ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

The Role of TAX1BP1 in Acute Kidney Injury

Enxian Chen[1,2,a,*], Chunyang Li[1,2,b]

[1]School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai, 200093, China
[2]School of Anesthesiology, Naval Medical University / Second Military Medical University, Shanghai, 200433, China
[a]18213404691@163.com, [b]lcy82229400@163.com
[*]Corresponding author

Abstract: *Acute kidney injury (AKI) is a prevalent clinical syndrome with high morbidity and mortality that frequently progresses to chronic kidney disease. Its pathogenesis involves complex interactions among oxidative stress, inflammation, and programmed cell death. Tax1-binding protein 1 (TAX1BP1) has recently emerged as a key regulator connecting selective autophagy with inflammatory signaling to protect renal function. Mechanistically, TAX1BP1 confers renal protection through two complementary pathways. As a selective autophagy receptor, it protects cellular function by clearing damaged mitochondria and pro-inflammatory substrates. Additionally, it can assemble the A20 ubiquitin-editing complex to suppress NF-κB-driven inflammation and modulate cell death. Given that TAX1BP1 overexpression attenuates renal injury in animal models, targeting this molecule represents a promising therapeutic strategy for AKI.*

Keywords: *TAX1BP1, Acute kidney injury, Selective autophagy, Mitochondrial autophagy, NF-κB signalling pathway*

1. Introduction

Acute kidney injury (AKI) is a common clinical syndrome with rising global incidence, particularly in intensive care units[1]. Its association with increased risk of chronic kidney disease progression underscores the urgent need for effective therapeutic interventions[2]. The pathogenesis of AKI involves multiple mechanisms, including oxidative stress, inflammatory responses, ischemia-hypoxia, and microvascular dysfunction[3, 4]. Thus, understanding AKI pathogenesis and developing effective interventions to attenuate renal injury hold important clinical implications, with autophagy increasingly recognized as a key protective mechanism[5, 6].Autophagy is an essential intracellular degradation mechanism that maintains cellular homeostasis by removing damaged organelles and misfolded proteins[7, 8]. Its protective role in AKI has been well documented. Studies using tubule-specific Atg5 knockout mice demonstrated that loss of proximal tubular autophagy markedly worsens ischemia-reperfusion-induced renal injury[9]. Consistently, pharmacological inhibition of autophagy with 3-MA intensifies cellular damage following hypoxia, supporting autophagy induction as a potential therapeutic strategy for AKI[10, 11].

Tax1-binding protein 1 (TAX1BP1), originally named for its interaction with the HTLV-1 Tax protein [12], has been identified as both a selective autophagy receptor and a negative regulator of NF-κB signaling[13, 14]. TAX1BP1 participates in clearing damaged mitochondria, protein aggregates, and invading pathogens[15, 16]. Recent studies have revealed that TAX1BP1 mediates VDAC1-dependent mitophagy through the PINK1/Parkin pathway to reduce oxidative injury, which revealed its renal protective functions[17, 18]. Moreover, other studies have found that it can promote autophagic degradation of the pro-inflammatory receptor TARM1 in macrophages to attenuate renal inflammation[19].These investigations establish that TAX1BP1 represents a promising molecular target linking autophagy and inflammation in AKI. Here, we summarize current understanding of TAX1BP1's structure, biological functions, and protective mechanisms, and discuss its therapeutic potential for AKI treatment.

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

2. Molecular Structure and Biological Functions of TAX1BP1

2.1 Domain Composition of TAX1BP1

TAX1BP1, also known as T6BP or CALCOCO3, is a conserved protein of 789 amino acids in mammals[20] (Figure 1). It contains three functional regions that cooperate in selective autophagy. At the N-terminus, the SKICH domain (~200 amino acids) binds RB1CC1/FIP200 to recruit the autophagy initiation complex[21–23], and also interacts with TBK1 adaptors NAP1 and SINTBAD[22, 24].The central region has three coiled-coil (CC) domains for homodimerization and binding with A20 and ITCH[25, 26]. At the C-terminus, two zinc finger domains (ZnF1 and ZnF2) are present, where ZnF2 recognizes K63-linked and M1-linked polyubiquitin chains[27, 28]. ZnF2 mutations (C716A/C719A) can disrupt substrate binding and block autophagosome recruitment[24].TAX1BP1 also has two LC3-interacting regions (LIR motifs) that bind ATG8 proteins (LC3, GABARAP) on autophagosome membranes [22]. Notably, TAX1BP1 uses a non-canonical binding mode when interacting with GABARAP[24]. Together, these domains allow TAX1BP1 to recognize ubiquitinated cargo (via ZnF2), anchor to autophagosomes (via LIR), and recruit initiation machinery (via SKICH), linking substrate recognition to autophagosome formation[24, 29, 30].

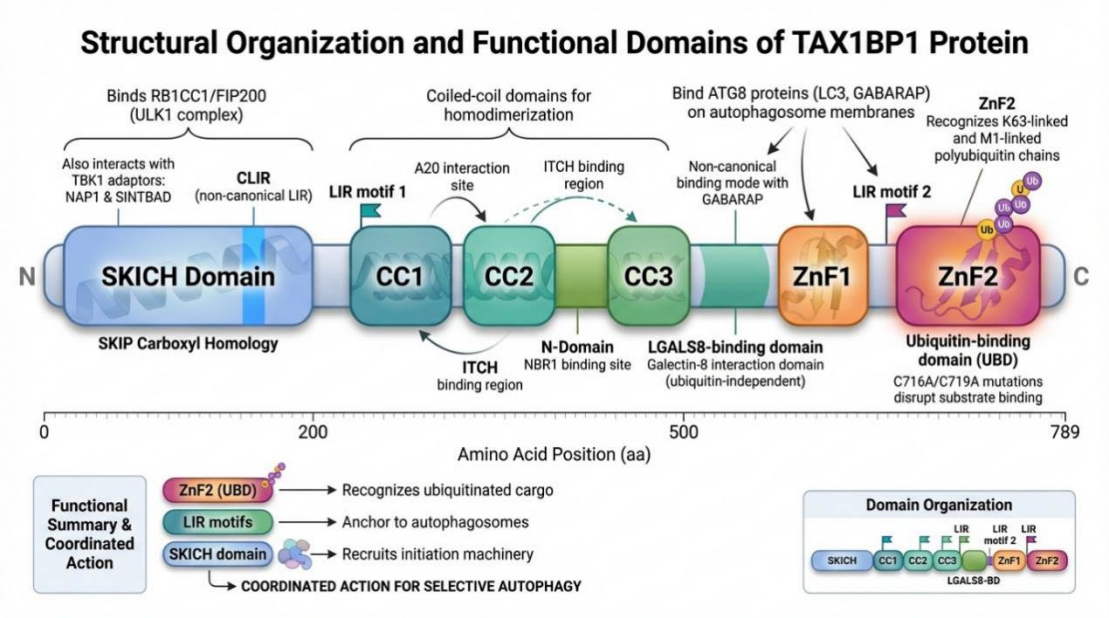

Figure 1. Structural organization and functional domains of TAX1BP1. The schematic illustrates the 789-amino acid sequence of mammalian TAX1BP1 from the N-terminus to the C-terminus. Annotated structures include the N-terminal SKICH domain, three central coiled-coil domains (CC1–CC3), and two C-terminal zinc-finger domains (ZnF1 and ZnF2). Key functional motifs, such as the non-canonical LIR (CLIR), typical LIR motifs (1 and 2), and the ubiquitin-binding domain (UBD) within ZnF2, are highlighted. Binding regions for major interacting partners (e.g., the ULK1 complex, ATG8 proteins, and polyubiquitin chains) are indicated along the sequence. The lower panels provide a concise domain summary and outline the coordinated roles of the SKICH, LIR, and ZnF2 domains during selective autophagy.

2.2 Function of TAX1BP1 as a selective autophagy receptor

2.2.1 Molecular Mechanism of Selective Autophagy

Selective autophagy degrades specific intracellular substrates through autophagy receptors. TAX1BP1 executes this process via three coordinated steps: recognition, recruitment, and isolation[31].During recognition, the ZnF2 domain identifies substrates tagged with K63- or M1-linked ubiquitin chains, such as damaged mitochondrial membrane proteins or invading bacteria[32]. For recruitment, TAX1BP1 binds LC3/GABARAP on autophagosome membranes through its LIR motif and simultaneously engages RB1CC1 via its SKICH domain[33, 34]. In the isolation step, a "two-step model" has been proposed: receptors like p62/NBR1 first aggregate the cargo, then recruit TAX1BP1, whose SKICH domain brings in RB1CC1 to initiate autophagosome membrane formation around the cargo[34, 35]. Beyond cargo

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

recognition, TAX1BP1 also acts downstream of NBR1 in selective autophagy, where its SKICH-RB1CC1 interaction is essential for autophagosome nucleation[34, 36, 37].

2.2.2 TAX1BP1-mediated selective autophagy types

TAX1BP1 was first identified as an autophagy receptor for clearing intracellular bacteria[38]. Its ZnF2 domain binds K63-linked ubiquitin chains on bacterial surfaces and recruits Myosin VI to transport bacteria to lysosomes[39, 40]. TAX1BP1 knockdown leads to accumulation of ubiquitin-tagged Salmonella and increased bacterial survival[39]. Similar functions were observed in Mycobacterium tuberculosis clearance[41, 42].Interestingly, galectin-8 (LGALS8) serves as a co-receptor that cooperates with TAX1BP1 to degrade bacteria in damaged phagosomes through a ubiquitin-independent pathway[43, 44].TAX1BP1 also clears protein aggregates. Mice lacking the ZnF2 domain show significant lipofuscin accumulation in aged brains, indicating impaired aggregate clearance[45]. In vitro studies confirm that TAX1BP1 limits aggregation of disease-related proteins, including polyQ-HTT (Huntington's disease) and TDP-43 (amyotrophic lateral sclerosis)[45, 46].Beyond classical aggrephagy, TAX1BP1 regulates innate immunity by degrading aggregated signaling adaptors. It targets TICAM1 (TRIF) oligomers for TRIM32-dependent autophagic degradation, thereby suppressing TLR3/4 signaling[47, 28]. Notably, TAX1BP1 deficiency increases susceptibility to TLR3/4-induced necroptosis, while p62 or CALCOCO1 deficiency does not, suggesting a unique role for TAX1BP1 in necrosome clearance [48].

TAX1BP1 also participates in organelle-specific autophagy. In mitophagy, TAX1BP1 is recruited to depolarized mitochondria along with OPTN and NDP52 via the PINK1/Parkin pathway, though its contribution appears minor compared to other receptors[49, 50]. In contrast, TAX1BP1 plays a more prominent role in lysophagy. Upon lysosomal damage, TAX1BP1 recognizes ubiquitinated membrane proteins and recruits TBK1 and RB1CC1 to initiate clearance of damaged lysosomes [51].

2.3 Regulatory Role of TAX1BP1 in Inflammatory Signalling Pathways

2.3.1 Negative Regulation of the NF-κB Signalling Pathway

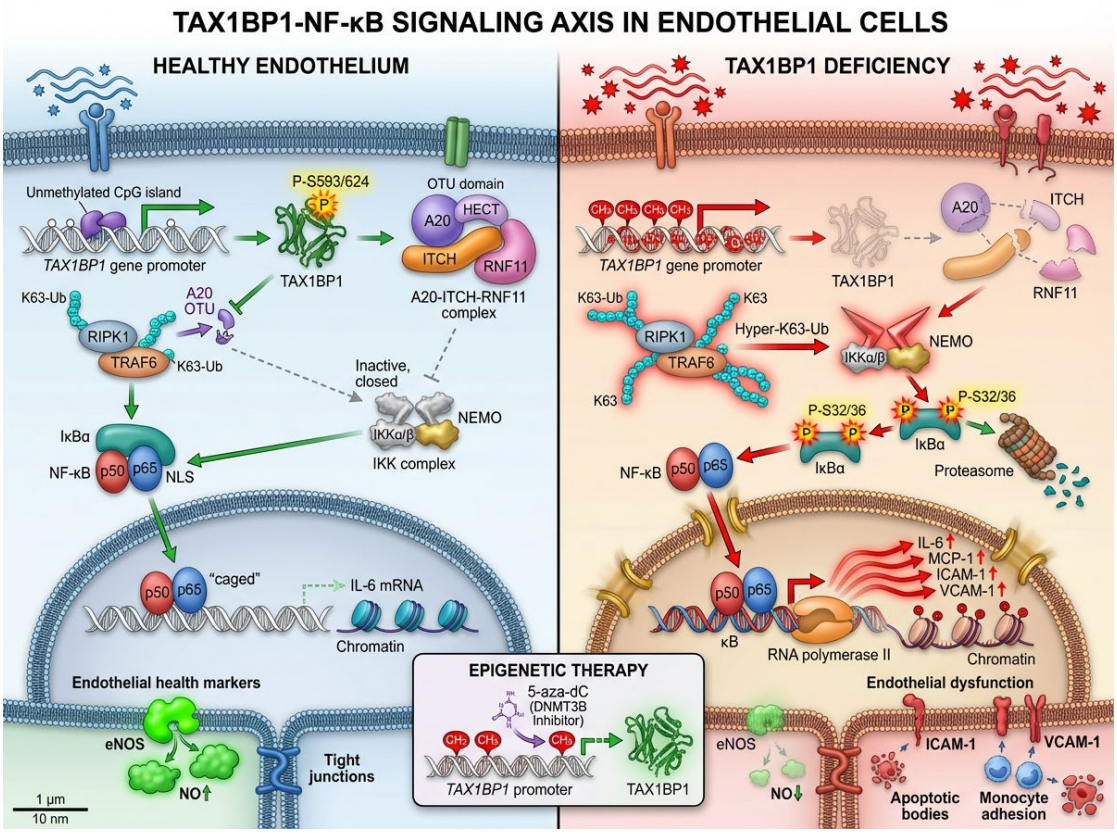

Figure 2. Epigenetic regulation of the TAX1BP1–NF-κB signaling axis in endothelial cells.In healthy e ndothelium, an unmethylated TAX1BP1 promoter permits TAX1BP1 expression and assembly of the A2 0–ITCH–RNF11 complex, which restrains NF-κB activation and maintains endothelial homeostasis. In contrast, promoter hypermethylation suppresses TAX1BP1 expression, disrupts this inhibitory complex

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

, enhances IKK activation and IκBα degradation, and promotes NF-κB nuclear translocation and trans cription of pro-inflammatory genes, including IL-6, MCP-1, ICAM-1, and VCAM-1, leading to endothe lial dysfunction. The inset shows that demethylating therapy (e.g., 5-aza-dC) may restore TAX1BP1 exp ression and suppress this inflammatory pathway.

Prior to its identification as an autophagy receptor, TAX1BP1 was extensively studied for its regulatory role in NF-κB signaling[52, 53]. NF-κB is a key transcription factor that drives inflammatory responses[54]. Under basal conditions, it remains inactive in the cytoplasm bound to IκB. Upon stimulation, IKK phosphorylates IκB, leading to its degradation and NF-κB nuclear translocation[55, 56].TAX1BP1 serves as a scaffold in the A20 ubiquitin-editing complex, which includes A20 (TNFAIP3), ITCH, and RNF11[52, 53]. After TNF-α stimulation, IKKα/β phosphorylates TAX1BP1 at Ser-418, enabling it to bind A20 and ITCH and target upstream molecules like RIPK1 and NEMO[57]. The complex then removes K63-linked ubiquitin chains while adding K48-linked chains, promoting substrate degradation and terminating NF-κB activation[53, 58]. TAX1BP1 also interacts with ABIN-1 to enhance A20 activity[59]. Loss of TAX1BP1 disrupts A20 complex formation, causing persistent RIPK1 ubiquitination and sustained NF-κB activation[52, 53]. It was observed in disease models that TAX1BP1 promoter hypermethylation in endothelial cells reduces its expression and leads to chronic inflammation and endothelial dysfunction[60] (Figure 2).

2.3.2 Regulation of Innate Immune Signalling

Besides NF-κB, TAX1BP1 also regulates innate immune pathways including RLR and TLR signaling[28]. In the RLR pathway, viral RNA activates RIG-I or MDA5, which recruit the adaptor MAVS to trigger downstream TBK1-IRF3 and IKK-NF-κB signaling[61, 62]. TAX1BP1 negatively regulates this pathway by interacting with MAVS at mitochondria and recruiting ITCH to promote MAVS ubiquitination and degradation[63]. TAX1BP1 knockdown enhances virus-induced apoptosis, while TAX1BP1-deficient cells show increased MAVS aggregates, indicating its role in MAVS clearance[26]. In the TLR pathway, TLR3/4 activation leads to TICAM1 (TRIF) oligomerization and downstream signaling[64] (Figure 3). TAX1BP1 cooperates with TRIM32 to promote TICAM1 ubiquitination and autophagic degradation, thereby suppressing TLR3/4 signaling[47]. Proteomic studies confirmed that TICAM1 aggregates accumulate in autophagy-deficient macrophages, while TAX1BP1 mediates their clearance[47, 65].

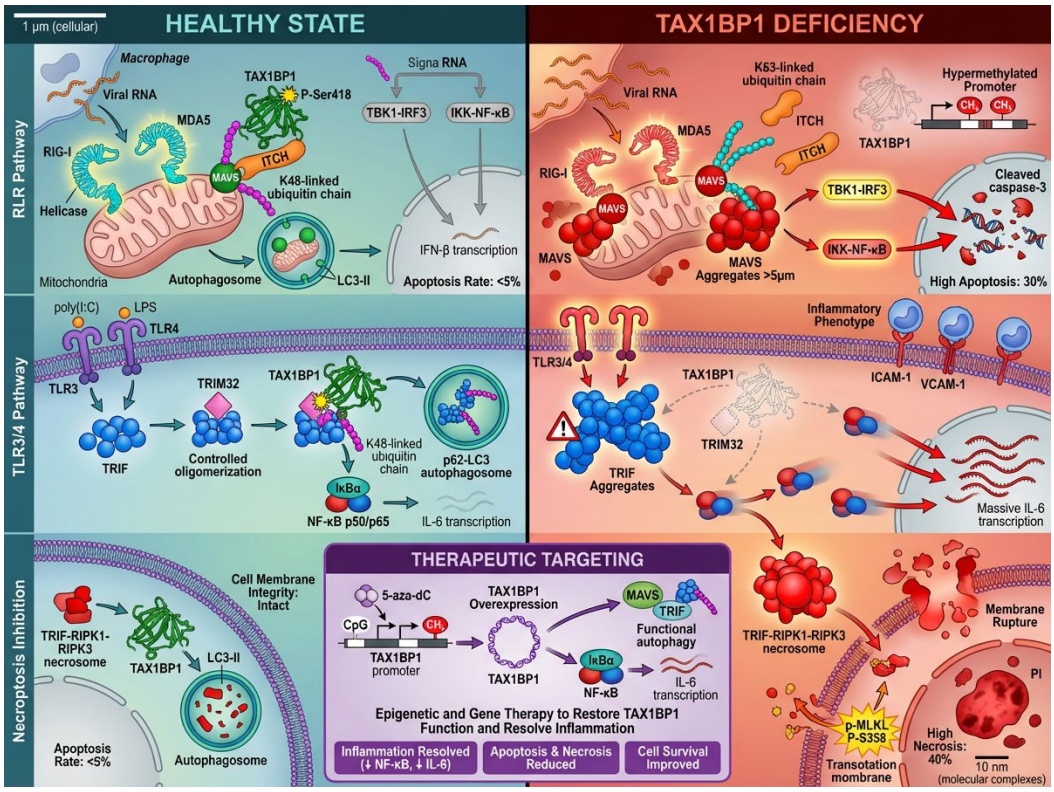

Figure 3. Regulation of RLR, TLR3/4, and necroptosis pathways by TAX1BP1.In the RLR pathway, TA X1BP1 limits antiviral signaling by promoting MAVS ubiquitination and clearance, thereby restraining downstream TBK1–IRF3 and IKK–NF-κB activation. In the TLR3/4 pathway, TAX1BP1 cooperates wi

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

th TRIM32 to facilitate TRIF ubiquitination and autophagic degradation, suppressing inflammatory sig naling. TAX1BP1 also inhibits TRIF–RIPK1–RIPK3 necrosome accumulation and thereby limits necro ptosis. By contrast, TAX1BP1 deficiency enhances MAVS and TRIF aggregation, amplifies inflammato ry signaling, and increases apoptosis and necrosis. The inset illustrates potential therapeutic strategies to restore TAX1BP1 function and resolve inflammation.

Importantly, TAX1BP1 also limits necroptosis. TLR3/4 activation induces TICAM1-RIPK1-RIPK3 necrosome formation, and TAX1BP1 deficiency specifically increases necroptosis susceptibility[48]. This suggests TAX1BP1 suppresses both inflammatory signaling and programmed necrosis through aggregate clearance.

3. The Role of TAX1BP1 in Acute Kidney Injury

3.1 Expression Changes of TAX1BP1 in AKI

TAX1BP1 expression in AKI was first characterized using a bilateral renal ischemia-reperfusion (I/R) mouse model[66]. Under normal conditions, TAX1BP1 levels in kidney tissue are low. After I/R injury, its expression increases within hours, peaks at 24 hours, and then declines. Immunofluorescence showed that TAX1BP1 is mainly expressed in proximal tubular epithelial cells (PTECs).Functional studies using AAV-mediated overexpression and shRNA knockdown revealed the protective role of TAX1BP1 in AKI. Overexpression reduced serum creatinine, blood urea nitrogen, and tubular injury scores after I/R, while knockdown worsened renal damage. TUNEL staining further confirmed that TAX1BP1 overexpression decreased apoptosis, whereas its knockdown increased tubular cell death[66]. These findings establish TAX1BP1 as a renal protective factor in AKI.

3.2 Lipid droplet autophagy and lipotoxicity

Lipophagy denotes autophagy-mediated degradation of lipid droplets, supplying fatty acids for cellular energy metabolism[67, 68]. Renal tubular cells rely on fatty acid β-oxidation (FAO) for energy supply. During AKI, impaired FAO causes lipid droplet accumulation and lipotoxicity, triggering ER stress, mitochondrial damage, and inflammation, which accelerate AKI-to-CKD progression[69, 70].Direct evidence linking TAX1BP1 to renal lipophagy is still lacking, but indirect findings suggest a possible role. Lipid droplet proteins like perilipin are ubiquitinated and may serve as TAX1BP1 substrates[34, 71, 72]. TAX1BP1 also binds myosin VI, a motor protein involved in lipid droplet transport to lysosomes[39, 73]. Moreover, p62 participates in hepatic lipophagy and often cooperates with TAX1BP1 in other autophagy pathways, implying potential functional overlap[34, 74]. Validating TAX1BP1's role in tubular lipophagy using lipotoxicity-induced AKI models remains an important future direction[69, 75].

3.3 TAX1BP1 regulates macrophage autophagy and inflammation

Macrophages play dual roles in AKI: M1 macrophages promote inflammation through TNF-α, IL-6, and IL-1β secretion, while M2 macrophages facilitate tissue repair. Dysregulated macrophage polarization contributes to AKI-to-CKD progression[76].Recent studies using macrophage-specific Atg5 knockout mice showed that autophagy deficiency in macrophages worsens LPS- or I/R-induced AKI, with increased tubular injury and inflammatory infiltration[19]. Mechanistically, the pro-inflammatory receptor TARM1 was identified as a key TAX1BP1 substrate[77]. TARM1 activates MAPK and NF-κB signaling to drive cytokine production. After LPS or I/R stimulation, TARM1 undergoes K63-linked ubiquitination and is recognized by TAX1BP1 and p62, which cooperatively target it for autophagic degradation. Knockdown of either receptor impairs TARM1 clearance, and dual knockdown shows additive effects. In vivo validation using macrophage-specific TAX1BP1 knockout mice confirmed that TAX1BP1 loss increases renal TARM1 levels, enhances pro-inflammatory cytokine production, and aggravates kidney injury[19]. These results demonstrate that TAX1BP1 suppresses renal inflammation by promoting TARM1 degradation in macrophages.

3.4 Relationship between TAX1BP1 and autophagy flux

Autophagy flux refers to the complete process from autophagosome formation to lysosomal fusion and substrate degradation[88, 79]. In AKI, autophagy flux is often impaired due to energy depletion, lysosomal dysfunction, or defective autophagosome-lysosome fusion[80]. TAX1BP1 participates in multiple steps of autophagy flux. It initiates selective autophagy by recognizing ubiquitinated substrates such as damaged

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

mitochondria and pro-inflammatory receptors. Through its SKICH domain, TAX1BP1 recruits RB1CC1/FIP200 and the autophagy initiation complex (ULK1-ATG13-RB1CC1-ATG101) to promote autophagosome nucleation[36, 81]. Additionally, TAX1BP1 interacts with Myosin VI to facilitate autophagosome transport along actin filaments toward lysosomes[39, 82]. Therefore, insufficient TAX1BP1 expression or function in AKI may impair substrate recognition, reduce autophagosome formation, and disrupt autophagosome-lysosome fusion, collectively worsening autophagy flux impairment.

4. TAX1BP1 regulation of inflammation and cell death in AKI

4.1 Inflammatory Cascade and Programmed Cell Death in AKI

The pathological hallmarks of AKI comprise sterile inflammation and extensive tubular epithelial cell death[79, 83]. Ischemia or toxins induce apoptosis, necroptosis, or ferroptosis in renal tubular epithelial cells (RTECs), releasing damage-associated molecular patterns (DAMPs) such as HMGB1, mtDNA, and ATP[84–86]. These DAMPs activate pattern recognition receptors (TLRs, RAGE, NLRP3) on neighboring and immune cells, triggering NF-κB-mediated production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and chemokines that recruit neutrophils and monocytes, further worsening RTEC injury[84]. Among cell death forms, apoptosis is non-lytic and less inflammatory, whereas necroptosis and ferroptosis cause membrane rupture and content release, provoking strong inflammatory responses[87]. In AKI, these cell death pathways coexist and reinforce each other, forming a vicious cycle of "injury-inflammation-cell death"[88] .

4.2 TAX1BP1 regulates NF-κB and RIPK1 signaling via the A20 complex

4.2.1 Assembly and Function of the TAX1BP1-A20 Complex

TAX1BP1 functions as the core scaffold for the A20 ubiquitin-editing complex [60]. In the context of AKI, pathogenic stimuli such as ischemia-reperfusion (I/R) or LPS activate TNF receptors or TLRs, triggering upstream kinases (IKKα/β) to phosphorylate TAX1BP1[57]. This phosphorylation facilitates the recruitment of the A20 complex to key signaling hubs, including RIPK1, TRAF6, and NEMO[52]. By executing ubiquitin-editing on these substrates, the complex effectively terminates IKK and TAK1 activation, blocks NF-κB nuclear translocation, and prevents excessive inflammatory damage in renal tissues [86, 91].

4.2.2 TAX1BP1 Dysfunction and Inflammatory Dysregulation

Downregulation or functional defects in TAX1BP1 lead to failure in A20 complex assembly, resulting in loss of negative feedback regulation of the NF-κB signaling pathway[57, 52]. In AKI, this leads to persistent NF-κB activation. Studies in I/R-AKI mice showed elevated nuclear NF-κB p65 and increased IL-6 and TNF-α expression. TAX1BP1 knockdown further amplified NF-κB activation and cytokine production, while overexpression suppressed these effects[66].TAX1BP1 also regulates RIPK1-dependent cell death[49, 52]. RIPK1 is a key branch point in TNF signaling: when K63-ubiquitinated, it activates NF-κB and promotes survival[89, 90].When deubiquitinated, it triggers apoptosis via Caspase-8 cleavage or necroptosis via RIPK3 binding[91, 92]. The TAX1BP1-A20 complex controls RIPK1 ubiquitination status, and TAX1BP1 deficiency causes excessive RIPK1 deubiquitination, increasing susceptibility to necroptosis.[28, 52]

4.3 TAX1BP1 regulates apoptosis in renal tubular epithelial cells

4.3.1 NF-κB/PMAIP1 pathway

PMAIP1 (NOXA), a BH3-only protein, is a direct transcriptional target of NF-κB[93–95]. It binds and neutralizes anti-apoptotic proteins Mcl-1 and A1, releasing Bax/Bak to trigger mitochondrial cytochrome c release and caspase activation[96, 97]. Studies in I/R-AKI models revealed that TAX1BP1 regulates RTEC apoptosis through this pathway [66]. TAX1BP1 knockdown increased NF-κB p65 nuclear translocation and PMAIP1 expression, leading to more TUNEL-positive cells and elevated cleaved Caspase-3. ChIP assays confirmed enhanced NF-κB p65 binding to the PMAIP1 promoter. Conversely, TAX1BP1 overexpression suppressed NF-κB activation, reduced PMAIP1 levels, and decreased apoptosis. In vivo, TAX1BP1-knockdown mice showed elevated tubular PMAIP1, increased apoptosis, and worsened renal function after I/R, while TAX1BP1-overexpressing mice exhibited opposite effects[66].

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

These findings establish a regulatory axis: TAX1BP1 deficiency → NF-κB activation → PMAIP1 upregulation → RTEC apoptosis, representing an autophagy-independent protective mechanism (Figure 4).

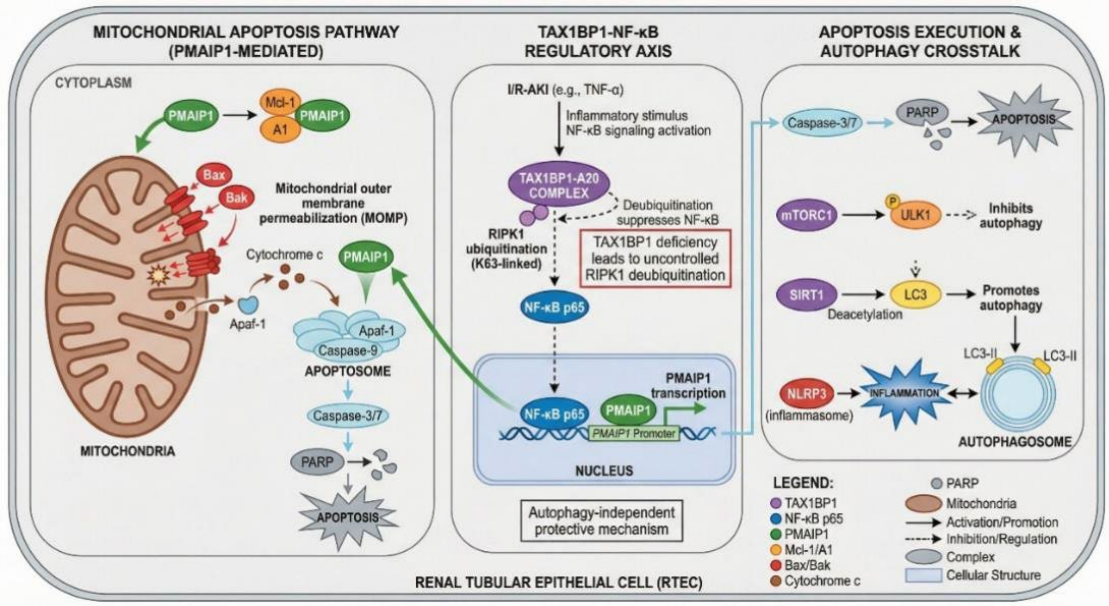

Figure 4. TAX1BP1–NF-κB–PMAIP1 regulatory axis in renal tubular epithelial cell apoptosis.In renal tubular epithelial cells, the TAX1BP1–A20 complex suppresses RIPK1/NF-κB signaling and limits PMAIP1 transcription. When TAX1BP1 is deficient, enhanced NF-κB activation increases PMAIP1 expression, which promotes mitochondrial apoptosis through Bax/Bak activation, cytochrome c release, apoptosome formation, and downstream caspase-3/7 and PARP cleavage. The right panel shows the execution phase of apoptosis and its crosstalk with autophagy- and inflammation-related pathways, including mTORC1, SIRT1, LC3, and NLRP3. Overall, TAX1BP1 protects renal tubular epithelial cells through an autophagy-independent anti-apoptotic mechanism.

4.3.2 Regulation of Necroptosis

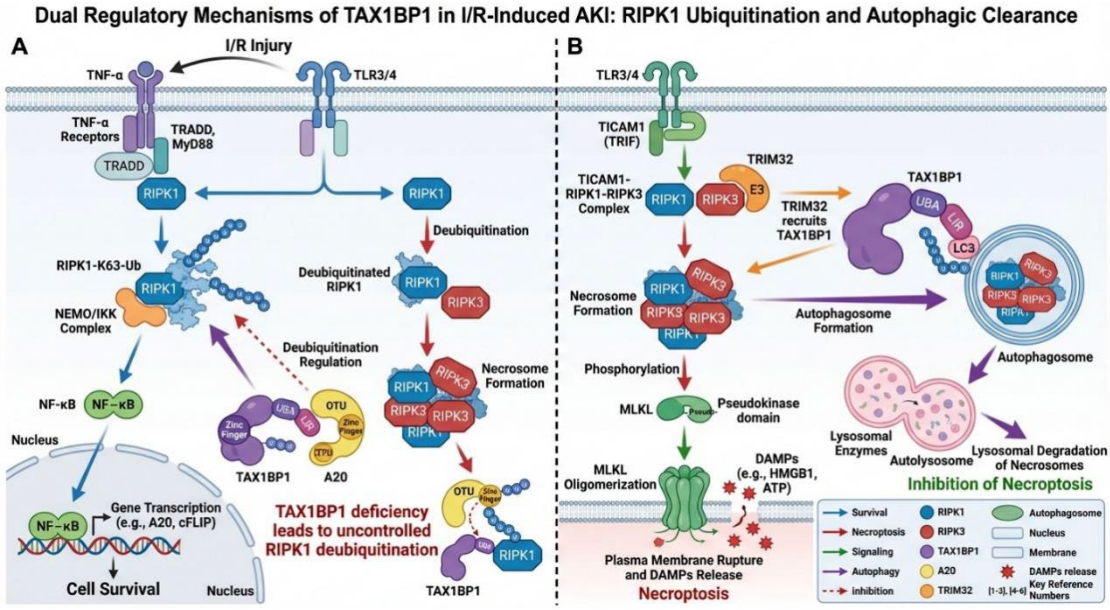

Figure 5. Dual regulatory roles of TAX1BP1 in ischemia–reperfusion-induced acute kidney injury.(A) In response to ischemia–reperfusion injury, TNF-α and TLR3/4 signaling regulate the balance between NF-κB-mediated survival and necroptosis through RIPK1. TAX1BP1, together with A20, controls RIPK1 ubiquitination and restrains the switch to necrosome formation. Loss of TAX1BP1 promotes RIPK1 deubiquitination, facilitates RIPK1–RIPK3 necrosome assembly, and enhances necroptosis. (B) TAX1BP1 also mediates selective autophagic clearance of necrosomes in the TLR3/4–TRIF pathway. Followi

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

ng TRIM32-dependent ubiquitination, TAX1BP1 recruits the necrosome to autophagosomes for lysoso mal degradation, thereby preventing MLKL activation, membrane rupture, DAMPs release, and necro ptosis.

Necroptosis plays a crucial role in I/R-induced AKI. TNF-α and other stimuli induce RIPK1-RIPK3 interaction via their RHIM domains to form necrosomes. RIPK3 then phosphorylates MLKL, which oligomerizes and translocates to the plasma membrane, causing membrane rupture[91, 92, 98, 99]. TAX1BP1 inhibits programmed necrosis through multiple mechanisms[100, 101]. The TAX1BP1-A20 complex regulates RIPK1 ubiquitination status[52, 102]. K63-ubiquitinated RIPK1 activates NF-κB and promotes survival, while deubiquitinated RIPK1 binds RIPK3 to initiate necroptosis[103, 104]. TAX1BP1 deficiency leads to uncontrolled RIPK1 deubiquitination, amplifying necrosis signals[101, 105].Additionally, TAX1BP1 clears necrosome aggregates via autophagy[100]. TLR3/4 activation induces TICAM1-RIPK1-RIPK3 aggregation, and TAX1BP1 mediates their autophagic clearance[106]. Notably, TAX1BP1 deletion specifically enhances TLR3/4-induced necroptosis, while p62 or CALCOCO1 deletion does not, indicating a unique role for TAX1BP1 in necrosome clearance[100] (Figure 5). Although direct evidence in I/R-AKI is lacking, TAX1BP1 likely exerts similar protective effects, which warrants future investigation.

4.4 TAX1BP1 as a Hub in the "Autophagy-Inflammation-Death" Signalling Network

TAX1BP1 functions as a multifaceted regulator in AKI, integrating three major pathological processes: autophagy, inflammation, and cell death[28]. As a selective autophagy receptor, TAX1BP1 clears damaged mitochondria, lipid droplets, and inflammatory aggregates (TARM1, MAVS, TICAM1), maintaining intracellular homeostasis[19, 28, 50] . As a scaffold in the A20 complex, it suppresses NF-κB signaling and also degrades pro-inflammatory receptors via autophagy, achieving dual inhibition of inflammation[52, 107, 108]. For cell death, TAX1BP1 reduces apoptosis by inhibiting the NF-κB/PMAIP1 axis and suppresses programmed necrosis by regulating RIPK1 ubiquitination and necrosome clearance[66, 109]. When TAX1BP1 function is defected, all three pathways are disrupted: damaged organelles and toxic proteins accumulate, inflammatory signaling becomes uncontrolled, and cell death programs are overactivated[28, 52, 100](Figure 6). This combined dysfunction drives irreversible AKI injury and progression to CKD.

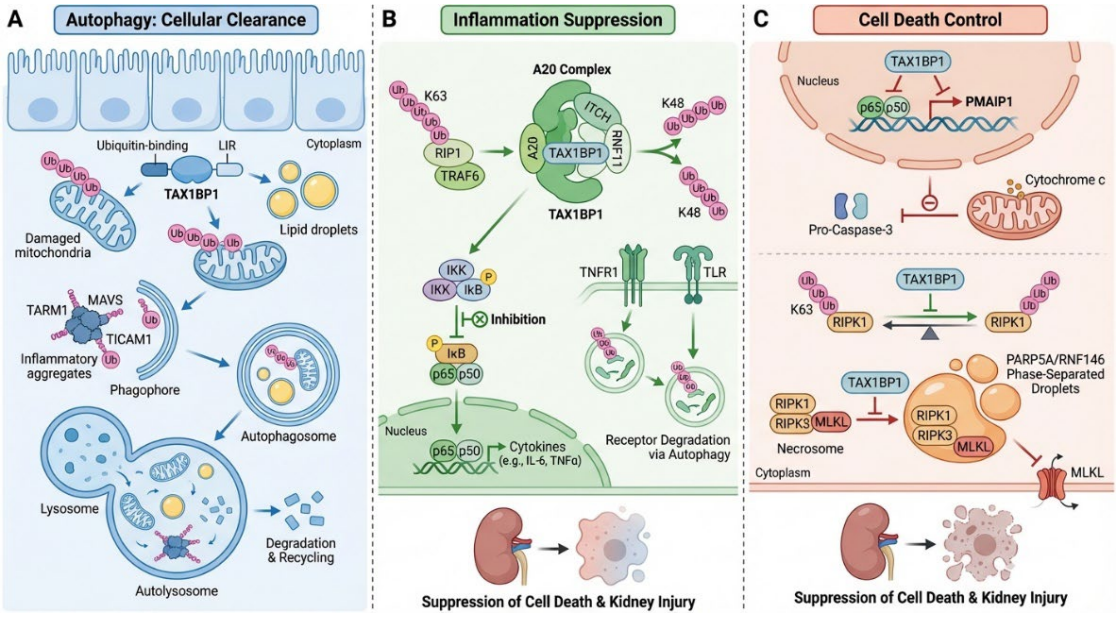

Figure 6. Multifaceted protective roles of TAX1BP1 in renal homeostasis and injury response.(A) TAX 1BP1 functions as a selective autophagy receptor that recognizes ubiquitinated cargoes, including dam aged mitochondria, lipid droplets, and inflammatory aggregates, and delivers them to autophagosomes for lysosomal degradation. (B) TAX1BP1 suppresses inflammation by serving as a scaffold for the A20 complex, thereby regulating RIP1 and TRAF6 ubiquitination, inhibiting IKK/NF-κB signaling, and red ucing pro-inflammatory cytokine production. (C) TAX1BP1 also limits cell death by repressing PMAIP 1-dependent apoptosis and by regulating RIPK1 signaling and necrosome clearance to suppress MLKL -dependent necroptosis. Together, these actions protect against kidney injury.

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

5. Prospects and Challenges of TAX1BP1 as a Therapeutic Target for AKI

5.1 Theoretical Basis for Targeting TAX1BP1 in AKI Therapy

Given TAX1BP1's multifaceted protective roles in AKI, targeting its upregulation or activation may represent a novel therapeutic strategy[66]. Upregulating TAX1BP1 may benefit AKI through multiple mechanisms. It promotes mitophagy to clear damaged mitochondria and reduce ROS production[110, 111]. It also accelerates autophagic degradation of pro-inflammatory molecules (TARM1, MAVS, TICAM1) while enhancing A20-mediated NF-κB suppression[26, 47, 53]. Additionally, it inhibits apoptosis via the NF-κB/PMAIP1 axis and necroptosis via RIPK1 regulation and necrosome clearance[66, 100, 101].This strategy has been validated in animal studies, where AAV-mediated TAX1BP1 overexpression significantly improved renal function and reduced histological damage in I/R-induced AKI[53, 66].

5.2 Key scientific questions requiring resolution

5.2.1 Cell Type Specificity

Current research primarily focuses on renal tubular epithelial cells and macrophages[112]. However, AKI involves multiple cell types, and TAX1BP1's role in other cells remains unknown. In vascular endothelial cells, TAX1BP1 expression is downregulated due to promoter hypermethylation, leading to sustained NF-κB activation and endothelial dysfunction[60]. This is relevant because endothelial injury occurs early in AKI and contributes to increased vascular permeability and microthrombosis[113]. For pericytes and myofibroblasts, TAX1BP1 function has not been studied. Pericyte-to-myofibroblast transition is a key event in AKI-to-CKD progression, and myofibroblasts drive renal fibrosis[114, 115]. Myofibroblasts constitute the primary source of extracellular matrix, driving renal fibrosis, but the role of TAX1BP1 in these cells remains unexplored[115]. Notably, sustained autophagy activation is recognized as a pro-fibrotic factor[75, 116]. Future studies using cell-specific TAX1BP1 knockout or overexpression models are needed to clarify its functions across different renal cell populations[114].

5.2.2 Disease stage specificity

The course of AKI can be divided into the initiation, prolongation, maintenance and recovery phase[117]. Existing research predominantly focuses on the acute injury phase (24–72 hours), but TAX1BP1 expression and function may differ across these stages[118]. During acute injury, autophagy activation protects cells from oxidative stress and inflammatory injury[119, 120], with TAX1BP1 upregulation exerting a protective effect[66]. However, in the repair/fibrosis phase, autophagy plays a more complex role[121]. Moderate autophagy promotes repair, but sustained autophagy activation may contribute to fibrosis[116, 122, 123]. Indeed, autophagy "stalling" rather than activation has been linked to aging- and obesity-associated nephropathy progression[124].Whether TAX1BP1 exerts protective or detrimental effects at different AKI stages requires further investigation.

5.3 Drug Development Strategy

5.3.1 Gene Therapy

AAV-mediated gene therapy has shown protective effects in animal models[125, 126]. AAV9 exhibiting pronounced tropism for renal tissue, enabling efficient transduction of renal tubular epithelial cells[127, 128]. Theoretically, prophylactic AAV-TAX1BP1 administration before high-risk procedures (e.g., cardiac surgery or contrast agent use) could upregulate renal TAX1BP1 and enhance kidney protection against subsequent injury[129–131].

5.3.2 Small-Molecule Modulators

Developing small-molecule drugs that directly target TAX1BP1 presents challenges, as TAX1BP1 primarily functions through protein-protein interactions and has traditionally been considered "undruggable"[36, 108, 132, 133]. However, several emerging strategies offer potential solutions. Molecular glues can stabilize TAX1BP1 binding with partners like RB1CC1, A20, and LC3 to enhance its function[36, 108, 134]. PROTAC technology can degrade negative regulators of TAX1BP1 (e.g., deubiquitinating enzymes or phosphatases), indirectly boosting its activity[135–137]. Targeting upstream kinases such as TBK1 is another option, though this requires careful consideration given TBK1's dual roles discussed earlier[26, 57]. Additionally, autophagy activators like rapamycin and rapalogs show protective effects in AKI models by inhibiting mTOR[138–140]. Combining these with TAX1BP1 upregulation may produce synergistic benefits.

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

5.4 Challenges in Clinical Translation

Several challenges remain between animal models and clinical application. Species differences between mice and humans in renal anatomy, physiology, and injury responses have caused many promising therapies to fail in clinical trials[141]. Using humanized mice, large animal models (porcine), or human kidney organoids may help bridge this gap[141–143].AKI heterogeneity is another concern. Clinical AKI arises from diverse causes (ischemia, toxins, sepsis, etc.) with distinct mechanisms, and TAX1BP1's protective effect needs validation across multiple AKI models[144–146]. Safety is also critical. Gene therapies and novel drugs require careful evaluation, especially in critically ill patients. Clinical trials should begin with healthy volunteers before progressing to AKI patients. Finally, comorbidities must be considered. AKI patients often have diabetes, hypertension, or cancer[144]. Since TAX1BP1 may promote STING1 degradation and attenuate anti-tumor immunity[142]. Whether TAX1BP1 upregulation is safe in cancer patients needs further study.

6. Conclusions and Outlook

Acute kidney injury is a common and serious clinical condition involving oxidative stress, inflammation, mitochondrial dysfunction, and programmed cell death. Recent studies reveal that TAX1BP1, as a pivotal hub linking autophagy, inflammation, and cell death, exerts significant protective effects in AKI pathogenesis.TAX1BP1 exerts its protective effects through two pathways. As a selective autophagy receptor, TAX1BP1 recognizes and clears damaged mitochondria, lipid droplets, and inflammatory signaling platforms (such as TARM1 and MAVS), maintaining cellular homeostasis in renal tubular epithelial cells and macrophages. Simultaneously, as a core linker protein within the A20 ubiquitin-editing complex, it suppresses NF-κB signaling and regulates programmed cell death by remodeling ubiquitin chains on molecules like RIPK1. When TAX1BP1 function is impaired, both autophagy and inflammation become dysregulated. Damaged mitochondria and pro-inflammatory proteins accumulate, NF-κB activation leads to excessive cytokine release, and PMAIP1 upregulation and RIPK1 dysregulation promote tubular cell apoptosis and necrosis. This disruption of cellular homeostasis is a key driver of irreversible AKI and progression to CKD.

Understanding TAX1BP1's mechanisms gives new opportunities for AKI clinical treatment, but clinical translation remains challenging. Key questions include its roles in different cell types and disease stages, upstream regulatory mechanisms, and optimal therapeutic windows. From gene therapy to small molecule development, each approach faces technical and safety hurdles. Despite these challenges, TAX1BP1's protective impact has been confirmed in multiple studies. With advances in single-cell technologies, structural biology, and drug platforms like molecular glues and PROTACs, TAX1BP1-targeted therapies hold promise. By restoring the autophagy-inflammation balance early in disease, such therapies may prevent AKI-to-CKD progression and improve long-term patient outcomes.

References

[1] Hu Q, Zhang Y, Xu H, et al (2021) Association between admission serum procalcitonin and the occurrence of acute kidney injury in patients with septic shock: a retrospective cohort study. Sci Prog 104:00368504211043768. https://doi.org/10.1177/00368504211043768

[2] Gansevoort RT, Wheeler DC, Debén FM, et al (2025) The soluble guanylate cyclase activator runcaciguat significantly improves albuminuria in patients with chronic kidney disease: a randomized placebo-controlled clinical trial. Nephrol Dial Transplant: Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc 40:1147–1160. https://doi.org/10.1093/ndt/gfae261

[3] Pan C, Zhao H, Cai X, et al (2024) The connection between autophagy and ferroptosis in AKI: recent advances regarding selective autophagy. Ren Fail 46:2379601. https://doi.org/10.1080/0886022X.2024.2379601

[4] Zhang Q, Yu Z (2025) The clinical value of apolipoprotein C3 combined with FAR and RWT in heart failure with preserved ejection fraction. Int J Gen Med Volume 18:3823–3835. https://doi.org/10.2147/IJGM.S532542

[5] Lin S, Wang J, Cao B, et al (2023) Cofilin-1 induces acute kidney injury via the promotion of endoplasmic reticulum stress-mediated ferroptosis. Human Cell 36:1928–1937. https://doi.org/10.1007/s13577-023-00949-9

[6] Jin H, Yang Y, Zhu X, et al (2024) DDRGK1-mediated ER-phagy attenuates acute kidney injury through ER-stress and apoptosis. Cell Death Dis 15:63. https://doi.org/10.1038/s41419-024-06449-4

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

[7] Cai L, Fan Q, Pang R, et al (2025) Microglia programmed cell death in neurodegenerative diseases and CNS injury. Apoptosis 30:446–465. https://doi.org/10.1007/s10495-024-02041-5
[8] X T, Y O, S S, et al (2024) SIRT1-dependent neuroprotection by resveratrol in TOCP-induced spinal cord injury: modulation of ER stress and autophagic flux. Toxics 12:. https://doi.org/10.3390/toxics12110810
[9] Hu X, Ma Z, Wen L, et al (2021) Autophagy in cisplatin nephrotoxicity during cancer therapy. Cancers 13:5618. https://doi.org/10.3390/cancers13225618
[10] Liang P, Jiang B, Li Y, et al (2018) 10.Autophagy promotes angiogenesis via AMPK/akt/mTOR signaling during the recovery of heat-denatured endothelial cells. Cell Death Dis 9:1152. https://doi.org/10.1038/s41419-018-1194-5
[11] Cao Y, Chen Z, Yin Y, et al (2025) Autophagy-dependent hepatocyte apoptosis mediates gilteritinib-induced hepatotoxicity. Toxicol Lett 410:189–196. https://doi.org/10.1016/j.toxlet.2025.06.018
[12] Shembade N, Harhaj EW (2012) Regulation of NF-κB signaling by the A20 deubiquitinase. Cell Mol Immunol 9:123–130. https://doi.org/10.1038/cmi.2011.59
[13] Su R, Kang X, Niu Y, et al (2024) PCBP1 interacts with the HTLV-1 tax oncoprotein to potentiate NF-κB activation. Front Immunol 15:. https://doi.org/10.3389/fimmu.2024.1375168
[14] Goodwin JM, Dowdle WE, DeJesus R, et al (2017) Autophagy-independent lysosomal targeting regulated by ULK1/2-FIP200 and ATG9. Cell Reports 20:2341–2356. https://doi.org/10.1016/j.celrep.2017.08.034
[15] Rogov VV, Stolz A, Ravichandran AC, et al (2017) Structural and functional analysis of the GABARAP interaction motif (GIM). EMBO Rep 18:1382–1396. https://doi.org/10.15252/embr.201643587
[16] Towards a better understanding of the neuro-developmental role of autophagy in sickness and in health. http://www.cell-stress.com/researcharticles/2021a-zapata-munoz-cell-stress/. Accessed 17 Jan 2026
[17] Dai X-G, Xu W, Li T, et al (2019) Involvement of phosphatase and tensin homolog-induced putative kinase 1–parkin-mediated mitophagy in septic acute kidney injury. Chin Med J (Engl) 132:2340. https://doi.org/10.1097/CM9.0000000000000448
[18] Chen J, Chen C, Lv C, et al (2025) Vitexin enhances mitophagy and improves renal ischemia-reperfusion injury by regulating the p38/MAPK pathway. Ren Fail 47:2463572. https://doi.org/10.1080/0886022X.2025.2463572
[19] Huang X-R, Ye L, An N, et al (2025) Macrophage autophagy protects against acute kidney injury by inhibiting renal inflammation through the degradation of TARM1. Autophagy 21:120–140. https://doi.org/10.1080/15548627.2024.2393926
[20] Morriswood B, Ryzhakov G, Puri C, et al (2007) T6BP and NDP52 are myosin VI binding partners with potential roles in cytokine signalling and cell adhesion. J Cell Sci 120:2574–2585. https://doi.org/10.1242/jcs.007005
[21] Fu T, Zhang M, Zhou Z, et al (2021) Structural and biochemical advances on the recruitment of the autophagy-initiating ULK and TBK1 complexes by autophagy receptor NDP52. Sci Adv. https://doi.org/10.1126/sciadv.abi6582
[22] Zhou Z, Liu J, Fu T, et al (2021) Phosphorylation regulates the binding of autophagy receptors to FIP200 claw domain for selective autophagy initiation. Nat Commun 12:1570. https://doi.org/10.1038/s41467-021-21874-1
[23] Sarraf SA, Shah HV, Kanfer G, et al (2020) Loss of TAX1BP1-directed autophagy results in protein aggregate accumulation in the brain. Mol Cell 80:779-795.e10. https://doi.org/10.1016/j.molcel.2020.10.041
[24] Zhang M, Wang Y, Gong X, et al (2024) Mechanistic insights into the interactions of TAX1BP1 with RB1CC1 and mammalian ATG8 family proteins. Proc Natl Acad Sci U S A 121:e2315550121. https://doi.org/10.1073/pnas.2315550121
[25] Gibertini S, Ruggieri A, Cheli M, Maggi L (2023) Protein aggregates and aggrephagy in myopathies. Int J Mol Sci 24:8456. https://doi.org/10.3390/ijms24098456
[26] Ren H, Wang Y, Li L-F, et al (2025) The african swine fever virus p22 inhibits the JAK-STAT signaling pathway by promoting the TAX1BP1-mediated degradation of the type I interferon receptor. PLOS Pathog 21:e1013319. https://doi.org/10.1371/journal.ppat.1013319
[27] White J, Choi YB, Zhang J, et al (2025) Phosphorylation of the selective autophagy receptor TAX1BP1 by TBK1 and IKBKE/IKKi promotes ATG8-family protein-dependent clearance of MAVS aggregates. Autophagy 21:160–177. https://doi.org/10.1080/15548627.2024.2394306
[28] White J, Suklabaidya S, Vo MT, et al (2023) Multifaceted roles of TAX1BP1 in autophagy. Autophagy 19:44–53. https://doi.org/10.1080/15548627.2022.2070331
[29] Liu Y, Wang M, Hou X-O, Hu L-F (2022) Roles of microglial mitophagy in neurological disorders.

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

Front Aging Neurosci 14. https://doi.org/10.3389/fnagi.2022.979869
[30] Kruppa AJ, Buss F (2021) Motor proteins at the mitochondria–cytoskeleton interface. J Cell Sci 134:jcs226084. https://doi.org/10.1242/jcs.226084
[31] Lu Z, Luo R, Lan J, et al (2024) The MGF300-2R protein of african swine fever virus promotes IKKβ ubiquitination by recruiting the E3 ubiquitin ligase TRIM21. Viruses 16:949. https://doi.org/10.3390/v16060949
[32] Bullones-Bolaños A, Bernal-Bayard J, Ramos-Morales F (2022) The NEL family of bacterial E3 ubiquitin ligases. Int J Mol Sci 23:7725. https://doi.org/10.3390/ijms23147725
[33] Le Guerroué F, Bunker EN, Rosencrans WM, et al (2023) TNIP1 inhibits selective autophagy via bipartite interaction with LC3/GABARAP and TAX1BP1. Mol Cell 83:927-941.e8. https://doi.org/10.1016/j.molcel.2023.02.023
[34] Turco E, Savova A, Gere F, et al (2021) Reconstitution defines the roles of p62, NBR1 and TAX1BP1 in ubiquitin condensate formation and autophagy initiation. Nat Commun 12:5212. https://doi.org/10.1038/s41467-021-25572-w
[35] Zhang M, Wang Y, Gong X, et al (2024) Mechanistic insights into the interactions of TAX1BP1 with RB1CC1 and mammalian ATG8 family proteins. Proc Natl Acad Sci U S A 121:e2315550121. https://doi.org/10.1073/pnas.2315550121
[36] Mechanistic insights into the interactions of TAX1BP1 with RB1CC1 and mammalian ATG8 family proteins | PNAS. https://www.pnas.org/doi/10.1073/pnas.2315550121. Accessed 17 Jan 2026
[37] Yeo SK, Haas M, Manupati K, et al (2024) AZI2 mediates TBK1 activation at unresolved selective autophagy cargo receptor complexes with implications for CD8 T-cell infiltration in breast cancer. Autophagy 20:525–540. https://doi.org/10.1080/15548627.2023.2259775
[38] Chen, W., Shen, T., Wang, L., & Lu, K. (2021). Oligomerization of Selective Autophagy Receptors for the Targeting and Degradation of Protein Aggregates. Cells, 10(8), 1989. https://doi.org/10.3390/cells10081989
[39] Tumbarello DA, Manna PT, Allen M, et al (2015) The autophagy receptor TAX1BP1 and the molecular motor myosin VI are required for clearance of salmonella typhimurium by autophagy. PLOS Pathogens 11:e1005174. https://doi.org/10.1371/journal.ppat.1005174
[40] Tumbarello DA, Manna PT, Allen M, et al (2016) Correction: the autophagy receptor TAX1BP1 and the molecular motor myosin VI are required for clearance of salmonella typhimurium by autophagy. PLOS Pathog 12:e1005433. https://doi.org/10.1371/journal.ppat.1005433
[41] Huang L, Yu L-J, Zhang X, et al (2019) Autophagy regulates glucose-mediated root meristem activity by modulating ROS production in arabidopsis. Autophagy 15:407–422. https://doi.org/10.1080/15548627.2018.1520547
[42] Wu S, Shen Y, Zhang S, et al (2020) Salmonella interacts with autophagy to offense or defense. Front Microbiol 11. https://doi.org/10.3389/fmicb.2020.00721
[43] Lindsey ARI, Bhattacharya T, Hardy RW, Newton ILG (2021) Wolbachia and virus alter the host transcriptome at the interface of nucleotide metabolism pathways. mBio 12:10.1128/mbio.03472-20. https://doi.org/10.1128/mbio.03472-20
[44] Cadwell K, Abraham C, Bel S, et al (2025) Autophagy and bacterial infections. Autophagy Rep 4:2542904. https://doi.org/10.1080/27694127.2025.2542904
[45] Wilfling F, Lee C-W, Erdmann PS, et al (2020) A selective autophagy pathway for phase-separated endocytic protein deposits. Mol Cell 80:764-778.e7. https://doi.org/10.1016/j.molcel.2020.10.030
[46] Sarraf SA, Shah HV, Kanfer G, et al (2022) Loss of TAX1BP1-directed autophagy results in protein aggregate accumulation in the brain. Mol Cell 82:1383–1385. https://doi.org/10.1016/j.molcel.2022.03.020
[47] Yang Q, Liu T-T, Lin H, et al (2017) TRIM32-TAX1BP1-dependent selective autophagic degradation of TRIF negatively regulates TLR3/4-mediated innate immune responses. PLOS Pathogens 13:e1006600. https://doi.org/10.1371/journal.ppat.1006600
[48] Samie M, Lim J, Verschueren E, et al (2018) Selective autophagy of the adaptor TRIF regulates innate inflammatory signaling. Nat Immunol 19:246–254. https://doi.org/10.1038/s41590-017-0042-6
[49] Lorentzen KC, Prescott AR, Ganley IG (2025) Artificial targeting of autophagy components to mitochondria reveals both conventional and unconventional mitophagy pathways. Autophagy 21:315–337. https://doi.org/10.1080/15548627.2024.2395149
[50] Lazarou M, Sliter DA, Kane LA, et al (2015) The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature 524:309–314. https://doi.org/10.1038/nature14893
[51] Park NY, Jo DS, Yang J-Y, et al (2025) Activation of lysophagy by a TBK1-SCFFBXO3-TMEM192-TAX1BP1 axis in response to lysosomal damage. Nat Commun 16:1109. https://doi.org/10.1038/s41467-025-56294-y
[52] Shembade N, Harhaj NS, Liebl DJ, Harhaj EW (2007) Essential role for TAX1BP1 in the

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

termination of TNF-α-, IL-1- and LPS-mediated NF-κB and JNK signaling. EMBO J 26:3910–3922. https://doi.org/10.1038/sj.emboj.7601823

[53] Verstrepen L, Verhelst K, Carpentier I, Beyaert R (2011) TAX1BP1, a ubiquitin-binding adaptor protein in innate immunity and beyond. Trends in Biochemical Sciences 36:347–354. https://doi.org/10.1016/j.tibs.2011.03.004

[54] Sen R, Baltimore D (1986) Inducibility of κ immunoglobulin enhancer-binding protein NF-κB by a posttranslational mechanism. Cell 47:921–928. https://doi.org/10.1016/0092-8674(86)90807-X

[55] Oeckinghaus A, Ghosh S (2009) The NF-κB family of transcription factors and its regulation. Cold Spring Harbor Perspect Biol 1:a000034. https://doi.org/10.1101/cshperspect.a000034

[56] Liu T, Zhang L, Joo D, Sun S-C (2017) NF-κB signaling in inflammation. Signal Transduction Targeted Ther 2:17023. https://doi.org/10.1038/sigtrans.2017.23

[57] Shembade N, Pujari R, Harhaj NS, et al (2011) The kinase IKKα inhibits activation of the transcription factor NF-κB by phosphorylating the regulatory molecule TAX1BP1. Nat Immunol 12:834–843. https://doi.org/10.1038/ni.2066

[58] Shembade N, Harhaj NS, Parvatiyar K, et al (2008) The E3 ligase itch negatively regulates inflammatory signaling pathways by controlling the function of the ubiquitin-editing enzyme A20. Nat Immunol 9:254–262. https://doi.org/10.1038/ni1563

*[59] Gao L, Coope H, Grant S, et al (2011) ABIN1 protein cooperates with TAX1BP1 and A20 proteins to inhibit antiviral signaling *. J Biol Chem 286:36592–36602. https://doi.org/10.1074/jbc.M111.283762*

[60] Yang M, Liu X, Jiang M, et al (2024) TAX1BP1/A20 inhibited TLR2-NF-κB activation to induce tolerant expression of IL-6 in endothelial cells. International Immunopharmacology 139:112789. https://doi.org/10.1016/j.intimp.2024.112789

[61] Seth RB, Sun L, Ea C-K, Chen ZJ (2005) Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-κB and IRF3. Cell 122:669–682. https://doi.org/10.1016/j.cell.2005.08.012

[62] Meylan E, Curran J, Hofmann K, et al (2005) Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. Nature 437:1167–1172. https://doi.org/10.1038/nature04193

[63] Choi YB, Shembade N, Parvatiyar K, et al (2016) TAX1BP1 restrains virus-induced apoptosis by facilitating itch-mediated degradation of the mitochondrial adaptor MAVS. Mol Cell Biol 37:e00422. https://doi.org/10.1128/MCB.00422-16

[64] Z J, Tw M, G S, X L (2004) Toll-like receptor 3-mediated activation of NF-kappaB and IRF3 diverges at toll-IL-1 receptor domain-containing adapter inducing IFN-beta. Proc Natl Acad Sci U S A 101:3533–3538. https://doi.org/10.1073/pnas.0308496101

[65] Reggiori F, Monastyrska I, Verheije MH, et al (2010) Coronaviruses hijack the LC3-I-positive EDEMosomes, ER-derived vesicles exporting short-lived ERAD regulators, for replication. Cell Host Microbe 7:500–508. https://doi.org/10.1016/j.chom.2010.05.013

[66] Wu Z, Tan W, Wang C, et al (2025) TAX1BP1 regulates the apoptosis of renal tubular epithelial cells in ischemia/reperfusion injury via the NF-kB/PMAIP1 signaling pathway. Inflamm Res: Off J Eur Histamine Res Soc [et Al,] 74:9. https://doi.org/10.1007/s00011-024-01976-4

[67] Liu K, Czaja MJ (2013) Regulation of lipid stores and metabolism by lipophagy. Cell Death Differ 20:3–11. https://doi.org/10.1038/cdd.2012.63

[68] Zhang S, Peng X, Yang S, et al (2022) The regulation, function, and role of lipophagy, a form of selective autophagy, in metabolic disorders. Cell Death Dis 13:132. https://doi.org/10.1038/s41419-022-04593-3

[69] Hm K, Sh A, P C, et al (2015) Defective fatty acid oxidation in renal tubular epithelial cells has a key role in kidney fibrosis development. Nature medicine 21. https://doi.org/10.1038/nm.3762

[70] Jang H-S, Noh MR, Kim J, Padanilam BJ (2020) Defective mitochondrial fatty acid oxidation and lipotoxicity in kidney diseases. Front Med 7:65. https://doi.org/10.3389/fmed.2020.00065

[71] Mallia A, Papaianni GG, Brocca L, et al (2025) Decoding the lipid droplet proteome: new frontiers in cardiovascular disease research. Int J Mol Sci 26:10280. https://doi.org/10.3390/ijms262110280

[72] Chung J, Park J, Lai ZW, et al (2023) The troyer syndrome protein spartin mediates selective autophagy of lipid droplets. Nat Cell Biol 25:1101–1110. https://doi.org/10.1038/s41556-023-01178-w

[73] Hu S, Guo Y, Wang Y, et al (2019) Structure of myosin VI/Tom1 complex reveals a cargo recognition mode of myosin VI for tethering. Nat Commun 10:3459. https://doi.org/10.1038/s41467-019-11481-6

[74] L W, J Z, S Y, et al (2017) Ethanol-triggered lipophagy requires SQSTM1 in AML12 hepatic cells. Sci Rep 7. https://doi.org/10.1038/s41598-017-12485-2

[75] Yan Q, Song Y, Zhang L, et al (2018) Autophagy activation contributes to lipid accumulation in tubular epithelial cells during kidney fibrosis. Cell Death Discovery 4:2. https://doi.org/10.1038/s41420-

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

018-0065-2
[76] X M, J J, Hy L (2022) Driving role of macrophages in transition from acute kidney injury to chronic kidney disease. Chin Med J (Engl) 135. https://doi.org/10.1097/CM9.0000000000002100
[77] Radjabova V, Mastroeni P, Skjødt K, et al (2015) TARM1 is a novel leukocyte receptor complex-encoded ITAM receptor that costimulates proinflammatory cytokine secretion by macrophages and neutrophils. J Immunol 195:3149–3159. https://doi.org/10.4049/jimmunol.1401847
[78] Gottlieb RA, Andres AM, Sin J, Taylor DPJ (2015) Untangling autophagy measurements: all fluxed up. Circ Res 116:504–514. https://doi.org/10.1161/CIRCRESAHA.116.303787
[79] Klionsky DJ, Abdel-Aziz AK, Abdelfatah S, et al (2021) Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)1. Autophagy 17:1–382. https://doi.org/10.1080/15548627.2020.1797280
[80] Tang C, Livingston MJ, Liu Z, Dong Z (2020) Autophagy in kidney homeostasis and disease. Nat Rev Nephrol 16:489–508. https://doi.org/10.1038/s41581-020-0309-2
[81] Bauer B, Idinger J, Schuschnig M, et al (2024) Recruitment of autophagy initiator TAX1BP1 advances aggrephagy from cargo collection to sequestration. EMBO J 43:5910–5940. https://doi.org/10.1038/s44318-024-00280-5
[82] Tumbarello DA, Waxse BJ, Arden SD, et al (2012) Autophagy receptors link myosin VI to autophagosomes to mediate Tom1-dependent autophagosome maturation and fusion with the lysosome. Nat Cell Biol 14:1024–1035. https://doi.org/10.1038/ncb2589
[83] Lv L-L, Wang C, Li Z-L, et al (2021) SAP130 released by damaged tubule drives necroinflammation via miRNA-219c/mincle signaling in acute kidney injury. Cell Death Dis 12:866. https://doi.org/10.1038/s41419-021-04131-7
[84] DeWolf SE, Kasimsetty SG, Hawkes AA, et al (2022) DAMPs released from injured renal tubular epithelial cells activate innate immune signals in healthy renal tubular epithelial cells. Transplantation 106:1589–1599. https://doi.org/10.1097/TP.0000000000004038
[85] Fujiki K, Inamura H, Sugaya T, Matsuoka M (2019) Blockade of ALK4/5 signaling suppresses cadmium- and erastin-induced cell death in renal proximal tubular epithelial cells via distinct signaling mechanisms. Cell Death Differ 26:2371–2385. https://doi.org/10.1038/s41418-019-0307-8
[86] Murao A, Aziz M, Wang H, et al (2021) Release mechanisms of major DAMPs. Apoptosis: Int J Program Cell Death 26:152–162. https://doi.org/10.1007/s10495-021-01663-3
[87] Riegler AN, Benson P, Long K, Leal SM (2023) Differential activation of programmed cell death in patients with severe SARS-CoV-2 infection. Cell Death Discov 9:420. https://doi.org/10.1038/s41420-023-01715-4
[88] Zhang Y, Hu J, Zhang Y, Ci X (2025) Amentoflavone protects against cisplatin-induced acute kidney injury by modulating Nrf2-mediated oxidative stress and ferroptosis and partially by activating Nrf2-dependent PANoptosis. Front Pharmacol 16:1508047. https://doi.org/10.3389/fphar.2025.1508047
[89] Song HY, Régnier CH, Kirschning CJ, et al (1997) Tumor necrosis factor (TNF)-mediated kinase cascades: bifurcation of nuclear factor-kappaB and c-jun N-terminal kinase (JNK/SAPK) pathways at TNF receptor-associated factor 2. Proc Natl Acad Sci U S A 94:9792–9796. https://doi.org/10.1073/pnas.94.18.9792
[90] Wertz IE, O'Rourke KM, Zhou H, et al (2004) De-ubiquitination and ubiquitin ligase domains of A20 downregulate NF-kappaB signalling. Nature 430:694–699. https://doi.org/10.1038/nature02794
[91] Li J, McQuade T, Siemer AB, et al (2012) The RIP1/RIP3 necrosome forms a functional amyloid signaling complex required for programmed necrosis. Cell 150:339–350. https://doi.org/10.1016/j.cell.2012.06.019
[92] Duprez L, Takahashi N, Van Hauwermeiren F, et al (2011) RIP kinase-dependent necrosis drives lethal systemic inflammatory response syndrome. Immunity 35:908–918. https://doi.org/10.1016/j.immuni.2011.09.020
[93] Seo Y-W, Shin JN, Ko KH, et al (2003) The molecular mechanism of noxa-induced mitochondrial dysfunction in p53-mediated cell death. J Biol Chem 278:48292–48299. https://doi.org/10.1074/jbc.M308785200
[94] Martin AG, Trama J, Crighton D, et al (2009) Activation of p73 and induction of noxa by DNA damage requires NF-kappa B. Aging (Milano) 1:335–349. https://doi.org/10.18632/aging.100026
[95] Msaki A, Sánchez AM, Koh LF, et al (2011) The role of RelA (p65) threonine 505 phosphorylation in the regulation of cell growth, survival, and migration. Mol Biol Cell 22:3032–3040. https://doi.org/10.1091/mbc.E11-04-0280
[96] Oda E, Ohki R, Murasawa H, et al (2000) Noxa, a BH3-only member of the bcl-2 family and candidate mediator of p53-induced apoptosis. Sci (N Y NY) 288:1053–1058. https://doi.org/10.1126/science.288.5468.1053
[97] Huang DC, Strasser A (2000) BH3-only proteins-essential initiators of apoptotic cell death. Cell

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

103:839–842. https://doi.org/10.1016/s0092-8674(00)00187-2
[98] Cho YS, Challa S, Moquin D, et al (2009) Phosphorylation-driven assembly of the RIP1-RIP3 complex regulates programmed necrosis and virus-induced inflammation. Cell 137:1112–1123. https://doi.org/10.1016/j.cell.2009.05.037
[99] Wang H, Sun L, Su L, et al (2014) Mixed lineage kinase domain-like protein MLKL causes necrotic membrane disruption upon phosphorylation by RIP3. Mol Cell 54:133–146. https://doi.org/10.1016/j.molcel.2014.03.003
[100] J L, H P, J H, et al (2019) Autophagy regulates inflammatory programmed cell death via turnover of RHIM-domain proteins. eLife 8:. https://doi.org/10.7554/eLife.44452
[101] Hou S, Zhang J, Jiang X, et al (2024) PARP5A and RNF146 phase separation restrains RIPK1-dependent necroptosis. Mol Cell 84:938-954. https://doi.org/10.1016/j.molcel.2023.12.041
[102] Shembade N, Parvatiyar K, Harhaj NS, Harhaj EW (2009) The ubiquitin-editing enzyme A20 requires RNF11 to downregulate NF-kappaB signalling. EMBO J 28:513–522. https://doi.org/10.1038/emboj.2008.285
[103] Tang Y, Tu H, Zhang J, et al (2019) K63-linked ubiquitination regulates RIPK1 kinase activity to prevent cell death during embryogenesis and inflammation. Nat Commun 10:4157. https://doi.org/10.1038/s41467-019-12033-8
[104] Witt A, Vucic D (2017) Diverse ubiquitin linkages regulate RIP kinases-mediated inflammatory and cell death signaling. Cell Death Differ 24:1160–1171. https://doi.org/10.1038/cdd.2017.33
[105] H I, Jm P, L V, et al (2008) Inflammatory cardiac valvulitis in TAX1BP1-deficient mice through selective NF-kappaB activation. EMBO J 27. https://doi.org/10.1038/emboj.2008.5
[106] Kaiser WJ, Sridharan H, Huang C, et al (2013) Toll-like receptor 3-mediated necrosis via TRIF, RIP3, and MLKL. J Biol Chem 288:31268–31279. https://doi.org/10.1074/jbc.M113.462341
[107] Jacque E, Ley SC (2009) RNF11, a new piece in the A20 puzzle. EMBO J 28:455–456. https://doi.org/10.1038/emboj.2009.18
[108] Shembade N, Ma A, Harhaj EW (2010) Inhibition of NF-kappaB signaling by A20 through disruption of ubiquitin enzyme complexes. Sci (N Y NY) 327:1135–1139. https://doi.org/10.1126/science.1182364
[109] H X, Z H, M X, et al (2025) The role of post-translational modifications in necroptosis. Biomolecules 15. https://doi.org/10.3390/biom15040549
[110] Y F, Z C, L M, et al (2022) PINK1/TAX1BP1-directed mitophagy attenuates vascular endothelial injury induced by copper oxide nanoparticles. Journal of nanobiotechnology 20. https://doi.org/10.1186/s12951-022-01338-4
[111] Wang S, Long H, Hou L, et al (2023) The mitophagy pathway and its implications in human diseases. Signal Transduct Target Ther 8:304. https://doi.org/10.1038/s41392-023-01503-7
[112] Li Z-L, Li X-Y, Zhou Y, et al (2024) Renal tubular epithelial cells response to injury in acute kidney injury. EBioMedicine 107:105294. https://doi.org/10.1016/j.ebiom.2024.105294
[113] Verma SK, Molitoris BA (2015) Renal endothelial injury and microvascular dysfunction in acute kidney injury. Semin Nephrol 35:96–107. https://doi.org/10.1016/j.semnephrol.2015.01.010
[114] Xu C, Hong Q, Zhuang K, et al (2023) Regulation of pericyte metabolic reprogramming restricts the AKI to CKD transition. Metab, Clin Exp 145:155592. https://doi.org/10.1016/j.metabol.2023.155592
[115] Kim KP, Williams CE, Lemmon CA (2022) Cell-matrix interactions in renal fibrosis. Kidney Dial 2:607–624. https://doi.org/10.3390/kidneydial2040055
[116] Liang S, Wu Y-S, Li D-Y, et al (2022) Autophagy and renal fibrosis. Aging dis 13:712–731. https://doi.org/10.14336/AD.2021.1027
[117] Basile DP, Anderson MD, Sutton TA (2012) Pathophysiology of acute kidney injury. Compr Physiol 2:1303–1353. https://doi.org/10.1002/cphy.c110041
[118] Fu Y, Xiang Y, Wei Q, et al (2024) Rodent models of AKI and AKI-CKD transition: an update in 2024. Am J Physiol Renal Physiol 326:F563–F583. https://doi.org/10.1152/ajprenal.00402.2023
[119] Gong L, Pan Q, Yang N (2020) Autophagy and inflammation regulation in acute kidney injury. Front Physiol 11:576463. https://doi.org/10.3389/fphys.2020.576463
[120] Leventhal JS, Ni J, Osmond M, et al (2016) Autophagy limits endotoxemic acute kidney injury and alters renal tubular epithelial cell cytokine expression. PLOS One 11:e0150001. https://doi.org/10.1371/journal.pone.0150001
[121] Dai R, Zhang L, Jin H, et al (2022) Autophagy in renal fibrosis: Protection or promotion? Front Pharmacol 13:963920. https://doi.org/10.3389/fphar.2022.963920
[122] Lin F (2017) Autophagy in renal tubular injury and repair. Acta Physiol (Oxf Engl) 220:229–237. https://doi.org/10.1111/apha.12852
[123] Livingston MJ, Ding H-F, Huang S, et al (2016) Persistent activation of autophagy in kidney tubular cells promotes renal interstitial fibrosis during unilateral ureteral obstruction. Autophagy

ISSN 2616-5791 Vol. 7, Issue 2: 40-55, DOI: 10.25236/AJMHS.2026.070207

12:976–998. https://doi.org/10.1080/15548627.2016.1166317
[124] T Y (2025) Autophagic stagnation: a key mechanism in kidney disease progression linked to aging and obesity. Clin exp nephrol 29. https://doi.org/10.1007/s10157-025-02653-4
[125] Wu G, Liu S, Hagenstein J, et al Adeno-associated virus–based gene therapy treats inflammatory kidney disease in mice. J Clin Invest 134:e174722. https://doi.org/10.1172/JCI174722
[126] Tavakolidakhrabadi N, Ding WY, Saleem MA, et al (2024) Gene therapy and kidney diseases. Mol Ther--Methods Clin Dev 32. https://doi.org/10.1016/j.omtm.2024.101333
[127] Furusho T, Das R, Hakui H, et al (2024) Enhancing gene transfer to renal tubules and podocytes by context-dependent selection of AAV capsids. Nat Commun 15:10728. https://doi.org/10.1038/s41467-024-54475-9
[128] Peek JL, Rosales A, Qi J, et al (2025) Efficient kidney gene transfer and proximal tubule transduction using self-complementary AAV.cc47 vectors. Mol Ther, Methods Clin Dev 33:101606. https://doi.org/10.1016/j.omtm.2025.101606
[129] Ding WY, Kuzmuk V, Hunter S, et al (2023) Adeno-associated virus gene therapy prevents progression of kidney disease in genetic models of nephrotic syndrome. Sci Transl Med 15:eabc8226. https://doi.org/10.1126/scitranslmed.abc8226
[130] Xu Q, Li Z-L, Zhang Y-L, et al (2025) Kidney hepcidin protects the collecting duct against ferroptosis in ischemia/reperfusion-induced acute kidney injury. Kidney Int 108:394–410. https://doi.org/10.1016/j.kint.2025.05.030
[131] Ortega-Loubon C, Fernández-Molina M, Carrascal-Hinojal Y, Fulquet-Carreras E (2016) Cardiac surgery-associated acute kidney injury. Ann Card Anaesth 19:687–698. https://doi.org/10.4103/0971-9784.191578
[132] Hong SH, Nguyen T, Ongkingco JF, et al (2025) From concepts to inhibitors: a blueprint for targeting protein-protein interactions. Chem Rev 125:6819–6869. https://doi.org/10.1021/acs.chemrev.5c00046
[133] Xie X, Yu T, Li X, et al (2023) Recent advances in targeting the "undruggable" proteins: from drug discovery to clinical trials. Signal Transduction Targeted Ther 8:335. https://doi.org/10.1038/s41392-023-01589-z
[134] Soini L, Leysen S, Davis J, Ottmann C (2022) Molecular glues to stabilise protein-protein interactions. Curr Opin Chem Biol 69:102169. https://doi.org/10.1016/j.cbpa.2022.102169
[135] Békés M, Langley DR, Crews CM (2022) PROTAC targeted protein degraders: the past is prologue. Nat Rev Drug Discov 21:181–200. https://doi.org/10.1038/s41573-021-00371-6
[136] Murgai A, Sosič I, Gobec M, et al (2022) Targeting the deubiquitinase USP7 for degradation with PROTACs. Chem Commun Camb Engl 58:8858–8861. https://doi.org/10.1039/d2cc02094g
[137] Miao J, Zhang Z-Y (2024) Drugging protein tyrosine phosphatases through targeted protein degradation. ChemMedChem 19:e202300669. https://doi.org/10.1002/cmdc.202300669
[138] Waldner M, Fantus D, Solari M, Thomson AW (2016) New perspectives on mTOR inhibitors (rapamycin, rapalogs and TORKinibs) in transplantation. British Journal of Clinical Pharmacology 82:1158–1170. https://doi.org/10.1111/bcp.12893
[139] Su Y, Lu J, Gong P, et al (2018) Rapamycin induces autophagy to alleviate acute kidney injury following cerebral ischemia and reperfusion via the mTORC1/ATG13/ULK1 signaling pathway. Mol Med Rep 18:5445–5454. https://doi.org/10.3892/mmr.2018.9586
[140] Panwar V, Singh A, Bhatt M, et al (2023) Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. Signal Transduction Targeted Ther 8:375. https://doi.org/10.1038/s41392-023-01608-z
[141] B P, Ij S, Dm B, et al (2020) Large animal models for translational research in acute kidney injury. Renal failure 42. https://doi.org/10.1080/0886022X.2020.1830108
[142] Noel S, Kurzhagen JT, Lee SA, et al (2023) Kidney immune cell characterization of humanized mouse models. Kidney360 5:96. https://doi.org/10.34067/KID.0000000000000300
[143] Pode-Shakked N, Devarajan P (2022) Human stem cell and organoid models to advance acute kidney injury diagnostics and therapeutics. Int J Mol Sci 23:7211. https://doi.org/10.3390/ijms23137211
[144] Bellomo R, Kellum JA, Ronco C (2012) Acute kidney injury. Lancet (Lond Engl) 380:756–766. https://doi.org/10.1016/S0140-6736(11)61454-2
[145] Zarbock A, Nadim MK, Pickkers P, et al (2023) Sepsis-associated acute kidney injury: consensus report of the 28th acute disease quality initiative workgroup. Nat Rev, Nephrol 19:401–417. https://doi.org/10.1038/s41581-023-00683-3
[146] Chen Z, Li Y, Yuan Y, et al (2023) Single-cell sequencing reveals homogeneity and heterogeneity of the cytopathological mechanisms in different etiology-induced AKI. Cell Death Dis 14:318. https://doi.org/10.1038/s41419-023-05830-z