

GSK3 β and its Role in Sepsis

Tomeka Subber and Yutong Zhao*

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

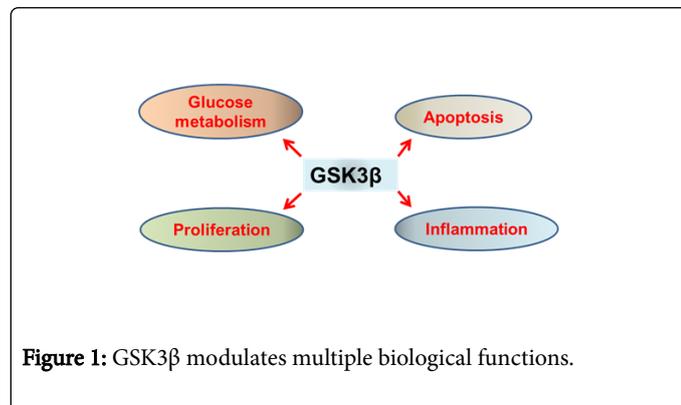
*Corresponding author: Yutong Zhao, Department of Medicine, The Acute Lung Injury Center of Excellence, The University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA, Tel: 412-648-9488; E-mail: zhaoy3@upmc.edu

Received date: March 19, 2017; Accepted date: March 21, 2017; Published date: March 28, 2017

Copyright: © 2017 Subber T, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

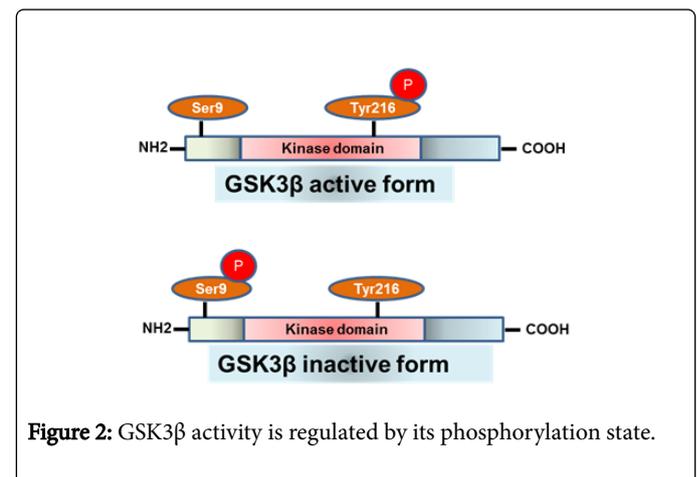
Sepsis is a leading cause of critical illness and death worldwide. The most recent consensus statement defines this complex clinical syndrome as “life-threatening organ dysfunction caused by a dysregulated host response to infection” [1]. Despite clinical studies that have led to improved quality of 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-3 β (GSK3 β), 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 GSK3 β . In experimental models of sepsis, inhibition of GSK3 β kinase activity decreases severity of organ dysfunction and reduces mortality. These studies suggest that GSK3 β is a promising therapeutic target in the treatment of sepsis.



GSK3 β as a Central Kinase in Inflammation

GSK3 β is a serine-threonine kinase that was first characterized in glucose metabolism [3]. It shares 85% homology with GSK3 α , but the C-terminal 76 residues only share 36% identity [4]. Both GSK3 α and GSK3 β 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 GSK3 β kinase activity (Ser21 on GSK3 α), while phosphorylation of Tyr216 (Tyr279 in GSK3 α) increases activity (Figure 2) [6,7]. Homozygous GSK3 β $-/-$ mouse embryos die from massive hepatocyte apoptosis and liver degeneration [8]. This phenotype is not rescued by expression of GSK3 α . Fibroblasts from GSK3 β $-/-$ were more sensitive to TNF α -induced apoptosis, and this effect was reversed with neutralizing TNF α antibodies or exogenous expression of GSK3 β . Later studies showed parallels between the GSK3 β $-/-$ and RelA $-/-$ phenotypes, raising more questions about the role of GSK3 β in the regulation of NF κ B pathways.

GSK3 β is required for efficient DNA binding of p65 and expression of IL-6 and MCP-1 in response to TNF α [9]. In contrast, a study by Vines et al. demonstrated that GSK3 β had anti-inflammatory effects downstream from NF κ B activation in human lung micro vascular endothelial cells after treatment with IL-1 β and TNF α [10]. Beurel and Jope showed that STAT3 and STAT5 activation depend on GSK3 β kinase activity, but STAT1 and STAT6 activation was not dependent on GSK3 β [11]. Evidence suggests that GSK3 β serves as a gatekeeper for NF κ B activation, modulating expression of pro- and anti-inflammatory genes in a cell type and stimuli-dependent manner.



GSK3 β 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 GSK3 β in TLR signaling [12]. LPS induces PI3K/Akt-mediated Ser9 phosphorylation and inhibition of GSK3 β , allowing for augmentation of anti-inflammatory cytokines in human peripheral blood monocytes (PBMCs). Treatment with a GSK3 β -specific inhibitor protected mice from endotoxin-induced sepsis and death. GSK3 β 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 GSK3 β 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 GSK3 β 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 GSK3 β occurred in a TLR2-dependent manner in murine macrophages. GSK3 β positively regulated NF κ B and p65 DNA binding affinity while negatively regulating CREB DNA binding [15]. These effects were reversed by lithium treatment, a known inhibitor of GSK3 β [6,16]. These early studies demonstrate a pivotal role of GSK3 β in innate immune responses that contribute to the pathogenesis of sepsis [17].

GSK3 β Inhibition is an Attractive Therapeutic Target in Sepsis

While GSK3 β has been identified as a central kinase in inflammation, translational studies have emerged demonstrating benefits of GSK3 β inhibition in animal models of sepsis and organ failure. In a rat model of sepsis, use of selective GSK3 β inhibitors reduced LPS-induced liver injury and failure [18]. GSK3 β inhibitors decreased severity of illness and improved survival in experimental models of acute lung injury [19,20]. GSK3 β 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), GSK3 β induces apoptosis of renal epithelial cells after ischemic injury and stress [23]. Deletion of GSK3 β expression or small molecule inhibition of GSK3 β protects mice from AKI both in ischemia-reperfusion models and models of sepsis [24-26]. This data support a role for GSK3 β 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

GSK3 β has become a focal point in research given its multifaceted role in inflammation. More studies are needed to understand how GSK3 β activity is dysregulated in the pathogenesis of sepsis and in host immune responses to pathogens. The goal is to tailor therapies for GSK3 β -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 GSK3 β that have produced striking data in animal models can be translated to treating patients with this devastating illness.

References

- Singer M, Deutschman CS, Seymour CW, Shankar HM, Annane D, et al. (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 315: 801-810.
- Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 348: 1546-1554.
- Embi N, Rylatt DB, Cohen P (1980) Glycogen synthase kinase-3 from rabbit skeletal muscle. Separation from cyclic-AMP-dependent protein kinase and phosphorylase kinase. *Eur J Biochem* 107: 519-527.
- Woodgett JR (1990) Molecular cloning and expression of glycogen synthase kinase-3/factor A. *EMBO J* 9: 2431-2438.
- Doble BW, Woodgett JR (2003) GSK-3: tricks of the trade for a multi-tasking kinase. *J Cell Sci* 116: 1175-1186.
- Beurel E, Grieco SF, Jope RS (2015) Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol Ther* 148: 114-131.
- Cohen P, Frame S (2001) The renaissance of GSK3. *Nat Rev Mol Cell Biol* 2: 769-776.
- Hoeflich KP, Luo J, Rubie EA, Tsao MS, Jin O, et al. (2000) Requirement for glycogen synthase kinase-3 β in cell survival and NF-kappaB activation. *Nature* 406: 86-90.
- Steinbrecher KA, Wilson W, Cogswell PC, Baldwin AS (2005) Glycogen synthase kinase 3 β functions to specify gene-specific, NF-kappaB-dependent transcription. *Mol Cell Biol* 25: 8444-8455.
- Vines A, Cahoon S, Goldberg I, Saxena U, Pillarisetti S, et al. (2006) Novel anti-inflammatory role for glycogen synthase kinase-3 β in the inhibition of tumor necrosis factor-alpha- and interleukin-1beta-induced inflammatory gene expression. *J Biol Chem* 281: 16985-16990.
- Beurel E, Jope RS (2008) Differential regulation of STAT family members by glycogen synthase kinase-3. *J Biol Chem* 283: 21934-21944.
- Martin M, Rehani K, Jope RS, Michalek SM (2005) Toll-like receptor-mediated cytokine production is differentially regulated by glycogen synthase kinase 3. *Nat Immunol* 6: 777-784.
- Wang H, Brown J, Gu Z, Garcia CA, Liang R, et al. (2011) Convergence of the mammalian target of rapamycin complex 1- and glycogen synthase kinase 3- β -signaling pathways regulates the innate inflammatory response. *J Immunol* 186: 5217-5226.
- Ko R, Park JH, Ha H, Choi Y, Lee SY, et al. (2015) Glycogen synthase kinase 3 β ubiquitination by TRAF6 regulates TLR3-mediated pro-inflammatory cytokine production. *Nat Commun* 6: 6765.
- Zhang P, Katz J, Michalek SM (2009) Glycogen synthase kinase-3 β (GSK3 β) inhibition suppresses the inflammatory response to *Francisella* infection and protects against tularemia in mice. *Mol Immunol* 46: 677-687.
- Klein PS, Melton DA (1996) A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci U S A* 93: 8455-8459.
- Wang H, Kumar A, Lamont RJ, Scott DA (2014) GSK3 β and the control of infectious bacterial diseases. *Trends Microbiol* 22: 208-217.
- Dugo L, Collin M, Allen DA, Patel NSA, Bauer I, et al. (2005) GSK-3 β inhibitors attenuate the organ injury/dysfunction caused by endotoxemia in the rat. *Crit Care Med* 33: 1903-1912.
- Park DW, Jiang S, Liu Y, Siegal GP, Inoki K, et al. (2014) GSK3 β -dependent inhibition of AMPK potentiates activation of neutrophils and macrophages and enhances severity of acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 307: L735-45.
- Liu Z, Bone N, Jiang S, Park DW, Tadie JM, et al. (2015) AMP-activated protein kinase and Glycogen Synthase Kinase 3 β modulate the severity of sepsis-induced lung injury. *Mol Med*.
- Ren F, Zhang L, Zhang X, Shi H, Wen T, et al. (2016) Inhibition of glycogen synthase kinase 3 β promotes autophagy to protect mice from acute liver failure mediated by peroxisome proliferator-activated receptor α . *Cell Death Dis* 7: e2151.
- Ren F, Duan Z, Cheng Q, Shen X, Gao F, et al. (2011) Inhibition of glycogen synthase kinase 3 β ameliorates liver ischemia reperfusion injury by way of an interleukin-10-mediated immune regulatory mechanism. *Hepatology* 54: 687-696.
- Wang Z, Havasi A, Gall J, Bonogio R, Li Z, et al. (2010) GSK3 β promotes apoptosis after renal ischemic injury. *J Am Soc Nephrol* 21: 284-294.
- Jiang C, Zhu W, Yan X, Shao Q, Xu B, et al. (2016) Rescue therapy with Tanshinone IIA hinders transition of acute kidney injury to chronic kidney disease via targeting GSK3 β . *Sci Rep* 6: 36698.
- Howard C, Tao S, Yang HC, Fogo AB, Woodgett JR, et al. (2012) Specific deletion of glycogen synthase kinase-3 β in the renal proximal tubule protects against acute nephrotoxic injury in mice. *Kidney Int* 82: 1000-1009.
- Liu Z, Gong R (2015) Remote ischemic preconditioning for kidney protection: GSK3 β -centric insights into the mechanism of action. *Am J Kidney Dis* 66: 846-856.