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COMMENTARY

Targeting PARylated RACK1/HIF-1α axis: A novel mechanism in acute kidney injury and therapeutic promise

KEY WORDS

PARylation;
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PROTAC

Acute kidney injury (AKI), characterized by rapid deterioration of renal function, remains a clinical challenge with high incidence in hospitalized patients, especially exceeding 50% in intensive care[1]. In recent years, researchers have conducted in-depth explorations into the complex pathogenesis of AKI. At present, apart from renal replacement therapy, drug treatment still faces numerous challenges. Tubular epithelial cells (TECs), the most abundant cell type in the renal parenchyma, act as central regulators of both physiological functions and pathological processes in the kidney[2]. In AKI, TEC injury serves as the "initiating trigger" for renal dysfunction. Previously, Dr. Meng's lab found that the induction of insulin-like growth factor binding protein 7 (IGFBP7) in TECs promotes kidney inflammation and injury through enhanced interaction with poly-ADP-ribose polymerase 1 (PARP1) and elevated PARP1 expression[3]. However, the specific mechanism of PARP1 in AKI, as well as its potential to serve as an effective therapeutic target, remains unclear. Notably, as a core member of the PARP family, PARP1 executes over 90% of cellular poly (ADP-ribosyl)ation (PARylation) in non-neural tissues, driving this emerging post-translational modification (PTM) critical for cellular signaling[4]. Based on these findings, the team carried out follow-up experiments to investigate mechanisms through which PAPR1 modulates the severity of AKI. In this issue of *Acta Pharmaceutica Sinica B*, Li et al. demonstrated that the PARylation level mediated by PARP1 is significantly upregulated in AKI models, which exacerbates acute kidney injury. To leverage this knowledge for therapeutics, the research team innovatively synthesized the PARP1 PROTAC A19. This compound effectively degrades PARP1, reduces PARylation levels, and thereby alleviates acute kidney injury.

Trimethylation of histone H3 lysine 4 (H3K4me3) is one of the best characterized histone PTMs linked to transcriptional activity[5]. Li et al. observed that both PARylation and PARP1 expression are significantly upregulated in AKI, and this upregulation is primarily induced by H3K4me3 modifications. This epigenetic mechanism may thus underlie heightened PARylation in renal pathophysiology, offering novel insight into PARylation regulation in AKI. Moreover, PARylation is identified as a critical driver of renal injury and inflammation. To further confirm this, the research team performed functional validation by both increasing and decreasing PARylation levels. Specifically, Li et al. demonstrated that PARylation promotes cell damage and inflammation in cell models induced by cisplatin (CIS) and hypoxia reoxygenation. Its role in renal injury was further validated through adeno-associated virus (AAV)-mediated Parp1 knockdown in multiple AKI models. Additionally, enhancing PARylation with the PAR glycohydrolase (PARG) inhibitor PDD reinforced the hypothesis. Collectively, these findings confirm that PARylation may be a core factor responsible for kidney injury and inflammation.

Furthermore, elucidating the specific mechanism underlying the action of PARylation is of enormous scientific significance. In their study, liquid chromatography−mass spectrometry (LC−MS/MS) demonstrated a strong binding affinity between PAR and receptor for activated C kinase 1 (RACK1) in CIS-treated cells with PARP1 overexpression. Knockdown of PARP1 and treatment with PDD can reduce or increase the PARylation level of RACK1,

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respectively. This indicates RACK1 serves as the primary target of PARylation in AKI. In previous studies, RACK1 has been identified as a key regulator in the progression of renal fibrosis[6]. Li et al. demonstrated that the use of PDD elevated the level of RACK1 PARylation, which in turn exacerbated renal damage. Notably, RACK1 knockdown effectively reversed such damage. Thus, PARylation may promote kidney injury through RACK1-dependent mechanisms. Additionally, the crosstalk between PARylation and phosphorylation was elucidated: PARylation promoted the phosphorylation of RACK1 at serine, and phosphorylation at Ser^{146} subsequently promoted RACK1 dimerization. RACK1 dimerization is critical to its functional activity, as this dimerization can promote the ubiquitination-mediated degradation of hypoxia inducible factor-1α (HIF-1α)[7]. It has been reported that HIF-1α exerts a protective effect against the progression of AKI, primarily through the modulation of inflammation, immune responses, oxidative stress, and other related mechanisms[8]. This study confirms that PARylated RACK1 promotes the Ser^{146} phosphorylation, thereby accelerating the degradation of HIF-1α in CIS-induced TECs, which aggravates mitochondrial damage.

Proteolysis-targeting chimeras (PROTACs), as bifunctional molecules, bind to a protein of interest (POI) at one end and an E3 ubiquitin ligase at the other, forming a ternary complex[9]. This complex then recruits the cellular ubiquitin-proteasome system (UPS), facilitating the proteasomal degradation of the POI. A breakthrough in the study was the development of a novel PROTAC **A19**, a potent PARP1 degrader that achieves efficient PARP1 degradation *via* the UPS in renal tissues, thereby effectively reducing PARylation levels. Since PROTAC only requires two binding ligands to bring the POI into proximity with E3 ligases, **A19** is anticipated to overcome mutation-induced resistance, a challenge that often undermines the efficacy of small-molecule PARP1 inhibitors, which typically exert their effects through enzyme activity inhibition. Moreover, unlike small-molecule inhibitors, PROTAC **A19** does not require tight or prolonged binding to its targets, as its mechanism does not depend on sustained occupancy. This intervention balanced PARylation levels, markedly alleviating kidney injury and inflammation while offering innovative insights into the prevention and treatment of AKI.

In conclusion, Li et al. demonstrated that in AKI, both PARP1 and PARylation levels are markedly upregulated in tubular epithelial cells *via* an H3K4me3-dependent epigenetic mechanism. Specifically, PARylation primarily targets RACK1, promoting its phosphorylation and subsequent dimerization. The resultant RACK1 dimer accelerates HIF-1α degradation, ultimately exacerbating the progression of a renal injury. Notably, the development of PARP1 PROTAC **A19** represents a promising therapeutic strategy for precision modulation of PARylation in AKI treatment. Compared to traditional small-molecule PARP1 inhibitors, **A19** does not require tight or prolonged target binding and is expected to overcome mutation-induced resistance, a common issue with small-molecule inhibitors.

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