of organ dysfunction and reduces mortality. These studies suggest that GSK3β is a promising therapeutic target in the treatment of sepsis.

Figure 1: GSK3β modulates multiple biological functions.

GSK3β as a Central Kinase in Inflammation

GSK3β is a serine-threonine kinase that was first characterized in glucose metabolism [3]. It shares 85% homology with GSK3α, but the C-terminal 76 residues only share 36% identity [4]. Both GSK3α and GSK3β have high basal constitutive activity, but they have divergent functions beyond metabolic pathways [5]. Phosphorylation of Ser9 by upstream kinases such as PI3K-Akt inhibits GSK3β kinase activity (Ser21 on GSK3α), while phosphorylation of Tyr216 (Tyr279 in GSK3α) increases activity (Figure 2) [6,7]. Homozygous GSK3β -/- mouse embryos die from massive hepatocyte apoptosis and liver degeneration [8]. This phenotype is not rescued by expression of GSK3α. Fibroblasts from GSK3β -/- were more sensitive to TNFα-induced apoptosis, and this effect was reversed with neutralizing TNFα antibodies or exogenous expression of GSK3β. Later studies showed parallels between the GSK3β -/- and RelA -/- phenotypes, raising more questions about the role of GSK3β in the regulation of NFκB pathways. GSK3β is required for efficient DNA binding of p65 and expression of IL-6 and MCP-1 in response to TNFα [9]. In contrast, a study by Vines et al. demonstrated that GSK3β had anti-inflammatory effects downstream from NFκB activation in human lung micro vascular endothelial cells after treatment with IL-1β and TNFα [10]. Beurel and Jope showed that STAT3 and STAT5 activation depend on GSK3β kinase activity, but STAT1 and STAT6 activation was not dependent on GSK3β [11]. Evidence suggests that GSK3β serves as a gatekeeper for NFκB activation, modulating expression of pro- and anti-inflammatory genes in a cell type and stimuli-dependent manner.

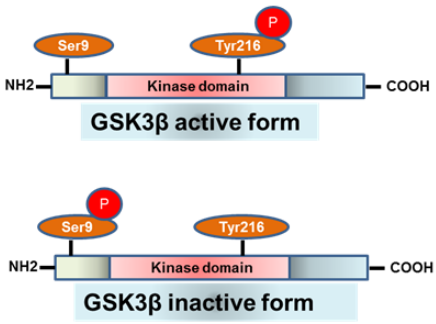

Figure 2: GSK3β activity is regulated by its phosphorylation state.

GSK3β Regulates Toll-Like Receptor Pathway Activation

In sepsis, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) propagate inflammation and tissue injury. These effects are mediated through pattern recognition receptors (PRRs) including toll-like receptors (TLRs). Martin et al. published the first study confirming a central role for GSK3β in TLR signaling [12]. LPS induces PI3K/Akt-mediated Ser9 phosphorylation and inhibition of GSK3β, allowing for augmentation of anti-inflammatory cytokines in human peripheral blood monocytes (PBMCs). Treatment with a GSK3β-specific inhibitor protected mice from endotoxin-induced sepsis and death. GSK3β inhibition in human PBMCs also reduced cytokine production in response to TLR2, TLR4, TLR5, and TLR9 ligands. Subsequent work identified mTORC1 as a negative regulator of GSK3β kinase activity through S6K, and this inhibition decreases LPS-induced proinflammatory cytokine production [13]. The field has since grown in the number of studies exploring how GSK3β regulates downstream signaling after TLR ligand binding. It has been found to be important in TLR3 signaling through its own K63-linked polyubiquitination and

subsequent phosphorylation of TRAF6, allowing assembly of the TRIF complex that is required for TLR3 signaling [14]. In a mouse model infected with a live vaccine strain of *Francisella tularensis*, inhibitory Ser9 phosphorylation of GSK3β occurred in a TLR2-dependent manner in murine macrophages. GSK3β positively regulated NFκB and p65 DNA binding affinity while negatively regulating CREB DNA binding [15]. These effects were reversed by lithium treatment, a known inhibitor of GSK3β [6,16]. These early studies demonstrate a pivotal role of GSK3β in innate immune responses that contribute to the pathogenesis of sepsis [17].

GSK3β Inhibition is an Attractive Therapeutic Target in Sepsis

While GSK3β has been identified as a central kinase in inflammation, translational studies have emerged demonstrating benefits of GSK3β inhibition in animal models of sepsis and organ failure. In a rat model of sepsis, use of selective GSK3β inhibitors reduced LPS-induced liver injury and failure [18]. GSK3β inhibitors decreased severity of illness and improved survival in experimental models of acute lung injury [19,20]. GSK3β kinase activity has also been implicated in organ damage from liver ischemia, often a result of hypoperfusion as seen in septic shock [21,22]. In acute kidney injury (AKI), GSK3β induces apoptosis of renal epithelial cells after ischemic injury and stress [23]. Deletion of GSK3β expression or small molecule inhibition of GSK3β protects mice from AKI both in ischemia-reperfusion models and models of sepsis [24-26]. This data support a role for GSK3β in potentiating end organ damage in sepsis and is an attractive therapeutic target in both prevention of and treatment for organ dysfunction and failure.

Conclusion

GSK3β has become a focal point in research given its multifaceted role in inflammation. More studies are needed to understand how GSK3β activity is dysregulated in the pathogenesis of sepsis and in host immune responses to pathogens. The goal is to tailor therapies for GSK3β-mediated pathways that contribute to uncontrolled inflammation that accelerates organ dysfunction and failure in sepsis. It remains to be seen if the studies of small molecule inhibitors of GSK3β that have produced striking data in animal models can be translated to treating patients with this devastating illness.

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