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REVIEW

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BK Polyomavirus and acute kidney injury in transplant recipients: signaling pathways and molecular mechanisms

Samar Bizhani[1], Afsoon Afshari[2*] and Ramin Yaghobi[1]

Abstract

Acute kidney injury (AKI) is a condition that can result in changes in both urine production and creatinine levels in the bloodstream, complicating the treatment process and worsening outcomes for many hospitalized patients. *BK polyomavirus* (BKPyV), a member of the Polyomaviridae family, is prevalent in the population and remains latent in the body. It can reactivate in individuals with a compromised immune system, particularly post-kidney transplant, and can activate various transcription factors and immune mediators. Although reactivation is often asymptomatic, it can present as AKI, which is a risk factor for early loss of the transplanted organ. The immune response to BKPyV is crucial in controlling the virus and safeguarding organs from damage during infection. Understanding BKPyV pathways may offer novel opportunities for effectively treating BKPyV-associated complications. This review seeks to elucidate the potential mechanisms by which BKPyV reactivation can lead to AKI by analyzing various signaling pathways, as well as the identification of molecular mechanisms that BKPyV may utilize to induce AKI.

Keywords *BK Polyomavirus*, Acute kidney injury, Transplant

Introduction

Acute kidney injury (AKI) encompasses a range of different types of conditions. Several health conditions can cause a sudden decline in kidney function, leading to elevated creatinine levels in the blood and insufficient urine output for at least a week [1]. AKI is usually a consequence of acute or chronic illness which affects roughly 20% of hospitalized patients and about 10% of them need kidney transplantation [2]. AKI in kidney transplant recipients (KTRs) is a leading cause of morbidity, hospitalization, and hospital readmission [3]. AKI in KTRs can be caused by acute rejection, due to drugs, infection, urinary obstruction, vascular thrombosis, and bacterial and viral infections [4].

Additionally, *BK polyomavirus* (BKPyV) is one of the viruses that can be cited as the reason for AKI in KTRs. The presence of BKPyV is widespread in nearly all human populations worldwide. The infection with this virus is asymptomatic in early childhood and persists in the kidneys for lifelong [5]. It is activated in pharmacological and pathological immunodeficient patients [6]. BKPyV infection can cause polyomavirus-associated nephropathy (BKPyVAN) in KTRs [7]. Although reactivation is often asymptomatic, it can manifest as AKI and is a risk factor for early allograft loss [8]. Therefore, this review describes the possible ways that BKPyV reactivation can cause AKI such as signaling pathways, including NF-κB and TGF-β, which are crucial in mediating BKPyV activity and the development of AKI. Various research findings have suggested that the NF-κB signaling pathway is essential for regulating the inflammatory response and

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is associated with the etiology of renal fibrosis [9]. And, TGF-β, existing as a dimer, facilitates kidney fibrosis through the activation of both canonical and non-canonical signaling pathways [10]. The recurrence of AKI is a prominent risk factor for the onset of chronic kidney disease, largely due to its role in inducing renal fibrosis, which is the ultimate pathological manifestation of chronic kidney disease [11].Additionally, the molecular mechanisms by which cytokines influence inflammatory processes are discussed. A shift in the expression of certain inflammatory mediators, such as TNF-α, IL-6, IL-15, and IL-11, may be implicated in the pathogenesis of AKI.

BK polyomavirus in KTRs

Dialysis and renal transplantation are treatment options for end-stage renal disease (ESRD) [12]. The increasing prevalence of ESRD and declining organ donation rates have resulted in a critical shortage of transplantable kidneys [13]. The average time between being on the transplant waiting list and receiving kidney transplantation has increased dramatically over the past years [14]. Although a kidney transplant is preferable to continuous dialysis, the need to take immunosuppressive medication remains a significant concern [15]. With the presentation of more powerful immunosuppression regimens and diminished acute rejection rates, viral infections after renal transplantation have developed as a critical cause of allograft loss [16]. BKPyV can be a common infection experienced after kidney transplantation [17]. BKPyV belongs to the *Polyomaviridae* family of double-stranded DNA (dsDNA) viruses [18]. It is a non-enveloped DNA virus that was first discovered in 1971 in the urine of a kidney transplant recipient [19]. The BKPyV genome contains an early domain encoding large and small T antigens (LT-Ag and st-Ag), a late domain for capsid proteins VP1-3 and anaproteins, and a non-coding regulatory domain (NCCR). Polymorphisms in VP1 and NCCR give rise to six different strains of BKPyV [20]. BKPyV is broadly predominant in the common populace with over 80% of people having antibodies against BKPyV. The foremost common mode of transmission is through respiratory secretions [20], which usually causes primary infection during childhood and infects the urinary epithelium, ureter, and bladder [21]. Reactivation of BKPyV is influenced by immunosuppression and various factors, including allograft, viral, and host components [22, 23]. Within 48 h of viral replication, human tubular epithelial cells experience various genomic changes that initiate key biological processes like the cell cycle, apoptosis, DNA damage, and the release of immune mediators. These processes collectively contribute to the lytic phase of virus reactivation and its persistence in the renal allograft [24]. During the lytic and latent phases of infection, viruses are able to control the expression of their viral proteins [25]. Due to suppression of cellular infection by combination therapy during the first year after transplantation, viral replication often occurs during this period. In KTRs, clinically significant disease arises from either the reactivation of a latent infection or the transmission of a new infection from the donor kidney. The disease progresses through the following stages: viruria, viremia, and allograft nephropathy [26]. Viruria was diagnosed in approximately 30% of kidney transplant recipients and viremia in 12% [27]. About half of all KTRs experience viremia within 2 to 6 weeks following the onset of viruria, and approximately 50% of viremic patients develop BKPyVAN within the defined time frame [28, 29]. The initial line of defense against BKPyV infection is innate immunity; however, it appears insufficient to effectively eliminate the viral presence [30].

The etiology of AKI

AKI is predominant in hospitalized patients, up to 10–20% of all patients and up to 50% of those in intensive care units (ICU) [31]. The causes of AKI are typically divided into three main categories: pre-renal, intra-renal, and pos-trenal (Fig. 1). Pre-renal AKI represents 55% of cases, and intra-renal AKI appears in 45% of all patients. Post-renal AKI is rare and occurs in 5% of cases. The foremost cause of pre-renal AKI is transitory renal hypoperfusion. A significant decrease in mean arterial blood pressure leads to AKI in 55% of cases [32]. Many conditions can lead to pre-renal AKI, but it can be reversed if the underlying cause is addressed and the tissue remains undamaged. Intra-renal AKI, which accounts for 45% of cases, is characterized by significant alterations in the kidney's structure or microscopic architecture and is not caused by urinary tract obstruction [33].

Any disease associated with ureteral obstruction can potentially trigger post-renal AKI. Hematomas within the renal pelvis or ureter, ureteral tumors, abdominal malignancies, and bladder and prostate diseases are significant conditions. Collectively, they contribute to only 5% of AKI cases [32].

Although this classification can be useful to determine the differential diagnosis, AKI is characterized by various factors and can be classified into different categories based on pathophysiology [34].

KTRs face an elevated risk of developing AKI during their stay in the intensive care unit, with a notable percentage necessitating renal replacement therapy. The process of kidney transplantation is identified as a significant risk factor for the development of AKI. Factors that predispose individuals to this condition include differing extents of ischemia–reperfusion injury during organ removal and transplantation, long-term administration

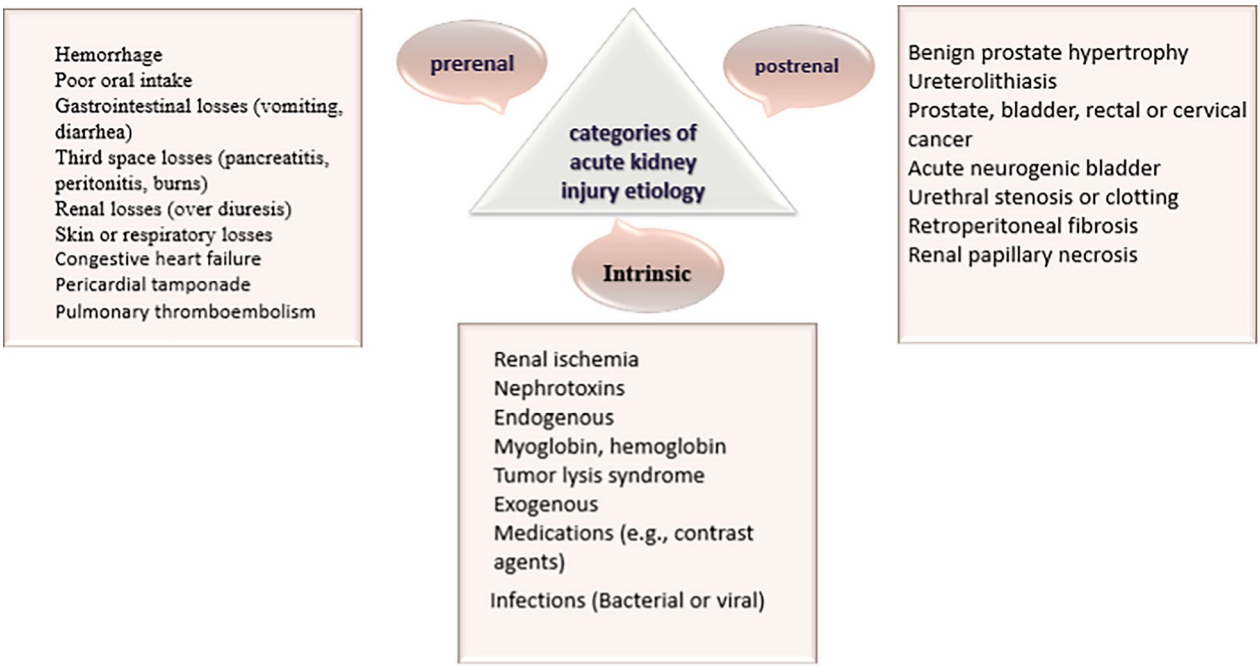

Fig. 1 Possible causes of AKI: The causes of AKI are typically divided into three main categories: pre-renal, intra-renal, and pos-trenal; pre-renal AKI is the most common type of AKI

of nephrotoxic calcineurin inhibitors, and the existence of a solitary functioning kidney [35]. The available data regarding the lifetime incidence of AKI in KTRs is limited and lacks clarity. It is estimated that approximately 6% of KTRs experience ICU admission during the delayed post-transplant phase [36].

By the way, sepsis and septic shock are commonly associated with the development of AKI. Among the various causes of sepsis, urinary tract infections (UTIs) are notable, as they can lead to a rapid decline in renal function. UTIs may be asymptomatic or symptomatic, presenting a diverse array of symptoms that range from mild irritative voiding to severe conditions such as bacteremia, sepsis, shock, or even death. Sepsis is a leading cause of AKI, with around 60% of patients suffering from septic shock experiencing this renal complication. Additionally, acute UTIs can result in a sudden worsening of renal function, particularly in the presence of urinary tract obstruction [37].

Infections such as BKPyV can manifest in form of AKI by either direct invasion, or indirectly by immune-mediated mechanisms [38].

Post kidney transplant AKI linked to BKPyV reactivation

AKI due to BKPyV infection affects up to 10% of transplant recipients. BK nephropathy usually develops early post-transplant, often within the first year, and is driven by persistent high-level viral replication in an immunosuppressed environment [39]. The presence of BKPyV in KTRs most often induces UTIs which is the most common cause of AKI in KTRs [40]. In the case of kidney transplantation, BKPyV infection occurs in the transplanted kidney, and in other organs such as heart, liver, and lung [6]. Also, tubulointerstitial nephritis (TIN) happens when an immune-mediated infiltration of the kidney, causes inflammation and leads to kidney injury [41]. BKPyV causes tubulointerstitial nephritis, which leads to AKI and ureteral obstruction [4]. This review will describe the possible pathways that BKPyV reactivation triggers to produce AKI in KTRs, summarized in Fig. 2.

Signaling pathways

Signaling pathways such as NF-κβ and TGF-β signaling can play important roles in BKPyV activity and the occurrence of AKI, which are discussed below.

NF-κβ signaling

The activation of NF-κB during viral infections is seen as a defensive mechanism against viruses and is characteristic of most viral infections because it enhances the expression of numerous proteins involved in both innate and adaptive immunity [42]. In some cases, viral molecules efficiently bind to receptors to trigger a signaling cascade that activates NF-κβ. In other cases, the activation of dsRNA-dependent protein kinase (PKR), which

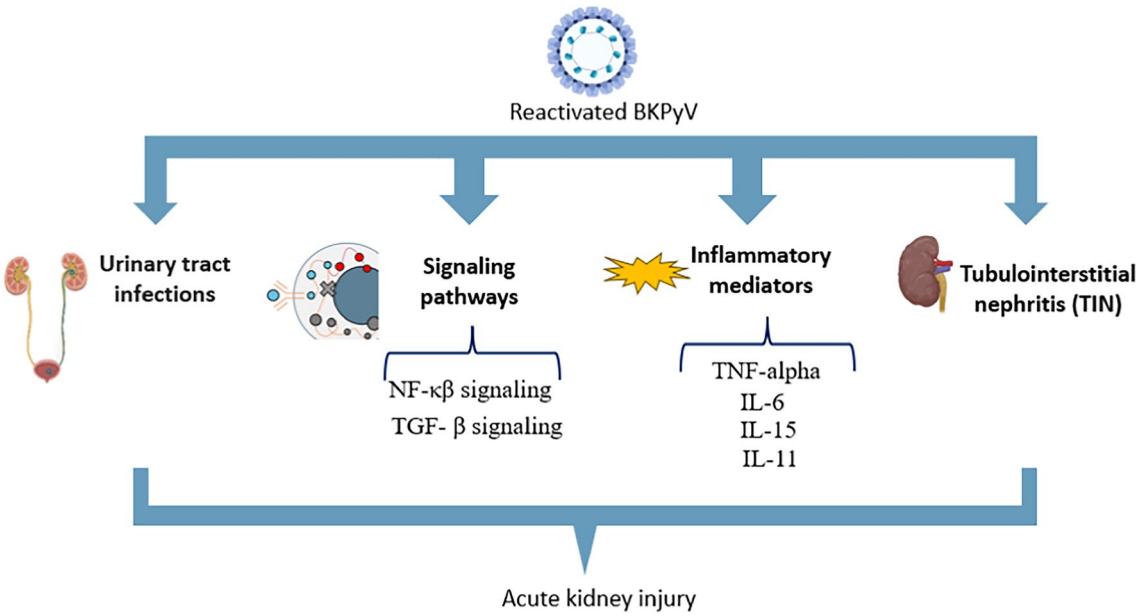

Fig. 2 The possible ways that BKPyV reactivation can cause AKI in KTRs

engages with the IKK complex via its catalytic domain and interacts with viral products like dsRNA and viral proteins, triggers NF-κB activation [42].

Once NF-κβ is activated, it triggers the production of antiviral substances such as type I IFNs and proinflammatory cytokines [43] through myeloid differentiation primary response 88 (MyD88) or TIR-domain-containing adapter-inducing interferon-β (TRIF) signaling pathways [44].

NF-κB is crucial as it enhances the production of chemokines, cytokines, adhesion molecules, and enzymes responsible for generating secondary inflammatory mediators [45] and, it is closely linked to the onset of AKI [46]. Studies demonstrate that NF-κB is downregulated by KIM-1-mediated epithelial cell phagocytosis, which can protect the kidney after ischemia- and cisplatin-induced AKI [47].

During AKI, NF-κB can induce an increase in the infiltration of M1 macrophages into the kidneys and cause more damage. In animal models, Mice are protected from kidney injury due to reduced NF-κβ activation, which leads to decreased cell death and chemokine expression (48). Hence, BKPyV infection can activate NF-κB which is one of the most important components of AKI pathogenesis, and can lead to major signaling pathways that involve mostly in inflammation (Fig. 3).

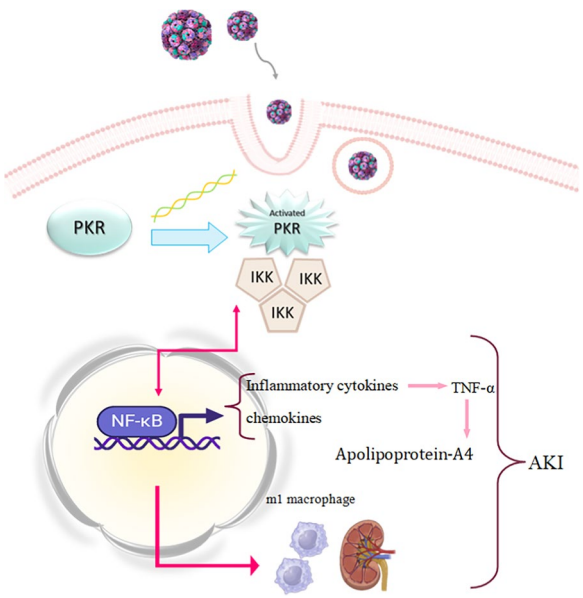

Fig. 3 Activation of NF-κβ during BKPyV infection triggers the production of antiviral molecules such as type I IFNs and proinflammatory cytokines like TNF-α which causes an elevation in apo-A4 levels during AKI, that results in aggravated inflammation and harm to the kidney. This process also, induces an increase in the infiltration of M1 macrophages into the kidneys by NF-κβ activation that can cause more damages

TGF-β signaling

TGF-β is produced by a variety of cells, including kidney cells, where BKPyV reactivates. Immunosuppressive medications taken by KTRs increase the activity of TGF-β [49]. Likewise, TGF-β enhances the BKPyV gene's activity, contributing to its

replication and subsequent reactivation in KTRs [49]. Researches revealed that when cells from individuals with BKPyV virus were activated, they produced IL-10 and TGF-β [50]. As well, inhibition of UL16-binding protein 3 (ULBP3) by BKPyV, leads to the production of TGF-β in infected cells, which then interferes with the functioning of NK cells [51].

All three isoforms of TGF-β bind to the type II TGF-β receptor, a serine/threonine kinase. Upon binding of the ligand, the type II receptor forms a heterodimer with the transforming growth factor-β type I receptor (TGFβRI), leading to the activation of Smad-dependent and independent pathways such as MAPK and GTPases, which subsequently modify gene expression. TGF-β is a crucial profibrotic growth factor that becomes activated in AKI [52].

In conclusion, BKPyV virus causes acute kidney injury through the upregulation of TGF-β, which leads to renal fibrosis and inflammation. BKPyV has been shown to enhance the activity of TGF-β, promoting its replication and reactivation within KTRs. As TGF-Beta levels rise due to BKPyV infection, the delicate balance of kidney function is disrupted. cells infected with BKPyV produce high levels of TGF-β, which can interfere with the functioning of NK cells. This interference, along with the inhibition of ULBP3 by BKPyV, leads to further upregulation of TGF-β and exacerbates kidney injury. Smad3, a key mediator of TGF-β signaling, plays a pathogenic role in renal inflammation and fibrosis [53]. Its interaction with cyclin-dependent kinase inhibitors (CDKIs) such as p21 and p27 can trigger tubular epithelial cell death by causing G1 cell-cycle arrest. This process is crucial in the pathogenesis of AKI as it triggers cell death pathways [53]. Various activators of TGF-β, such as matrix metalloproteinase and integrins, are upregulated in AKI, leading to increased TGF-β activation and subsequent tissue damage. The TGF-β signaling pathways play a role in sustaining damage to the proximal tubule by encouraging de-differentiation, cell cycle arrest, and heightened vulnerability to apoptosis. Moreover, TGF-β signaling is involved in macrophage chemotaxis, endothelial injury, and myofibroblast differentiation following AKI [54] (Fig. 4).

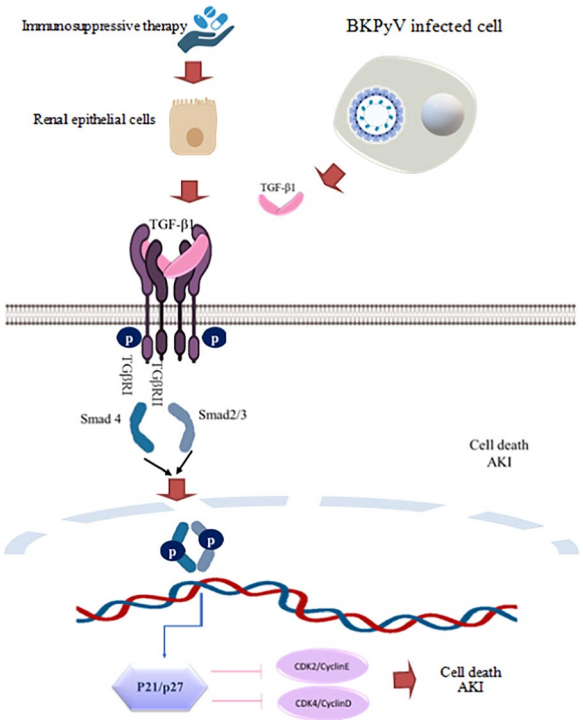

Fig. 4 BKPyV upregulates TGF-β; Smad3, an essential mediator of TGF-β signaling, promotes the expression of CDKIs like p21 and p27, leading to tubular epithelial cell death through G1 cell-cycle arrest which significantly contributes to AKI by activating cell death pathways

Inflammatory mediators

Numerous cytokines secreted by leukocytes and renal tubular cells within the damaged kidney are crucial factors in the onset and advancement of AKI inflammation, as well as contributing to BKPyVAN allograft dysfunction in kidney transplant recipients [55]. Some of the most critical cytokines are discussed below.

TNF-α

TNF-α, a multifunctional cytokine, is recognized for its various impacts on the immune system, maintaining a balance between proinflammatory and immunosuppressive effects. It plays a significant role in numerous types of renal inflammatory conditions. Although TNF-α is usually undetectable in normal kidneys, it is generated by most renal cells in the presence of inflammation. Mesangial cells and tubular epithelial cells, as well as epithelial cells and podocytes demonstrates an elevation in TNF-α expression after being exposed to certain danger signals [56].

Human collecting duct epithelial cells (HCDCs) can react to BKPyV infection through the activation of viral receptors like TLR3 and RIG-I. This activation triggers an inflammatory pathway resulting in the production of proinflammatory cytokines and chemokines. These inflammatory mediators, in conjunction with their receptors, play a crucial role in mounting an effective antiviral response. The TNF/TNFR system is often recognized as a key player in this antiviral activity [56].

In KTRs with BKPyV infection, the stimulation of TNF-α contributes to the replication of BKPyV, while the blockade of TNF-α suppresses viral replication,

presenting a potential therapeutic approach. These findings imply that neutralizing TNF-α could be a viable clinical strategy for treating BKPyV infection [57].

CD8 + T cells are essential in BKPyV infection, leading to the development of BKPyV-specific T cells in circulation and allograft tissue. Furthermore, the stimulation of VP1 and LT-Ag triggers the activation of numerous immune cells and cytokines, such as TNF-α, as the cascade continues [44]. Oxidative stress plays a significant role in ischemic and cisplatin-induced injuries by activating the NF-κB transcription factor. This activation leads to the production of proinflammatory cytokines, such as TNF-α, which is observed through increased TNF-α mRNA levels in both ischemic and cisplatin-induced renal injuries [58]. TNF-α and its receptors, TNFR1 and TNFR2 exhibit significant expression levels during renal inflammation. Upon activation of TNF-α, TNFR1's intracellular portion interacts with TNF receptor-associated death domain (TRADD), which then recruits additional adaptor proteins [59]. TNF-α triggers an elevation in apo-A4 levels during AKI, resulting in aggravated inflammation and harm to the kidney [60]. A study indicates that both LPS and intravenous TNF can lead to similar renal damage, including ultrastructural changes in the glomerular endothelial fenestrae and extensive modifications in the glomerular endothelial cell surface layer. These alterations increase albumin permeability and reduce GFR. The lack of these changes in the glomerular endothelial structure in LPS-treated Tnfr1 − / − mice, along with maintained GFR, highlights the crucial role of TNF-induced glomerular endothelial damage in LPS-induced AKI and suggests its significant involvement in the development of sepsis-induced AKI [61].

In conclusion, TNF-α plays a critical role in mediating inflammatory responses in the kidney, including in the context of BKPyV-induced AKI.

IL-6

Elevated levels of IL-6 and other proinflammatory cytokines were identified in kidney biopsies with BKPyVAN [62]. Moreover, a study indicated that IL-6 in urine rises with a high viral load of BKPyV infection [63]. The upregulation of IL-6 can be the result of TNF-α which has a role in BKPyV infection interacting with its receptors. TNF-α can enhance inflammation in human kidney cells by elevating IL-6 levels and at the same time allows for an amplification of renal tubular response to viral infection [56].

On the other hand, recent research has revealed a strong association between the expression of IL-6 and the occurrence of AKI. During the experimentation on animals with ischemic AKI, it was observed that the transcription and signaling of IL-6 were increased both locally and systemically after 60 min of bilateral kidney ischemia suggesting that the IL-6 signaling pathway has the potential to serve as both a biomarker and a target for therapeutic interventions in ischemic AKI [64]. In cases of nephrotoxin-induced AKI, there is a significant increase in IL-6 expression within the kidney, particularly in the renal TECs. This increase is strongly associated with kidney damage and plays a crucial role in activating neutrophils, which is a key mechanism underlying AKI [64]. Early elevation of urine IL-6 has been observed in patients with AKI. Studies in animals indicate that the inability of proximal tubules to metabolize IL-6 leads to higher levels of IL-6 in both the bloodstream and urine which could potentially contribute to the adverse systemic effects and heightened mortality rates associated with AKI [65].

IL-6 increases DNMT1 levels, leading to the methylation of FOXO3a and subsequent decrease in FOXO3a expression. FOXO3a inhibits the Wnt/β-catenin pathway, thereby mitigating renal fibrosis in AKI. IL-6 promotes renal fibrosis in AKI through the regulation of the DNMT1/FOXO3a/Wnt/β-catenin axis [11], highlighting the intricate role of IL-6 in the pathogenesis of AKI associated with BKPyV infection. The mechanism by which BKPyV leads to AKI through IL-6 is complex and multifaceted. The virus triggers an immune response that results in the release of IL-6, which then causes damage to the kidneys, ultimately resulting in AKI (Fig. 5).

IL-15

The upregulation of IL-15 expression by an infectious agent is essential for the activation of NK cells, CD8 T cells, and other immune system cells, allowing them to effectively eliminate pathogens. The availability of IL-15 can influence both innate and adaptive immune responses. [66]. BKPyV-infected endothelial cells exhibit a decrease in the expression of certain genes associated with the immune defense, such as IL-15, indicating the potential use of strategies by BKPyV to suppress the immune system by inhibiting the activation of genes involved in the anti-viral response[67]. Additionally, apoptosis plays a crucial role in the death of renal epithelial cells (REC) and the loss of function during AKI in various experimental models, such as sepsis, ischemia–reperfusion injury (IRI), cisplatin toxicity, mechanical obstruction, and polycystic disease, exhibit similar apoptotic features including nuclear condensation, caspase activation, DNA fragmentation, guanosine triphosphate (GTP) depletion, mitochondrial dysfunction, and the generation of reactive oxygen species [68]. IL-15's protective effects were shown in three different tests for apoptosis, which show both early and late stages of cell death. Several kidney diseases that progress to fibrosis,

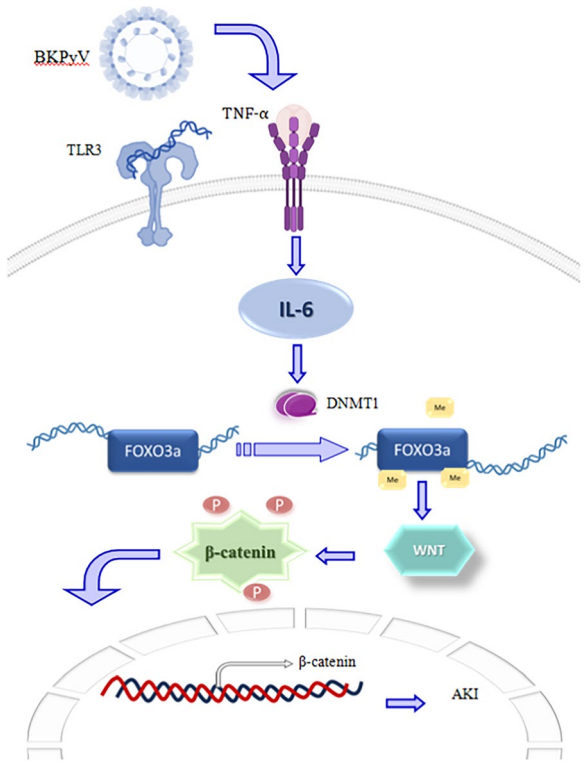

Fig. 5 During BKPyV infection, plenty of immune cells and cytokines are stimulated as the continuum cascades, including TNF-α that can enhance inflammation in human kidney cells by elevating IL-6 levels leading to elevation of DNMT1 to induce FOXO3a methylation and reduces FOXO3a expression. FOXO3a blocks the Wnt/β-catenin pathway to alleviate renal fibrosis in AKI

including acute interstitial nephritis, IgA nephropathy, and diabetic nephropathy, are also marked by an uneven ratio between IL-15 and TGF-β within the kidneys. Specifically, there is a decreased expression of IL-15 and an elevated expression of TGF-β [67].

In addition to its other functions, IL-15 can also hinder the formation of renal fibrosis. It opposes apoptosis and TGF-β induced-epithelial-mesenchymal transition in primary tubular epithelial cells through autocrine loops and membrane-bound forms. Moreover, IL-15 exhibits a protective effect on the kidneys in multiple in vivo models of acute renal injury by preventing cell death and mitigating inflammation through the inhibition of monocyte chemoattractant protein 1 (MCP-1) expression (69). Reduction of IL-15, along with the decrease in antifibrotic factors like BMP-7 and HGF, may serve as a pivotal event in the pathogenesis of renal fibrogenesis and acute and chronic kidney diseases [70].

the downregulation of IL-15 in AKI caused by the BKPyV can have detrimental effects on kidney function. IL-15 plays a crucial role in protecting the kidneys from apoptosis, inflammation, and fibrosis, and its reduction can contribute to the progression o f AKI to chronic kidney disease. Therefore, the reduction in IL-15 expression as a result of BKPyV infection can cause AKI by increasing apoptosis.

IL-11

A recent study has highlighted the roles of IL-6 and IL-11, particularly in the context of inflammatory responses (0, 3, 6, and 9 days post-infection) in the supernatants of the 3D BKPyV cell culture using enzyme-linked immunosorbent assay (ELISA). Notably, IL-11 showed a significant increase during infection, making it an interesting therapeutic target. Additionally, treating the infected 3D cultures with a neutralizing IL-11 antibody resulted in a substantial decrease in BKPyV copy rates in the treated cultures compared to the untreated ones [71].

Stimulation of tubular epithelial cells by IL-11 results in the inactivation of GSK3β through ERK- and p90RSK-mediated pathways, leading to the upregulation of SNAI1 and the expression of pro-inflammatory genes. In mice with AKI, IL-11 is upregulated in tubular epithelial cells, causing an increase in SNAI1 expression and kidney dysfunction. This effect is not observed in IL-11 deleted mice or mice treated with a neutralizing IL-11 antibody in either preemptive or treatment modes. Treatment with anti-IL11 in AKI reduces all pathological manifestations [72].

Upregulation of IL-11 in cells infected with BKPyV triggers the activation of ERK and p90RSK, leading to the phosphorylation of GSK3β at Thr43 and Ser9. This phosphorylation event results in the inactivation of GSK3β, which subsequently inhibits GSK3β-mediated SNAI1 phosphorylation. Consequently, SNAI1 accumulates and suppresses the transcription of its target genes, such as E-Cadherin, potentially contributing to the development of AKI (Fig. 6).

Conclusion

BKPyV can lead to AKI, which has implications for both short- and long-term graft function and typically involves a mortality risk. BKPyV has the potential to induce the onset of TIN via inflammatory mechanisms, which have been documented in adult individuals experiencing unexplained non-oliguric or AKI. The inflammatory substances released by leukocytes and renal tubular cells during BKPyV infection can stimulate immune cell activation and the production of various cytokines. The molecular processes underlying the inflammation of leukocytes and renal tubular cells release a variety of cytokines in the context of kidney damage that has the potential to induce AKI. Additionally, signaling pathways such as TGF-β and NF-κβ, which are activated during viral infections, may contribute to AKI by heightening

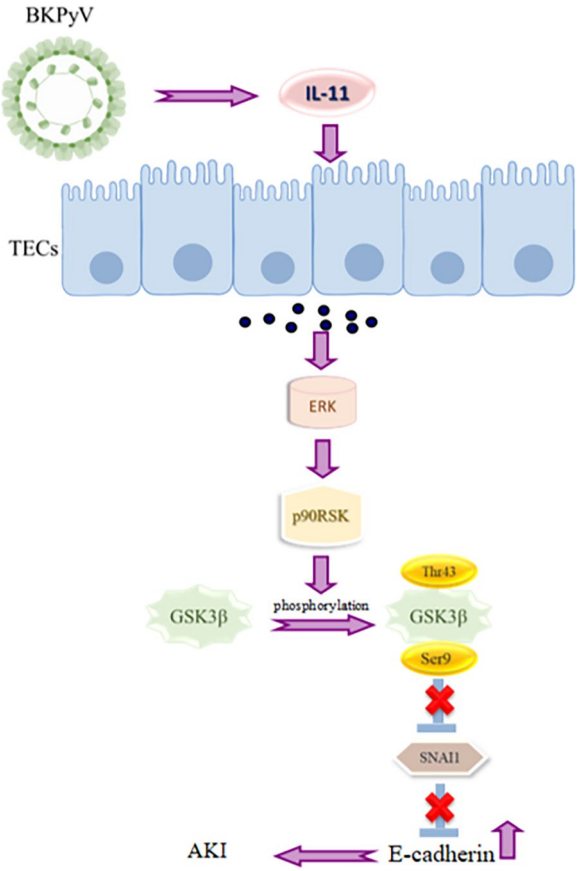

Fig. 6 Elevated IL-11 levels during BKPyV infection lead to increased activity of ERK and p90RSK. This results in GSK3β inactivation by phosphorylation of Thr43 and Ser9. This prevents GSK3β-mediated SNAI1 phosphorylation causing SNAI1 accumulation and the transcriptional suppression of its target genes, prototypically E-Cadherin which can lead to AKI

susceptibility to apoptosis and causing tissue damage. Detecting BKPyV infection at an early stage and promptly reducing immunosuppression can be a beneficial tactic in safeguarding the functionality of the allograft.

Abbreviations

AKI	Acute kidney injury
KTRs	Kidney transplant recipients
BKPyV	BK polyomavirus
ESRD	End-stage renal disease
LT-Ag	Large T antigen
st-Ag	Small T antigen
NCCR	Non-coding regulatory domain
ICU	Intensive care unit
UTIs	Urinary tract infections
TIN	Tubulointerstitial nephritis
MyD88	Myeloid differentiation primary response 88
TRIF	TIR-domain-containing adapter-inducing interferon-β
ULBP3	UL16-binding protein 3
TβRI	Transforming growth factor-β type I receptor
CDKIs	Cyclin-dependent kinase inhibitors
TRADD	TNF receptor-associated death domain
REC	Renal epithelial cells
IRI	Ischemia-reperfusion injury
GTP	Guanosine triphosphate
MCP-1	Of monocyte chemoattractant protein 1
ELISA	Enzyme-linked immunosorbent assay

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Author contributions
The study concept and design, drafting of manuscript and critical revision of the manuscript were done by S.B., A.A., and R.Y. All authors read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev. 2016;37(2):85.
2. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders H-J. Acute kidney injury. Nat Rev Dis Primers. 2021;7(1):1. https://doi.org/10.1038/s41572-021-00284-z.
3. Camargo-Salamanca A, Garcia-Lopez A, Patino-Jaramillo N, Giron-Luque F. Acute kidney injury in hospitalized kidney transplant recipients. Trans Proc. 2020;52(10):3209–13. https://doi.org/10.1016/j.transproceed.2019.12.046.
4. Abu BG, Jawdeh AG. Acute kidney injury in transplant setting: differential diagnosis and impact on health and health care. Adv Chronic Kidney Dis. 2017;24(4):228–32. https://doi.org/10.1053/j.ackd.2017.05.005.
5. Yogo Y, Sugimoto C, Zhong S, Homma Y. Evolution of the BK polyomavirus: epidemiological, anthropological and clinical implications. Rev Med Virol. 2009;19(4):185–99. https://doi.org/10.1002/rmv.613.
6. Furmaga J, Kowalczyk M, Zapolski T, Furmaga O, Krakowski L, Rudzki G, Jaroszyński A, Jakubczak A. Bk polyomavirus—biology, genomic variation and diagnosis. Viruses. 2021;13(8):1502. https://doi.org/10.3390/v13081502.
7. Papadimitriou JC, Randhawa P, Hanssen Rinaldo C, Drachenberg CB, Alexiev B, Hirsch HH. BK Polyomavirus Infection and Renourinary Tumorigenesis. Am J Trans. 2016;16(2):398–406. https://doi.org/10.1111/ajt.13550.
8. Limaye AP, Brennan DC. Kidney transplantation in adults: BK polyomavirus-associated nephropathy. UpToDate. 2021;
9. Ren N, Wang W-F, Zou L, Zhao Y-L, Miao H, Zhao Y-Y. The nuclear factor kappa B signaling pathway is a master regulator of renal fibrosis. Front Pharmacol. 2024;14:1335094. https://doi.org/10.3389/fphar.2023.1335094.

10. Park CH, Yoo T-H. TGF-β inhibitors for therapeutic management of kidney fibrosis. Pharmaceuticals. 2022;15(12):1485. https://doi.org/10.3390/ph15121485.
11. Guo X, Zhu Y, Sun Y, Li X. IL-6 accelerates renal fibrosis after acute kidney injury via DNMT1-dependent FOXO3a methylation and activation of Wnt/β-catenin pathway. Int Immunopharmacol. 2022;109:108746. https://doi.org/10.1016/j.intimp.2022.108746.
12. Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt K-U, Nahas ME, Jaber BL, Jadoul M, Levin A, Powe NR, Rossert J, Wheeler DC, Lameire N, Eknoyan G. Chronic kidney disease as a global public health problem: approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes. Kidney Int. 2007;72(3):247–59. https://doi.org/10.1038/sj.ki.5002343.
13. Wolfe RA, Roys EC, Merion RM. Trends in organ donation and transplantation in the United States, 1999-2008. Am J Trans. 2010;10(4):961–72. https://doi.org/10.1111/j.1600-6143.2010.03021.x.
14. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, Klarenbach S, Gill J. Systematic review: Kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Trans. 2011;11(10):2093–109. https://doi.org/10.1111/j.1600-6143.2011.03686.x.
15. Avihingsanon Y, Ingsathit A, Premasathian N, Pongskul C, Jittiganont S, Sumethkul V. Different etiologies of graft loss and death in asian kidney transplant recipients: a report from Thai transplant registry: 1329. Trans J. 2010;90:390. https://doi.org/10.1097/00007890-201007272-00721.
16. Sawinski D, Goral S. BK virus infection: an update on diagnosis and treatment. Nephrol Dialysis Trans. 2015;30(2):209–17. https://doi.org/10.1093/ndt/gfu023.
17. Safa K, Heher E, Gilligan H, Williams W Jr, Tolkoff-Rubin N, Wojciechowski D. BK virus after kidney transplantation: a review of screening and treatment strategies and a summary of the Massachusetts general hospital experience. Clin Trans. 2015;31:257–63.
18. Ambalathingal GR, Francis RS, Smyth MJ, Smith C, Khanna R. BK polyomavirus: Clinical aspects, immune regulation, and emerging therapies. Clin Microbiol Rev. 2017;30(2):503–28. https://doi.org/10.1128/CMR.00074-16.
19. Gardner S, Field A, Coleman D, Hulme B. New human papovavirus (BK) isolated from urine after renal transplantation. Lancet. 1971;297(7712):1253–7. https://doi.org/10.1016/S0140-6736(71)91776-4.
20. Sharma R, Zachariah M. Bk virus nephropathy: prevalence, impact and management strategies. Int J Nephrol Renovascular Dis. 2020;13:187–92. https://doi.org/10.2147/IJNRD.S236556.
21. Sahragard I, Mohammadi A, Yaghobi R, Pakfetrat M, Afshari A, Sharifi H, Ghaemi M. The relation of NCCR variations and host transcription factors gene regulation in BK polyomavirus infected kidney transplant patients. Gene. 2023;878:147567. https://doi.org/10.1016/j.gene.2023.147567.
22. Karantanos T, Kim HT, Tijaro-Ovalle NM, Li L, Cutler C, Antin JH, Ballen K, Marty FM, Tan CS, Ritz J, Politikos I, Boussiotis V. Reactivation of BK virus after double umbilical cord blood transplantation in adults correlates with impaired reconstitution of CD4+ and CD8+ T effector memory cells and increase of T regulatory cells. Clinical Immunol. 2019;207:18–23. https://doi.org/10.1016/j.clim.2019.06.010.
23. Cohen-Bucay A, Ramirez-Andrade SE, Gordon CE, Francis JM, Chitalia VC. Advances in BK virus complications in organ transplantation and beyond. Kidney Med. 2020;2(6):771–86. https://doi.org/10.1016/j.xkme.2020.06.015.
24. Abend JR, Low JA, Imperiale MJ. Global effects of BKV infection on gene expression in human primary kidney epithelial cells. Virology. 2010;397(1):73–9. https://doi.org/10.1016/j.virol.2009.10.047.
25. Afshari A, Yaghobi R, Rezaei G. Inter-regulatory role of microRNAs in interaction between viruses and stem cells. World J Stem Cells. 2021;13(8):985–1004. https://doi.org/10.4252/wjsc.v13.i8.985.
26. Kant S, Dasgupta A, Bagnasco S, Brennan DC. BK virus nephropathy in kidney transplantation: a state-of-the-art review. Viruses. 2022;14(8):1616. https://doi.org/10.3390/v14081616.
27. Manzano Sánchez D, Jimeno García L, Manzano Sánchez D, López Jiménez I, Saura Luján IM, González Soriano MJ, Llorente Viñas S, Gil Muñoz M, Carbajo Mateo T. Renal function impairment in kidney transplantation: importance of early BK virus detection. Trans Proc. 2019;51(2):350–2. https://doi.org/10.1016/j.transproceed.2018.12.016.
28. Höcker B, Schneble L, Murer L, Carraro A, Pape L, Kranz B, Jun O, Zirngibl M, Dello Strologo L, Büscher A, Weber LT, Awan A, Pohl M, Bald M, Printza N, Rusai K, Peruzzi L, Topaloglu R, Fichtner A, Krupka K, Köster L, Bruckner T, Schnitzler P, Hirsch HH, Tönshoff B. Epidemiology of and risk factors for BK polyomavirus replication and nephropathy in pediatric renal transplant recipients: an international CERTAIN registry study. Transplantation. 2019;103(6):1224–33. https://doi.org/10.1097/TP.0000000000002414.
29. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, Torrence S, Schuessler R, Roby T, Gaudreault-Keener M, Storch GA. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Trans. 2005;5(3):582–94. https://doi.org/10.1111/j.1600-6143.2005.00742.x.
30. Rahimi Z, Yaghobi R, Afshari A, Roozbeh J, Mokhtari MJ, Hosseini AM. The effect of BKV reactivation on cytokines behavior in kidney transplanted patients. BMC Nephrol. 2022;23(1):02645. https://doi.org/10.1186/s12882-021-02645-y.
31. Sarvestani FS, Afshari A, Azarpira N. The role of non-protein-coding RNAs in ischemic acute kidney injury. Front Immunol. 2024;15:1230742. https://doi.org/10.3389/fimmu.2024.1230742.
32. Kathuria P, Khurana A. Acute kidney injury. Nutr Ther Chronic Kidney Dis. 2016;7(1):55–72.
33. Devarajan P. Update on mechanisms of ischemic acute kidney injury. J Am Soc Nephrol. 2006;17(6):1503–20. https://doi.org/10.1681/ASN.2006010017.
34. Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A. Epidemiology and outcomes in community-acquired versus hospital-acquired aki. Clin J Am Soc Nephrol. 2014;9(6):1007–14. https://doi.org/10.2215/CJN.07920713.
35. Fiorentino M, Bagagli F, Deleonardis A, Stasi A, Franzin R, Conserva F, Infante B, Stallone G, Pontrelli P, Gesualdo L. Acute kidney injury in kidney transplant patients in intensive care unit: from pathogenesis to clinical management. Biomedicines. 2023;11(5):1474. https://doi.org/10.3390/biomedicines11051474.
36. Canet E, Zafrani L, Azoulay É. The critically Ill kidney transplant recipient. Chest. 2016;149(6):1546–55. https://doi.org/10.1016/j.chest.2016.01.002.
37. Hsiao C-Y, Yang H-Y, Hsiao M-C, Hung P-H, Wang M-C. Risk factors for development of acute kidney injury in patients with urinary tract infection. PLoS ONE. 2015;10(7):e0133835. https://doi.org/10.1371/journal.pone.0133835.
38. Prasad N, Patel MR. Infection-induced kidney diseases. Front Med. 2018;5:00327. https://doi.org/10.3389/fmed.2018.00327.
39. Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. Clin J Am Soc Nephrol. 2007;2(Supplement_1):S36–46. https://doi.org/10.2215/CJN.00920207.
40. Alangaden GJ, Thyagarajan R, Gruber SA, Morawski K, Garnick J, El-Amm JM, et al. Infectious complications after kidney transplantation: Current epidemiology and associated risk factors. Clin Trans. 2006;20(4):401–9.
41. Joyce E, Glasner P, Ranganathan S, Swiatecka-Urban A. Tubulointerstitial nephritis: diagnosis, treatment, and monitoring. Pediatric Nephrol. 2017;32(4):577–87. https://doi.org/10.1007/s00467-016-3394-5.
42. Santoro MG. NEW EMBO MEMBER'S REVIEW: NF-kappaB and virus infection: who controls whom. EMBO J. 2003;22(11):2552–60. https://doi.org/10.1093/emboj/cdg267.
43. Pichlmair A, Schulz O, Tan CP, Naslund TI, Liljestrom P, Weber F, et al. RIG-I-mediated antiviral responses to single-stranded RNA bearing 5'-phosphates. Science. 2006;314(5801):997–1001.
44. Chancharoenthana W, Leelahavanichkul A. Innate immunity response to BK virus infection in polyomavirus-associated nephropathy in kidney transplant recipients. Transplantology. 2022;3(1):20–32. https://doi.org/10.3390/transplantology3010003.
45. Song K, Li S. The role of ubiquitination in NF-κB signaling during virus infection. Viruses. 2021;13(2):145. https://doi.org/10.3390/v13020145.
46. Li N, Chen J, Wang P, Fan H, Hou S, Gong Y. Major signaling pathways and key mediators of macrophages in acute kidney injury (Review). Mol Med Rep. 2021;23(6):12094. https://doi.org/10.3892/mmr.2021.12094.
47. Yang L, Brooks CR, Xiao S, Sabbisetti V, Yeung MY, Hsiao L-L, Ichimura T, Kuchroo V, Bonventre JV. KIM-1–mediated phagocytosis reduces acute injury to the kidney. J Clin Invest. 2015;125(4):1620–36. https://doi.org/10.1172/JCI75417.
48. Song N, Thaiss F, Guo L. NFκB and kidney injury. Front Immunol. 2019;10:00815. https://doi.org/10.3389/fimmu.2019.00815.
49. Abend JR, Imperiale MJ. Transforming growth factor-beta-mediated regulation of BK virus gene expression. Virology. 2008;378(1):6–12. https://doi.org/10.1016/j.virol.2008.05.009.

50. Sais G, Wyler S, Hudolin T, Banzola I, Mengus C, Bubendorf L, Wild PJ, Hirsch HH, Sulser T, Spagnoli GC, Provenzano M. Differential patterns of large tumor antigen-specific immune responsiveness in patients with BK polyomavirus-positive prostate cancer or benign prostatic hyperplasia. J Virol. 2012;86(16):8461–71. https://doi.org/10.1128/JVI.00005-12.
51. Kariminik A, Yaghobi R, Dabiri S. Innate immunity and BK Virus: Prospective strategies. Viral Immunol. 2016;29(2):74–82. https://doi.org/10.1089/vim.2015.0099.
52. Peinado H, Quintanilla M, Cano A. Transforming growth factor β-1 induces Snail transcription factor in epithelial cell lines. J Biol Chem. 2003;278(23):21113–23. https://doi.org/10.1074/jbc.M211304200.
53. Wenjing W, Wang X, Xueqing Y, Lan H-Y. Smad3 signatures in renal inflammation and fibrosis. Int J Biol Sci. 2022;18(7):2795–806. https://doi.org/10.7150/ijbs.71595.
54. Gewin LS. Transforming growth factor-β in the acute kidney injury to chronic kidney disease transition. Nephron. 2019;143(3):154–7.
55. Akcay A, Nguyen Q, Edelstein CL. Mediators of inflammation in acute kidney injury. Med Inflam. 2009;2009:1–12. https://doi.org/10.1155/2009/137072.
56. Ribeiro A, Merkle M, Motamedi N, Nitschko H, Köppel S, Wörnle M. BK virus infection activates the TNFα/TNF receptor system in Polyomavirus-associated nephropathy. Mol Cell Biochem. 2016;411(1–2):191–9.
57. Li Y-J, Wang J-W, Hsin-Hsu W, Wang H-H, Chiang Y-J, Yang H-Y, Hsu H-H, Yang C-W, Tian Y-C. Tumor necrosis factor-alpha blockade suppresses BK polyomavirus replication. Infection. 2022;51(4):967–80. https://doi.org/10.1007/s15010-022-01962-0.
58. Ganesan Ramesh W, Reeves B. TNF-α mediates chemokine and cytokine expression and renal injury in cisplatin nephrotoxicity. J Clin Invest. 2002;110(6):835–42. https://doi.org/10.1172/JCI15606.
59. Al-Lamki RS, Mayadas TN. TNF receptors: signaling pathways and contribution to renal dysfunction. Kidney Int. 2015;87(2):281–96. https://doi.org/10.1038/ki.2014.285.
60. Lee HH, Cho YI, Kim SY, Yoon YE, Kim KS, Hong SJ, Han WK. TNF-α-induced inflammation stimulates apolipoprotein-A4 via activation of TNFR2 and NF-κB signaling in kidney tubular cells. Sci Rep. 2017;7(1):08785. https://doi.org/10.1038/s41598-017-08785-2.
61. Chang X, Chang A, Hack BK, Eadon MT, Alper SL, Cunningham PN. TNF-mediated damage to glomerular endothelium is an important determinant of acute kidney injury in sepsis. Kidney Int. 2014;85(1):72–81. https://doi.org/10.1038/ki.2013.286.
62. Zeng G, Wang Z, Huang Y, Abedin Z, Liu Y, Randhawa P. Cellular and viral miRNA expression in polyomavirus BK infection. Trans Infect Dis. 2019;21(5):13159. https://doi.org/10.1111/tid.13159.
63. Sadeghi M, Daniel V, Schnitzler P, Lahdou I, Naujokat C, Zeier M, Opelz G. Urinary proinflammatory cytokine response in Renal transplant recipients with polyomavirus BK Viruria. Transplantation. 2009;88(9):1109–16. https://doi.org/10.1097/TP.0b013e3181ba0e17.
64. Hua S, Lei C-T, Zhang C. Interleukin-6 signaling pathway and its role in kidney disease: an update. Front Immunol. 2017;8:1–10. https://doi.org/10.3389/fimmu.2017.00405.
65. Dennen P, Altmann C, Kaufman J, Klein CL, Andres-Hernando A, Ahuja NH, Edelstein CL, Cadnapaphornchai MA, Keniston A, Faubel S. Urine interleukin-6 is an early biomarker of acute kidney injury in children undergoing cardiac surgery. Crit Care. 2010;14:1–13. https://doi.org/10.1186/cc9289.
66. Verbist KC, Klonowski KD. Functions of IL-15 in anti-viral immunity: multiplicity and variety. Cytokine. 2012;59(3):467–78. https://doi.org/10.1016/j.cyto.2012.05.020.
67. Van Aalderen MC, Heutinck KM, Huisman C, Ten Berge IJ. BK virus infection in transplant recipients: clinical manifestations, treatment options and the immune response. Neth J Med. 2012;70(4):172–83.
68. Stoian M, Dumitrache AM, Cîrciu F, Stănică R, Stoica V. Apoptosis in acute kidney injury. Int Med. 2020;17(1):45–53. https://doi.org/10.2478/inmed-2020-0101.
69. Shinozaki M, Hirahashi J, Lebedeva T, Liew FY, Salant DJ, Maron R, Kelley VR. IL-15, a survival factor for kidney epithelial cells, counteracts apoptosis and inflammation during nephritis. J Clin Invest. 2002;109(7):951–60. https://doi.org/10.1172/JCI0214574.
70. Devocelle A, Lecru L, Ferlicot S, Bessede T, Candelier J-J, Giron-Michel J, François H. IL-15 prevents renal fibrosis by inhibiting collagen synthesis: A new pathway in chronic kidney disease? Int J Mol Sci. 2021;22(21):11698. https://doi.org/10.3390/ijms222111698.
71. Schneidewind L, Neumann T, Krüger W, Hakenberg OW, Schmidt CA. Targeting IL-11 in the treatment of BK virus-associated haemorrhagic cystitis—A promising new approach. J Cel Mol Med. 2020;24(16):9097–100. https://doi.org/10.1111/jcmm.15546.
72. Widjaja AA, Viswanathan S, Shekeran SG, Adami E, Lim WW, Chothani S, et al. Targeting endogenous kidney regeneration using anti-IL11 therapy in acute and chronic models of kidney disease. Nat Commun. 2022;13(1):7497.

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