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Review Article

The Role of GSK-3β in Modulating Autophagy during Renal Ischemia-Reperfusion Injury

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Abstract

Renal ischemia-reperfusion injury is a complicated but common condition in clinic. Previous research on the mechanism was focused on cell apoptosis and necrosis. Recent years it is found that autophagy is inevitable in renal ischemia/reperfusion injury. Autophagy is involved in either protecting or damaging process in renal ischemia-reperfusion injury. Glycogen Synthase Kinase-3β (GSK-3β) is a kind of protein kinase with multiple functions in the cell, the change of its activity can regulate the level of autophagy in the renal ischemia-reperfusion. In this paper, we combine the relevant literature of GSK-3β and autophagy to brief the relationship between the activity changes of GSK-3β and autophagy in the renal ischemia-reperfusion injury.

Keywords: Glycogen synthase kinase-3β (GSK-3β); Renal ischemia-reperfusion injury (R/I/R); Apoptosis; Autophagy

Introduction

Autophagy existing widely in eukaryotic cells is a bulk degradation pathway responsible for degrading protein aggregates and damaged organelles [1]. In the early phase, autophagy can generate additional energy supply for starved cells, which maintains cell survival, while sustained cellular digestion through the process that lead to excessive autophagic cycling eventually results in cell death, known as autophagy-dependent cell death [2]. Recently, a large body of literature demonstrates that there are multiple interchanges at different molecular levels between autophagy and apoptosis pathways. As we all know, autophagy activation relevant to many biological responses, including inflammation, Endoplasmic Reticulum (ER) stress, deprivation of nutrients, a decrease in ATP, and an increase in reactive oxygen species, all these biological responses also elicit renal ischemia-reperfusion. GSK-3β is a Ser/Thr protein kinase, the activity of which is regulated by phosphorylation and complex formation with other proteins. Recently, accumulating evidence suggests that GSK-3β is also critically involved in the fate of cells subjected to extracellular stress including ischemia-reperfusion, but the signaling pathways through which these ischemia-reperfusion stressors induce autophagy have not been fully worked out. In this article, we review the role of GSK-3β in modulating autophagy during renal ischemia-reperfusion injury.

Autophagy and GSK-3β

Autophagy is a catabolic progress that degrades long-lived proteins, pathogens and damaged organelles [1]. Autophagy is a well-coordinated multi-step process regulated by Autophagy-Related Gene (Atg) products originally identified in yeast. In mammals, the formation of autophagosomes are involved in initiation, nucleation, elongation, and closure, the initiation step of autophagosome formation involves the Unc-51-like kinase 1/2 (Ulk1/2) mediated phosphorylation of Atg13 and FIP200, comprising Ulk1/2-Atg13-FIP200 [3]; vesicle nucleation and phagophore formation is dependent on a Beclin1 (Atg6 in yeast), hVps34 complex, or class III Phosphatidylinositol 3-Kinase (PI3K) complex; autophagosome elongation/closure involves Atg12 and Light Chain 3 (LC3), the mammalian ortholog of yeast Atg8, the Atg12-Atg5 conjugate, which forms the Atg12-Atg5-Atg16 complex, contributes to the stimulation and localization of the LC3 conjugation reaction, then the formation of Atg12-Atg5-Atg16-Atg8 recruits Atg9 complete autophagosome elongation/closure [4]. After formation, the autophagosomes merge with lysosomal compartments to form autolysosomes. Finally, autophagosome containing macromolecules can be degraded by lysosome enzymes.

Glycogen Synthase Kinase-3 (GSK3) is a glycogen synthase, with two isoforms in mammals, GSK-3α and GSK-3β, although these two isoforms are expressed over 98% identity within their kinase domains. But GSK-3β loss is not compensated by GSK-3α, so GSK-3β is important in catabolic progress [5,6]. GSK-3β activity is regulated by site-specific phosphorylation. The activity is upregulated by phosphorylation on Try^{216} residue, and conversely phosphorylation on Ser^{9} inhibits GSK-3β activity [5,6]. Normally, GSK-3β is suppressed by proliferative, pro-survival signals that increase Ser9 phosphorylation, such as WNT ligands, p90RSK, EGF, IGF-I and -II, and Fibroblast Growth Factor (FGF)16, FGF19, FGF 23, as well as Akt [7,8]. Conversely, GSK-3β is activated by noxious stimuli, including serum starvation, hypertonic stress, potassium deprivation, hypoxia, endotoxin exposure, and tissue ischemia [6]. GSK-3β is an ideal "survival" enzyme, because it controls several extra metabolic processes that are perturbed by ischemia, including cytoskeletal dynamics, gene expression, proliferation, and apoptosis [8,9].

The Relationship between GSK-3β, Apoptosis and Autophagy

Autophagy and apoptosis are linked by aspartic protease (caspase), caspase activation will reduces proteins (Beclin-1, Atg5 and Atg7) related with autophagy and then close the autophagic response; autophagy can also block apoptosis pathway by reducing caspase-8 [10,11]. For example, autophagy inhibition using an Atg5 siRNA

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resulted in increased cleaved caspase-3 and increased apoptotic cells during renal tubular epithelial cells during prolonged Cold Storage and Re-Warming (CS/REW) [12]. The relationships between GSK-3β, apoptosis and autophagy are closely, and there are also differences. A large body of literature has also found that the activity of GSK-3β was upregulated in the situation of endoplasmic reticulum stress, chemotherapy, oncogene activation, abnormal glucose metabolism and so on, then will inhibit apoptosis and protect cells from damage. For example, exposure of renal epithelial cells to metabolic stress activated GSK-3β, Bax, and caspase 3 and induced apoptosis, contributing to tubular injury and organ dysfunction after acute renal ischemia [13]. Likewise, GSK-3β has a dual effect on autophagy, when GSK-3β negatively activation by Ultraviolet B enhancing phosphorylation at Ser^{9} and suppressing Try^{216} phosphorylation, then activated autophagy in epidermal cells, which was evident by the formation of LC3 puncta, the induction of LC3 lipidation, the increase in beclin 1 expression, and the decrease in the levels of p62. GSK-3β appeared negatively regulated autophagy, and inhibition of GSK-3β activity can increase cell survival and cell autophagy [14]. Interestingly, some scholars found that under conditions of serum starvation, GSK-3β inhibition-induced cell death was in parallel with an extensive autophagic response, finally a profound necrotic cell death was observed as evidenced by cellular morphologic features and biochemical markers [15]. These show that blocking the autophagic response switched GSK-3β inhibition induced necrosis to apoptotic cell death. On the contrary, scholars have found that treatment of human lung cancer cells with perifosine can activate GSK-3β activity, furthermore GSK-3β can inhibit mTOR and activate autophagy [16,17]. In summary, changes of GSK-3β activity can affect the cell death pathway, autophagy and apoptosis.

The Role of GSK-3β in Modulating Autophagy during Renal Ischemia-Reperfusion Injury

Ischemia-Reperfusion (IR) results in tissue injury in a number of organs, including the heart, brain, kidney, and gastrointestinal tract, which has important implications for patient morbidity and mortality. The kidney is one of the high perfusion organ, it is sensitive to ischemia-reperfusion injury, during the process of kidney transplantation, partial nephrectomy, arterial bypass surgery, accidental trauma, hydronephrosis and ureter surgery, it can occur in varying degrees of ischemia-reperfusion injury, and it is one of the most common reasons that resulting acute renal failure.

Pathogenesis of renal ischemia-reperfusion injury is very complicated, renal tissue is in the state of energy metabolism and mitochondrial damage during ischemia, during reperfusion the recovery of blood flow can cause more damage than tissue ischemia injury, there are some of the more important pathological mechanisms like intracellular Ca^{2+} overload, oxygen free radicals, activate their own inflammatory response mechanisms, apoptosis, no-reflow phenomenon and so on. Primarily studies found that pathological changes of renal ischemia-reperfusion injury mainly express for the occurrence of renal tubular cell apoptosis in cortex and medulla, inhibition of renal tubular epithelial cell apoptosis can reduce renal ischemia-reperfusion injury and protect renal function [18]. Acute ischemic renal failure remains a common cause of death that precipitates organ failure by activate GSK-3β, Bax, and caspase 3 and induced apoptosis, necrosis, and the desquamation of viable proximal tubule epithelial cells from the basement membrane [19]. Another study found that silencing of p53 RNA through transarterial delivery ameliorated renal tubular injury and downregulated GSK-3β expression after ischemia-reperfusion injury [20]. During renal ischemia-reperfusion injury, downregulating GSK-3β activity led to an attenuation of apoptosis and mitochondrial damage ameliorated renal tubular injury.

Baseline autophagy plays an adaptive role in the renal, and contributes to the maintenance of renal structure and function [21]. Activation of autophagy during renal ischemia-reperfusion injury is beneficial because of intracellular ATP quickly decreased in tissue. Activation of autophagy improves renal cell structure and function [22]. For example, the damage of kidney function was increased due to ischemia-reperfusion injury and tubular epithelial cell apoptosis was increased after the autophagy-related genes Atg5 knockout of mice [23], it also showed that autophagy mechanism can maintain renal tubular epithelial cell homeostasis and reduce ischemia-reperfusion injury. At the same time the degree of autophagy activation is inconsistent in different stages of renal ischemia-reperfusion. Although activated during renal ischemia-reperfusion appears to be safeguard, excessive autophagy during reperfusion enhance autophagy-dependent cell death, which is detrimental to the renal, whether autophagy induced during reperfusion is protective or harmful to the renal has been controversial.

Conclusions

With the deepening research of autophagy, regulation of autophagy by activity changes of GSK-3β could become a new therapeutic target for prevention and treatment of renal ischemia-reperfusion injury. Because the activity changes of GSK-3β have a dual effect in the different stages of renal ischemia-reperfusion injury. It is very important to identify whether the activity changes of GSK-3β play a protective role to the body or aggravate tissue damage when use GSK-3β as therapeutic targets. Regulate the activity of GSK-3β to protect renal function by genetic or pharmacological methods also need further research about the relationships between molecular pathways, activation level and cell survival caused by the activity changes of GSK-3β in different conditions. Many studies show that apoptosis-related genes Bcl-2 and Bax [24], autophagy-related genes Beclin-1, and GSK-3β are all involved in the process of ischemia-reperfusion injury, therefore, further study is needed for the role of GSK-3β in modulating autophagy and apoptosis during renal ischemia-reperfusion injury needed.

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References

1. Yang Z, Klionsky DJ. Eaten alive: a history of macroautophagy. Nature Cell Biology. 2010; 12: 814-822.

2. Fougeray S, Pallet N. Mechanisms and biological functions of autophagy in diseased and ageing kidneys. Nature reviews Nephrology. 2015; 11: 34-45.

3. Hosokawa N, Hara T, Kaizuka T, Kishi C, Takamura A, Miura Y, et al. Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. Molecular Biology of the Cell. 2009; 20: 1981-1991.

4. Hurley JH, Schulman BA. Atomistic autophagy: the structures of cellular self-digestion. Cell. 2014; 157: 300-311.

5. McCubrey JA, Steelman LS, Bertrand FE, Davis NM, Sokolosky M, Abrams SL, et al. GSK-3 as potential target for therapeutic intervention in cancer. Oncotarget. 2014; 5: 2881-2911.

6. Park CH, Lee BH, Ahn SG, Yoon JH, Oh SH. Serine 9 and tyrosine 216 phosphorylation of GSK-3beta differentially regulates autophagy in acquired cadmium resistance. Toxicological Sciences: an official journal of the Society of Toxicology. 2013; 135: 380-389.

7. Fukumoto S, Hsieh CM, Maemura K, Layne MD, Yet SF, Lee KH. Akt participation in the Wnt signaling pathway through Dishevelled. The Journal of Biological Chemistry. 2001; 276: 17479-17483.

8. Jope RS, Johnson GV. The glamour and gloom of glycogen synthase kinase-3. Trends in Biochemical Sciences. 2004; 29: 95-102.

9. Kaidanovich-Beilin O, Woodgett JR. GSK-3: Functional Insights from Cell Biology and Animal Models. Frontiers in Molecular Neuroscience. 2011; 4: 40.

10. Wu H, Che X, Zheng Q, Wu A, Pan K, Shao A, et al. Caspases: a molecular switch node in the crosstalk between autophagy and apoptosis. International Journal of Biological Sciences. 2014; 10: 1072-1083.

11. Hou W, Han J, Lu C, Goldstein LA, Rabinowich H. Autophagic degradation of active caspase-8: a crosstalk mechanism between autophagy and apoptosis. Autophagy. 2010; 6: 891-900.

12. Jain S, Keys D, Nydam T, Plenter RJ, Edelstein CL, Jani A. Inhibition of autophagy increases apoptosis during re-warming after cold storage in renal tubular epithelial cells. Transplant International: Official Journal of the European Society for Organ Transplantation. 2015; 28: 214-223.

13. Jacobs KM, Bhave SR, Ferraro DJ, Jaboin JJ, Hallahan DE, Thotala D. GSK-3beta: A Bifunctional Role in Cell Death Pathways. International Journal of Cell Biology. 2012; 2012: 930710.

14. Yang Y, Wang H, Wang S, Xu M, Liu M, Liao M, et al. GSK3beta signaling is involved in ultraviolet B-induced activation of autophagy in epidermal cells. International Journal of Oncology. 2012; 41: 1782-1788.

15. Yang J, Takahashi Y, Cheng E, Liu J, Terranova PF, Zhao B, et al. GSK-3beta promotes cell survival by modulating Bif-1-dependent autophagy and cell death. Journal of Cell Science. 2010; 123: 861-870.

16. Inoki K, Ouyang H, Zhu T, Lindvall C, Wang Y, Zhang X, et al. TSC2 integrates Wnt and energy signals *via* a coordinated phosphorylation by AMPK and GSK3 to regulate cell growth. Cell. 2006; 126: 955-968.

17. Fu L, Kim YA, Wang X, Wu X, Yue P, Lonial S, et al. Perifosine inhibits mammalian target of rapamycin signaling through facilitating degradation of major components in the mTOR axis and induces autophagy. Cancer Research. 2009; 69: 8967-8976.

18. Chatterjee PK, Brown PA, Cuzzocrea S, Zacharowski K, Stewart KN, Mota-Filipe H, et al. Calpain inhibitor-1 reduces renal ischemia/reperfusion injury in the rat. Kidney International. 2001; 59: 2073-2083.

19. Wang Z, Havasi A, Gall J, Bonegio R, Li Z, Mao H, et al. GSK3beta promotes apoptosis after renal ischemic injury. J Am Soc Nephrol. 2010; 21: 284-294.

20. Fujino T, Muhib S, Sato N, Hasebe N. Silencing of p53 RNA through transarterial delivery ameliorates renal tubular injury and downregulates GSK-3beta expression after ischemia-reperfusion injury. American Journal of Physiology Renal Physiology. 2013; 305: F1617-1627.

21. Suzuki C, Isaka Y, Takabatake Y, Tanaka H, Koike M, Shibata M, et al. Participation of autophagy in renal ischemia/reperfusion injury. Biochemical and Biophysical Research Communications. 2008; 368: 100-106.

22. Jiang M LK, Luo J, Dong Z. Autophagy is a renoprotective mechanism during *in vitro* hypoxia and *in vivo* ischemia-reperfusion injury. Am J Pathol. 2010; 176: 1181-1192.

23. Kimura T, Takahashi A, Kaimori JY, Matsui I, Namba T, Kitamura H, et al. Autophagy protects the proximal tubule from degeneration and acute ischemic injury. Am Soc Nephrol. 2011; 22: 902-913.

24. Chien CT, Shyue SK, Lai MK. Bcl-xL augmentation potentially reduces ischemia/reperfusion induced proximal and distal tubular apoptosis and autophagy. Transplantation. 2007; 84: 1183-1190.

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