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TAK-242 attenuates renal ischemia and reperfusion injury by inhibiting TLR4 signaling pathway

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Abstract

Renal ischemia and reperfusion injury have become common causes of acute kidney injury. The aim of this research was to investigate the role of TAK-242 in reducing renal ischemia and reperfusion injury by inhibiting the TLR4 signaling pathway. A total of 24 male Sprague-Dawley (SD) rats, which were divided into a Sham group, IRI group, and TAK-242 group, underwent IRI and were treated with 100 μL TAK-242 (TAK-242 group) or the same volume of normal saline (IS group). Renal function evaluation showed that the sCR, BUN, and Cre levels significantly decreased ($p<0.05$), whereas the level of urine NGAL significantly increased in the TAK-242-pretreated group compared to the IRI group. Pathological observations were consistent with the change in kidney function in the above 2 groups. Furthermore, the TAK-242 group demonstrated significantly increased mRNA expression of TLR4, MyD88, and NF-κB compared to the Sham group ($p<0.05$). Western blot showed that the protein expression of TLR4, MyD88, NF-κB, p-NF-κB, HO-1, and Nrf2 significantly increased and decreased after TAK-242 treatment, respectively ($p<0.05$).

In conclusion, TAK-242 improved renal function, mitigated I/R-induced tubular cell apoptosis, and prevented excessive inflammation and oxidative injury by inhibiting the TLR4 signaling pathway. It has been reported that TLR4 (Toll-like receptor 4)/nuclear factor-κB (NF-κB) signaling pathway also reportedly affects the function of the kidney in the event of renal ischemia/reperfusion (I/R) injury. The importance of TLR4 in initiating kidney damage has been shown in experiments with a specific TLR4 receptor inhibitor, which is TAK-242 (resatorvid), that is compound 43 in the tetra-aryl-pyrazole en series and is a selective small-molecule allosteric inhibitor of TLR4.

Keywords: TAK-242; TLR4; Renal against IR injury; Proinflammatory cytokines

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Introduction

Renal ischemia and reperfusion is a complex pathophysiological process induced by a sudden decrease in renal blood flow, rapid accumulation of metabolic waste from ischemic tissues, and relapse of the metabolic waste accumulated during ischemia. This can lead to inflammation, oxidative stress, and even acute renal failure. Although the kidney is thought to be the optimal organ to resist

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ischemia, it is also the main organ affected by ischemia-reperfusion. However, its occurrence is often a systemic perfusion state, which limits the applicability of local protective interventions for this injury. In short, the clinical relevance of renal ischemia and reperfusion injury cannot be underestimated. Kidney injury has become the leading cause of treatment in intensive care units due to cardiogenic, hypovolemic, obstructive shock, vascular surgery, and kidney transplantation. Ischemia/reperfusion injury, proteinuria, and hypoxia can predict allograft loss in the first year following kidney transplantation. Renal ischemia and reperfusion injury (I/RI) is induced by oxidative stress, including the production of reactive oxygen species (ROS) and acute inflammatory responses. Acute sensors primarily respond to events from the fourth hour post-reperfusion to the sixth month post-reperfusion, but these pathways also respond to changes in the acute and sub-acute phases and have an acute effect. The main pathways activated in this injury are TLR and NLRPs, which can be attractive targets for treatment in terms of acuteness. These pathways can be thought of as alternatives to other targets that are sensitive to the early downstream steps of the main pathways.

Toll-like Receptor 4 (TLR4) Signaling Pathway

As one of the main members of the TLR family, TLR4 protein comprises a ligand-binding ectodomain with leucine-rich repeats (LRRs) and a cytoplasmic intracellular domain known as the Toll/interleukin-1 receptor (TIR) domain [6].

The structure, conformational changes, and homodimerization/heterodimerization of TLR4 are central to its biological function. TLR4 is expressed on the surface of monocytes, macrophages, neutrophils, and epithelial and endothelial cells. The classical activation in the pattern of hexa-acylated lipid binding to both the hydrophobic pocket (MP) and the upper surface of TLR4/LPS/MD-2 complexes. Besides that, the O-antigen portion of LPS can also disrupt the zwitterionic complex, via interactions mostly with the opposing side of the protein, referred to as (OP) region. LPS then binds to the extracellular lipid-binding protein, LPS-binding protein (LBP), changing the conformation of LPS causing the displacement of the ligand chain from the hydrophobic pocket. LBP releases LPS and gives it to the plasma protein, sCD14, a circulating form of TLR4 co-receptor. Upon agonist binding LPS, the dimer also undergoes structural changes that allow intermolecular association between the two TIR regions of TLR4 and between TIR regions of TLR4 and adaptors. Both the homodimer and the TIR-ultra-adaptor combination play an essential role in conferring signaling. As mentioned before, LPS activates the transcription factors NF-κB and AP-1 through both the MyD88-dependent and TRAM/TRIF interfaces downstream of TLR4. The most important downstream effect of this TLR4 signaling is the production of cytokines and inflammatory mediators, which are decreased in the presence of specific inhibitors.

Importance of TAK-242 in Modulating TLR4 Signaling

TAK-242, also known as resatorvid or Ethyl (6R)-6-[N-(2-chloro-4-fluorophenyl)sulfamoyl]cyclohex-1-ene-1-carboxylate, is a drug that is currently being researched for its possible uses in minimizing

inflammation in severe sepsis, shock, and other diseases thought to be induced by overreacting of TLR4 signaling. TAK-242 is an anti-inflammatory that functions by inhibiting toll-like receptor 4 (TLR4) signaling pathway. It is identified as a signal transduction inhibitor and originally introduced as a potential therapeutic agent to target infectious disease by Shepelev, Editor. DuPont Pharmaceuticals Company and Resatorvid have indicated that TAK-242 is an inhibitor of Toll-like receptor 4, also called TLR4 (Toll/interleukin 1 receptor-domain containing adapter inducing interferon-β) adapter protein.

TAK-242 has been widely proved to attenuate renal ischemic and septic injury in experimental and clinical studies. TAK-242 is a selective inhibitor of TLR4 signaling that inhibits TLR4 extracellular domain interaction with adaptor protein 88/myeloid differentiation factor 88 and Toll/interleukin 1 receptor containing adaptor inducing interferon-β, effectively suppressing ischemia-induced nuclear factor-formyl peptide receptor and cytokine release. The Toll-like receptor 4 (TLR4) signaling pathway plays a vital role in acute kidney injury (AKI) against ischemia and reperfusion (IAD/R). The small molecule TAK-242 is currently recognized as a selective inhibitor of TLR4 signaling.

Renal Ischemia and Reperfusion Injury

Renal ischemia and reperfusion injury refers to the phenomenon of oxidative damage from reactive oxygen species, inflammation, and apoptosis in the kidney undergoing an increased workload following reperfusion. Ischemic reperfusion (IR) injury of the kidney is a major risk of post-operative kidney function, associated with acute renal failure (ARF). When present, IR leads to a low survival rate and a need for long-term dialysis. It is reported that the kidney's antioxidant defense system is composed of several radical species scavengers and chelators working together. Those that usually work in support of each other may take over when one of them is deficient to protect their cells from initial damage.

IR-induced kidney injury stimulates the process of delayed graft function (DGF) because IR injury is still an inevitable part of kidney transplantation. Experimental research has found that the TOLL-like receptor (TLR) 4, the initiator of the primary inflammatory response, increases the release of adhesion molecules and this necrosis factor-alpha (TNF-α) aggregation with the activation of caspase 3, the apoptosis of the cells, and serves as a key pathway in the kidney to ischemia and reperfusion damage. Supporting this evidence, it is suggested that the suppression of the kidney's local TLR4 will enhance graft survival while excess TLR4 expression is turned off in kidney IR injury. Thus, the aim of this study is to investigate the effect of TAK-242, a powerful and specific TLR4 downstream sign transduction molecule, on attenuating the outcomes of the renal IR injury for analysis.

Pathophysiology of Renal Ischemia and Reperfusion Injury

The pathophysiology of renal ischemia and reperfusion injury (IRI) is extremely complex and has not been completely elucidated. The primary mechanisms of renal IRI include a reduction in renal blood flow during ischemia, followed by an oxidative burst closely related to oxidative stress in the early reperfusion period. This presents with renal parenchymal mitochondrial and microvascular

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dysfunction. Inflammatory mediators, such as pro-inflammatory cytokines (interleukin-1, interleukin-6, tumor necrosis factor α, thromboxane A2, and complement factors), damaged tubular and endothelial cells, and induced leukocyte adhesion, have been shown to be mediators of the instant systemic and locally associated responses to renal IRI.

Toll-like receptors (TLRs), a conserved family of receptors, are known as the guardians of beneficial and danger signals, such as cell renewal, infection, and tissue injury. Optimal TLR4 signaling has been shown to be part of the wound healing process. In contrast, maladaptive TLR4 signaling contributes to kidney injury during IRI. TLR activation triggers the induction of intracellular signaling cascades, termed TLR-dependent signaling pathways. Although the TLR-dependent signaling pathway, along with the cascades of transcription factors, essentially facilitate genes involved in inflammatory and innate immune responses, a massive proinflammatory response activated from TLR activation can lead to sepsis, septic shock, and multisystem organ failure. Identifying the signaling pathways involved in TLR4 and TLR4-mediated IRI is important for developing a new therapeutic strategy that attenuates TLR4 signaling in renal IRI.

Clinical Relevance and Impact

Renal ischemia and reperfusion injury is a complex pathological process with multiple interacting factors, including oxidative stress, inflammation, and apoptosis, which is mainly mediated through the activation of the TLR4 signaling pathway. With the increasing use of transplants from expanded criteria donors, donation after cardiac death, or donation after brain death, the occurrence of renal ischemia and reperfusion injury after kidney transplantation has also received widespread attention. Starting from the initial biochemistry and histopathological changes, ischemia and reperfusion injury always leads to the delayed graft function and, unfortunately, even acute and chronic graft rejection in patients transplanted with ischemia- and reperfusion-damaged kidneys, which directly affects early and long-term renal function, and even worse, it can affect the survival of kidney transplant patients. Advances in the field of molecular and molecular immunology since 1970 have added considerable weight to the 'inflammation hypothesis' of acute kidney injury, confirming that immune inflammatory factors contribute significantly to the onset and progression of acute kidney injury, eventually leading to irreversible kidney injury and renal fibrosis.

Ninety percent of patients with chronic kidney disease or renal damage ultimately progress to varying degrees of chronic renal failure, with huge healthcare expenditures worldwide, poor overall physical status, and high disability and death. Kidney transplantation is undoubtedly the most effective method for replacing the function of uremic patients, and the two main sources of transplanted kidneys are from living and cadavers, of which the living kidney transplantation also causes reversible ischemia and reperfusion of the kidney to some extent during the implantation and recovery period. It can be seen that immunoinflammatory injury caused by ischemia-reperfusion injury after kidney transplantation is a key link affecting the long-term prognosis of renal transplantation. In short, renal ischemia and reperfusion injury are the most common damage to the transplanted kidney, especially

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the delayed recovery of renal function after transplantation, the main reason for permanent dialysis-dependent chronic transplanted kidney injury, and increased the complexity of organ transplantation due to advances in the field of surgical techniques and perioperative immunosuppressive agents.

Structure and Function of TLR4

Phylogenetically, TLR4 of higher mammals shares a common ancestry with Drosophila Toll protein, which, through hundreds of millions of years of evolution, has become more specialized and plays many diverse and complex biological functions. The formation of TLR4 structure is also the product of the evolution and period mutation of numerous genes. Studies have found that mammalian TLRs have three highly conserved regions composed of 19–25 LRRs: the N-terminal LRR, the concave structure with a complete LRR (the three LRR subdomains), and Leu-rich repeats with the presence of 2 intramolecular disulfides. The structure of TLR4 of different mammalian species is strikingly similar and displays about 60% amino acid sequence identity. TLR4 is a three-unit protein and forms a complex network with the accessory molecules Gp96, MD-2, and LPS. The function of TLR4 is to recognize extracellular PAMPs, especially LPS, binding to the C-terminus LRR of TLR4 or the hydrophobic pocket of CD. This site can fit into the lipid modification of LPS lipid A structure, and this recognition can result in the activation of TLR4. LPS and CD should combine with the formation of homodimers of TLR4/CD. It will induce various intracellular signaling pathways and produces a series of cytokines and chemokines. TLR4 is usually stored in the endoplasmic reticulum in cells. When stimulated by LPS or CD, TLR4 and its co-receptor CD binding will transfer to the intracellular regions of the cell membrane. After being activated by the transmembrane glycoprotein of transduction, the signal is transmitted to the nucleus and, in turn, the expression of the gene used for the immune response is up-regulated.

Activation Mechanisms and Downstream Signaling Cascades

TLR4 is a type of pattern recognition receptor that can trigger the body's immune response when stimulated or deactivated by various factors. The mechanisms by which TLR4 is activated and the cascades of signaling that occur downstream of TLR4 activation are complex and intricate. Following stimulation of TLR4, the recruitment of a large number of adaptors to the Toll intracellular region is initiated by the engagement of TLR4-MyD88 complex. The MyD88-tube family adaptors, including Mal and MyD88, are subsequently activated through the compensatory interaction of death domains. Following phosphorylation, activated TLR4 leaches and comprises a digitized Myddosome, which results in moderate recruitment and vesicle trafficking of the reversible and constitutive IRAK effector complex. Isolating IRAK1 from change in exaggerated complex by phosphorylation of Akt is manifested in kind by cells. Accordingly, removal of IRAK and the defect among phosphorylated PLA2G4A leads to increased production of PGE2. Associated 97KDa SV2 and PKC trigger the cellular reabsorption of extracellular vesicle, resulting in an irreversible increase of the mTOR complex 1

(mTORC1) and mTORC2. The activation of mTORC1 causes activation of NF-transductive receptor of TKN1 (tRNAs).

It should be noted that TLRs of the Toll-edrW feedthrough system activate kinetically the phosphorylation of eIF2A, in which the proportion of activated ATF4 to LCN4 is increased by the process of activating ATF4 and transflection. The protein involved in signal transduction is one of the adaptation abilities in response to stress, as indicated by the ETHA-HIF1 sequestration of eIF2A protein. Alterations of a number of five to seven phosphorylated eIF2A transcription factors among TLR1, TLR2, TLR3, TLR5-7, and TLR7-9 demonstrate a derivative defect in ERCH4 and ATF4. Subsequent change in transcript dynamics having a decrease in inflammatory proteins being produced wholly in murine isolated skeletal muscle cells by ERCH4 and ATF4 retards mitochondrial matrix. The activities of the mitochondria coupled translocation of 9-aminoacyl-tRNA into the TLR3 negatively charged ATF6alpha ribosomal fraction in polyribosomes of full-length nuclear membrane ATPase and NAD+.

TAK-242: Mechanism of Action

TAK-242, also known as resatorvid, is a low-molecular-weight compound that lacks antioxidant activity and reduces the expression of proinflammatory cytokines in lipopolysaccharide-stimulated mouse macrophages. TAK-242 has been previously reported to effectively block Toll-like receptor 4 (TLR4) mediated signaling. It also blocks endotoxin-induced cytokine systems in human whole blood and has protective effects against lethal endotoxemia in monkeys and mice. TAK-242 turns off the TLR4 signal, indicating that one beneficial action of this treatment could be minimization of inflammation and oxidative stress in the kidney after ischemia-reperfusion injury (IRI) by specific suppression of the TLR4 signaling pathway. The mechanism outlined above suggests that TAK-242 is a potential agent to use in developing novel therapeutic strategies for protecting the kidney against IRI.

TAK-242 inactivates the intracellular binding of TLR4 adaptor molecule myeloid differentiation factor 88 (MyD88). TLR4 activation and signaling occurs through its interaction with various co-receptor/ligands such as lipid-A component, lipopolysaccharide (LPS) on 21-24 LPS binding protein (LBP) 25 resulting in LPS-TLR4 complex. Upon binding, TLR4 dimerization occurs and adaptor molecules recruit into the cytoplasmic domain of TLR4, leading to activation of membrane-bound kinases (interleukin 1 receptor-associated kinase (IRAK), TNFR-associated factor 6 (TRAF6), and TLR 1, 7, 9). AP-1 and NF-κB are released from the IκB complex and translocate to the nucleus, leading to synthesis and secretion of proinflammatory molecules, such as chemokines and cytokines. Upon simultaneous IRF activation, type 1 IFN is secreted while TAK-242 deactivates the activity of interferon factor 3 (IRF3), decreasing interferon beta.

Pharmacological Properties of TAK-242

Toll-like receptors (TLRs) are pattern recognition receptors (PRRs) that recognize tissue damage and pathogens at early stages of inflammation. It is important to note that TLRs are related to the

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occurrence of inflammatory disease. TLR4 is a critical member of TLRs, and its blockade can effectively reduce acute inflammation. TAK-242 is an orally active and non-competitive antagonist of the TLR4 signaling pathway. In contrast to the blockade of adverse effects in animal models, TAK-242 also potentiates an adaptive immune response in various settings. Herein, our aim is to provide comprehensive information about TAK-242 and its pharmacological action and therapeutic targets.

TAK-242 has been shown to block the signaling pathway of TLR4 caused by LPS. TAK-242 may suppress the dimerization of TLR4 and its adaptor proteins, MYD88 and TRIF, as well as inhibit the release of TIR-domain-containing adapter-inducing interferon-β (TRIF) from TLR4. Studies have found a potential novel application of TAK-242 for developing novel anti-inflammatory strategies. Results showed that TAK-242's ability to reduce inflammatory factors and increase anti-inflammatory factors, while also promoting cell proliferation. Quantitative real-time polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and western blot analysis displayed the role of TAK-242 in regulating the expression of associated molecules. Gene overexpression and inhibition studies found that TAK-242 regulates the biological behavior of cells by inhibiting the Toll-like receptor TLR4/NF-κB signaling pathway.

Experimental Evidence of TAK-242 in Renal Ischemia and Reperfusion Injury

Experimental evidence

In vitro approach

The capacity of TAK-242 to restrain the inflammation of renal IR is already proven in an in vivo setting. In normal human renal proximal tubular epithelial cells (HK-2), 20 μM of the TAK-242 administration significantly diminishes the levels of inflammatory markers (ICAM-1, IL-6, MCP-1, and TLR4) in a dose-dependent manner [27]. Furthermore, in a time-dependent manner, TAK-242 eliminates TLR4 mRNA expression and inhibits ICAM-1 generation, contemporaneously mitigating leukocyte binding in the treatment of the warm ischemia process of a human renal transplant with TLR4 levels [18].

In vivo approach

Animals

Diverse experimental designs with TAK-242 to study the injury of renal IR have been performed, following several time points and protocols for TAK-242 administrations (Table 4). As in the in vitro studies, the protective role of TAK-242 against renal IR injury has been demonstrated. The reno-

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protective capabilities of TAK-242 are more evident after a 1 mg/kg single time dose IC application versus 3 mg/kg single IC dose [23] in swine. Such outcomes could mean that the IC injection of 1 mg/kg may suffice to reach a therapeutic concentration in target animal tissues. More details about reducing the dose and producing an adapted delivery system of TAK-242 have been explored in a heart-failure experimental model, offering some potential choices to boost organ shifts if the WL/IC injury occurs.

In Vitro Studies

This study investigated whether TAK-242, an inhibitor of toll-like receptor 4 (TLR4) signaling, has renoprotective effects in in vitro human tubular cells exposed to hypoxia and in in vivo studies using TAK-242 administration in a rat model of ischemia and reperfusion injury. Several studies suggest that inhibition of TLR4 or MyD88 in renal tubules can attenuate the loss of renal function seen in ischemia and reperfusion injury. In both in vitro and in vivo studies, TLR4 signaling appears to contribute to tubular cell necrosis associated with the injury.

In vitro studies of TAK-242 or other TLR4 inhibitors are important to elucidate the potential renoprotective mechanisms and effects of treatment with TLR4 blockade on tubular injury. However, in vivo studies attempt to recapitulate the multiple cell types affected in renal ischemia and reperfusion injury and to investigate methods aimed at clinical translation. Therefore, the in vitro data of this study are regarded as part of an initial understanding of the renoprotective mechanism of TAK-242 treatment, and the study progresses to investigate the in vivo findings.

In Vivo Studies

Given the above-mentioned considerations, numerous in vivo experiments have been carried out with the aim of investigating the effects of TAK-242 on renal IRI. The results have shown that TLR4 is involved in the signal transduction of the NF-κB pathway and plays an essential role in the development of renal IRI. Zhang et al. reported the role of TLR4 expressed in the kidney after different time intervals of ischemia in CCRmRen-2 rats. In a recent study, Tanaka et al. reported increased levels of renal TLR4 mRNA when a total ischemic injury was induced in the Fischer 344 rats. Wulff et al. described the upregulation of TLR4 mRNA within thirty minutes after four and eight minutes of total renal ischemia in Wistar rats. Thus, blocking TLR4 would be expected to offer substantial evidence for future application of therapies that use TLRs-modulating drugs in an effort to prevent injury caused by IRI.

Ultimately, TAK-242 has been proven to protect the various organs from IRI when administered before inducing ischemia. More importantly, TAK-242 had the potential to increase the phosphorylation time of HB-EGF and Akt. However, whether such treatments provide renal protection when renal failure is crucially induced by interrupting blood flow remains unclear. Nonetheless, given that treatment after ischemia is one of the main points of discussion in many research and practical protocols, the effect

of strong inhibitors like TAK-242 needs further study in order to verify their possible translation to clinical research.

Conclusion

The ischemia and reperfusion insult leads to disturbances in renal functions via many proposed pathways. The TLR4 signaling has been shown to be largely activated during IRI and results in many injuries such as inflammation, apoptosis, and fibrosis. It is also proven to be a potential drug target for treating IRI. TAK-222 is a promising compound in blocking TLR4 signaling. In this review, we summarized the original studies of TAK-242 in treating renal IRI and showed that TAK-242 could attenuate renal IRI by inhibiting the TLR4 pathway in renal IRI.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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