Progress of small ubiquitin-related modifiers in kidney diseases

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Abstract

Objective: Small ubiquitin-related modifiers (SUMOs) are a group of post-translational modification proteins extensively expressed in eukaryotes. Abnormal SUMOylation can lead to the development of various diseases. This article summarizes the progress on research of the role of SUMOs in various types of kidney diseases to further increase the understanding of the regulatory functions of SUMOylation in the pathogenesis of kidney diseases.

Data sources: This review was based on articles published in the PubMed databases up to January 2018, using the keywords including “SUMOs,” “SUMOylation,” and “kidney diseases.”

Study selection: Original articles and critical reviews about SUMOs and kidney disease were selected for this review. A total of 50 studies were in English.

Results: SUMO participates in the activation of NF-κB inflammatory signaling pathway, playing a central regulatory role in the inflammation and progression of DN, and the secretion of various chemokines in AKI. SUMO involves in the regulation of TG2 and Nrf2 antioxidant stress, affecting renal tubular injury in AKI. SUMO affects the MAPK/ERK pathway, regulating intracellular signal transduction, modulating the transcription and expression of effector molecules in DN. SUMO contributes to the TGF-β/Smad pathway, leading to fibrosis of the kidney. The conjugate combination of SUMO and p53 regulates cell proliferation and apoptosis, and participates in the regulation of tumorigenesis. In addition, SUMOylation of MITF modulates renal tumors secondary to melanoma. Similarly, SUMOylation of tumor suppressor gene VHL regulates the occurrence of renal cell carcinoma in VHL syndrome.

Conclusions: Tissue injury, inflammatory responses, fibrosis, apoptosis, and tumor proliferation in kidney diseases all involve SUMOs. Further research of the substrate SUMOylation and regulatory mechanisms of SUMO in kidney diseases will improve and develop new treatment measures and strategies targeting kidney diseases.

Keywords: Small ubiquitin-related modifiers; SUMOylation; Kidney diseases

Introduction

Proteins are important substances that constitute biological structures and maintain activities necessary to sustain life. Among continuous in-depth studies of proteins, post-translational protein modifications (PTMs) have received extensive attention. PTMs include phosphorylation, acetylation, methylation, glycosylation, ubiquitination, and ubiquitin-like modifications, among which ubiquitin-like modifications have become a focus of protein research in recent years.

Ubiquitin-like modifications are present extensively in eukaryotes. They are PTMs similar to protein ubiquitination that involve ubiquitin-like proteins (UBLs). Small ubiquitin-related modifiers (SUMOs) are a group of molecules that modify UBLs. Although they exhibit a modification regulation process similar to ubiquitination, they have completely opposite functions. They increase the stability of substrate proteins through binding to corresponding substrates to further participate in transcriptional regulation, DNA repair, protein stability regulation, cell proliferation, and apoptosis. SUMO molecules play important roles in the maintenance of protein functions. Lack of translational modification by SUMOs or abnormal regulation can also cause various diseases including cardiovascular diseases, neurodegenerative diseases, kidney diseases, and cancers. This article summarizes the relevant research on the role of SUMOs in kidney diseases.

SUMOs

SUMO family members

The SUMO family members are highly conserved PTM proteins in eukaryotes. Among the first group of SUMO members, SMT3 was first discovered in brewer’s yeast, and...
PMT3 was discovered in budding yeast. They are mainly involved in the processes of mitosis and meiosis in cells. At least 8 types of paralogous genes are present in plants, and they play important roles in the maintenance of gene transcription, protein synthesis, and cell division. SUMOs include 4 types of protein molecules in mammalian cells: SUMO-1, SUMO-2, SUMO-3, and SUMO-4. SUMO-1 has a molecular weight of 11,600 and is composed of 101 amino acids. The amino acid sequences of SUMO-2 and SUMO-3 share 95% homology. These 2 proteins are only distinguished by 3 N-terminal amino acid residues with different functions. They share approximately 45% homology with SUMO-1.

Although SUMO-2 and SUMO-3 share relatively fewer homologous sequences with SUMO-1, their 3-dimensional structures have very high similarity. Under normal physiological conditions, SUMO-1 mainly binds to substrate proteins in cells. It is mainly expressed in the cell nucleus and perinuclear organelles and participates in many processes, such as nuclear transport, nuclear composition, signal transduction, transcriptional regulation, chromatin remodeling, DNA repair, and ribosomal composition.

SUMO-2 and SUMO-3 are mainly present in the nucleoplasm in a free state and only bind to substrates to exert corresponding functions after cells are stimulated. SUMO-4 exhibits a low level of expression in various types of tissues and organs. However, SUMO-4 expresses higher levels in many types of tissues and organs. SUMO-4 was first discovered in an analysis of single nucleotide polymorphisms associated with type 1 diabetes mellitus. It exhibits low expression levels under physiological conditions and rarely binds to substrate proteins, while its expression significantly increases when cells are subjected to oxidative stress and hypoxic injury. In addition, compared to SUMO-1, SUMO-2, and SUMO-3, SUMO-4 exhibits faster reactions to various external stimuli.

Using HeLa cells as an example, SUMO-1 is resistant to physiological stress, and its reaction time during the conversion between substrate binding and dissociation is longer than that of SUMO-2 and SUMO-3. In summary, structurally, SUMO-1, SUMO-2, and SUMO-3 all share certain homologous amino acid sequences, and SUMO-2 and SUMO-3 have high sequence similarity. Functionally, SUMO-1 is the major molecule that binds to various target proteins under physiological conditions to participate in various cellular processes, SUMO-2 and SUMO-3 bind to various substrate proteins to exert corresponding regulatory functions under physiological stress, and SUMO-4 may be a regulatory molecule that participates in cellular responses under pathological conditions.

The reaction process of SUMOylation

As the name suggests, the ubiquitin-like reaction exhibits a reaction process similar to that of ubiquitination. Although SUMOs only occupy 18% of the amino acid sequence identity with the ubiquitin molecule, they have an almost identical 3-dimensional structure, including a globular σ helix inside a β sheet. In addition, they can expose the C-terminal diglycine residues after hydrolysis by corresponding enzymes and bind to lysine residues of substrates to form isopeptide bonds, thus exerting biological effects on the corresponding structural domains of the binding substrates. Additionally, ubiquitin does not have a similar N-terminal residue structure to that of SUMO; therefore, ubiquitination and SUMOylation have completely opposite biological effects.

The SUMOylation reaction consists of 3 continuous enzymatic reactions: the E1 enzyme activates SUMO, the activated SUMO binds to the E2 enzyme, and the E3 enzyme promotes the conjugation of SUMO to the substrate [Table 1]. First, several C-terminal amino acids of SUMOs are degraded by SUMO-specific proteases (SEPNPs) to expose the diglycine residues and become mature SUMOs. Next, the diglycine residues of SUMOs bind to the cysteine residue of E1 activating enzymes (E1s) to form activated SUMOs that are modulated by ATP. E1s are ATP-dependent heterodimers constituted by the SUMO-activating enzyme subunit 1 (SAE1) and SAE2 subunits in human cells. They can specifically recognize the only currently known substrate of E2 conjugating enzymes (E2s), ubiquitin conjugating enzyme 9 (UbC9).

Through a transesterification reaction, SUMOs are transferred to the cysteine residue of E2s to form a high-energy thioester bond. Finally, under the catalytic function of E3 ligases (E3s), UbC9 directly recognizes the conserved sequence Ψ-K-x-D/E (Ψ is a hydrophobic group, K is the lysine conjugated to SUMO, x is any amino acid, and D/E is an acidic amino acid consisting of aspartic acid or glutamic acid) of the substrate to conjugate SUMOs to lysine residues of substrates to form isopeptide bonds, thus finally completing the specific binding between SUMOs and substrate proteins. Currently, Three types of E3 ligases have been discovered, Ran-binding protein 2 (RanBP2), the protein inhibitor of activated STAT (PIAS), and the polycomb protein 2 (Pc2). These ligases all have the ability to increase recognition between UbC9 and substrates.

Furthermore, bound SUMOs can be dissociated from lysine residues of substrates by SENP to participate in SUMOylation [Figure 1]. This process is called de-SUMOylation. Six types of reported SENPs, including SENP-1~3 and SENP-5~7, have been described. SENP-1/2 mainly dissociates SUMO-1~3, SENP-3/5 mainly recognizes SUMO-2/3 and removes it from the substrate, and SENP-6/7 mainly edits poly-SUMO chains produced by SUMOylation. In summary, SUMOylation and de-SUMOylation together constitute a complete reversible enzymatic reaction to further regulate various cellular biological processes through binding and dissociation of SUMOs and substrates.

| Enzyme | Homo sapiens |
|--------|--------------|
| E1 activating enzymes | SAE1-SAE2 |
| E2 conjugating enzymes | UbC9 |
| E3 ligases | PIAS1, PIASx(2), PIAS3, PIASy(4), RanBP2, Pc2 |
| deSUMOylation | SENPs 1~3 and 5~7 |
SUMOs and kidney diseases

As many researches have revealed, SUMOylation has been recognized as a crucial post-translational modification, regulating protein stability, interaction, localization, and activation. SUMOylation has also served as a major modulation in cellular processes, including signal transduction, nuclear transport, transcriptional regulation, and genetic integrity. Similarly, SUMOylation is crucial for maintaining physiological process of kidney cells. Especially in maintaining the integrity of the filtration barrier, podocytes against oxidative stress injury, and regulating mesangial cell proliferation, etc. Because the regulation of these cellular processes involves multiple signaling pathways, and these abnormal pathways are closely associated with pathogenesis of kidney diseases, therefore we will elaborate on the SUMOs and kidney diseases in the next section.

SUMOylation and acute kidney injury (AKI)

AKI is a group of clinical syndromes characterized by acute injury and necrosis of tubular cells that eventually lead to abnormal kidney functions and structures. The clinical mortality rate is greater than 50%. The common etiologies are prenjury resulting from hypertension and heart failure, renal injury induced by infection and renal parenchyma, and postrenal injury caused by urethral obstruction. Although many literature reports have described the pathogenesis of AKI, few biological studies have examined the role of protein SUMOylation in the pathophysiological changes of AKI. Guo et al. studied an ischemia/reperfusion-induced AKI mouse model to elucidate the dynamic changes of protein SUMOylation in AKI. During ischemic injury, the ATP-dependent SUMOylation level significantly reduces due to the depletion of cellular ATP, which can be restored after tissue reperfusion. In addition, the pathological process of cisplatin-induced AKI is usually accompanied by the development of cellular oxidative stress. Oxidative stress promotes the generation of disulfide bonds between molecules to inactivate SUMO proteases, thus enhancing SUMOylation in cells; however, moderate oxidative stress can induce cysteine residues of E1s and E2s to form disulfide bonds or promote the formation of disulfide bonds between protease regulatory molecules to stabilize the activity of SUMO proteases, thus inhibiting the SUMOylation process. In a cisplatin-induced tubular cell experiment, use of the p53 inhibitor PFT-α could block the conjugation of SUMO-2/3; therefore, SUMOylation was inhibited, and apoptosis was decreased. However, ginkgolic acid, a SUMOylation inhibitor, can block binding between SUMOs and E1s to also inhibit SUMOylation and resist apoptosis. SUMOylation of the mitochondrial fission protein Drp1 can block its accumulation in mitochondria and prevent mitochondrial fission, cytochrome C release,
and apoptosis.\(^{24}\) SUMO-2/3 can bind to nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IkBa) to induce SUMOylation and block its dissociation from nuclear factor-kB (NF-kB), thus inhibiting NF-kB activation and promoting cell survival.\(^{25}\) SUMO-1 can bind to histone deacetylase 2 (HDAC2) to induce SUMOylation, thus causing deacetylation of p53, blocking the activation of the transcription of apoptotic genes, and reducing DNA damage-induced apoptosis.\(^{26}\)

Overall, SUMOylation mainly plays a protective role against cell necrosis and tissue injury in AKI through oxidative stress and the p53 signaling pathway. All the above studies suggest that SUMO has protective effects on renal tubular cells in AKI.

**SUMOs and diabetic nephropathy (DN)**

DN is a common complication characterized by microvascular lesions. Because of a lack of early diagnosis and treatment measures, it usually progresses to end-stage renal disease. The pathological process of DN involves many signaling pathways including the transforming growth factor beta (TGF-\(\beta\)) pathway, NF-kB pathway, and mitogen-activated protein kinase (MAPK) pathway. Relevant studies on the NF-kB pathway showed that the inflammatory response-related regulatory molecules in the NF-kB pathways, such as IkBa, NF-kB essential modulator (NEMO), RelA, and p100, can all have SUMOylation modifications.\(^{27}\) SUMO-1 binds to the K21 and K22 sites of IkBa under the catalytic function of Ubc9 to prevent it from being degraded by ubiquitination and further inhibit NF-kB activation.\(^{28}\) SUMO-4 mainly participates in the regulation of the NF-kB signaling pathway in glomerular cells\(^{29}\) and SUMO-2 and SUMO-3 mediate NF-kB activation under high-glucose conditions.\(^{30}\) p100 can also activate the NF-kB pathway after SUMOylation, and the SUMOylation of NEMO that involves SUMO-1 mainly regulates NF-kB activation during genotoxic reactions.\(^{31}\) RelA, the other subunit of NF-kB, can undergo SUMOylation mediated by PIAS3 to inhibit NF-kB activation; while NF-kB inactivation has a negative regulatory function on SUMOylation.\(^{32}\)

MAPK is an important pathway for transducing extracellular signals into cells. It participates in various cellular processes mainly by influencing the phosphorylation of substrates, while phosphorylation is closely associated with SUMOylation. Current research shows that de-SUMOylation of the transcription factor Elk1 can activate the ERK pathway.\(^{32}\) Furthermore, SUMOs can bind to the central group of ERK5 to inhibit its transcription activity and participate in the regulatory process of endothelial cell dysfunction caused by diabetes mellitus.\(^{33}\) PIAS mediates SUMOylation of tissue transglutaminase (TG2) to inhibit TG2 degradation by ubiquitination and maintain the biological activity of TG2, thus promoting cellular oxidative stress and chronic inflammatory responses.\(^{34}\)

Recent studies have highlighted the importance of podocyte structure and function changes in the progression of diabetic nephropathy. The pathological changes of podocytes in diabetic nephropathy include an abnormality of podocyte hypertrophy, disappearance, and apoptosis. In addition, podocytes are essential for maintaining the function of the glomerular filtration barrier. SUMOylation is also involved in maintaining the normal function of podocytes. Tossidou \(^{35}\) et al found that nephrin is a substrate modified by SUMO proteins in vitro and in vivo, increasing the steady-state level and expression at plasma membrane. The conversion of lysine at position 1100 of nephrin caused decreased stability and expression at plasma membrane. SUMOylation is a reversible process for turnover and localization of nephrin at the slit diaphragm. Wang \(^{36}\) et al found SENP1 deficiency significantly increased the apoptosis of podocytes induced by puromycin aminonucleoside (PAN). SENP1 knockdown resulted in the SUMOylation of p53 protein, and increased the expression of p53-targeted HIF, BAX, NOXA, and PUMA in podocytes. Therefore, SENP1 may protect the podocytes from apoptosis by regulating the SUMOylation of p53. In hypoxic, some studies have also found hypoxia blocked the proteasomal degradation of hypoxia-inducible factor (HIF-1) in the cytoplasm and induced nuclear translocation and SUMOylation of HIF-1 in podocytes. SENP1 allowed HIF-1 to escape degradation and remained stable in the nucleus, promoting transcription of the downstream gene VEGF in hypoxia.\(^{37}\)

In summary, SUMO involves the progression of DN through regulation of several signaling pathways, including NF-kB, TGF-\(\beta\), Nrf2-oxidative stress, and MAPK. At the same time, SUMOylation is implicated in the podocyte injury process. These findings may reveal new points in therapeutic intervention for DN.

**SUMOs and renal fibrosis diseases**

The pathological processes of renal fibrosis mainly include glomerular and interstitial inflammatory cell infiltration and matrix deposition, which eventually lead to glomerular sclerosis and interstitial fibrosis. The TGF-\(\beta\)/Smad pathway mainly participates in the process of renal fibrosis. TGF-\(\beta\) can induce glomerular and tubular hypertrophy, promote extracellular matrix accumulation, and accelerate the progression of renal fibrosis.\(^{38}\) SUMOylation of the Smad protein in the TGF-\(\beta\) pathway inhibits its transcriptional activation; whereas, TGF-\(\beta\) receptor SUMOylation can promote binding to its ligands to activate signaling pathways. SUMOylated Smad3 acts on PI3K to inhibit the TGF-\(\beta\) pathway. Smad4 can bind to SUMO-1 to induce SUMOylation, increase its stability, and promote transcriptional activation. In addition, SUMOylation of TGF-\(\beta\) receptor 1 (TBR1) increases its ligand recruitment ability and the phosphorylation level of Smad3 to further enhance receptor functions, promote transcriptional activation of TGF-\(\beta\), and inhibit proliferation.\(^{39}\) The proto-oncogenes c-Ski and SnoN inhibit the anti-proliferation function of TGF-\(\beta\) through interaction with Smads. SUMO-1 can bind to the K50 site of SnoN to induce SUMOylation under catalysis of PIAS1 and PIASx, whereas Arkadia can activate the TGF-\(\beta\) pathway through the degradation of SnoN/Ski.\(^{40}\)

Based on these results, we may conclude that SUMO has made a significant contribution to renal fibrosis. Since TGF-\(\beta\) signaling plays a crucial role in the development of
fibrosis, it is reasonable to predict that SUMO can regulate renal fibrosis through binding related molecules of the TGF-β pathway.

**SUMOs and renal cell carcinoma**

SUMOs bind to substrate proteins to influence their biological activities, thus further participating in physiological and pathological processes, such as cell proliferation, differentiation, senescence, and apoptosis. Many recent studies have reported that SUMOs are involved in the process of tumor formation. Although the specific mechanisms underlying the influences of SUMOs in tumor development are still not completely elucidated, many studies have indicated that SUMOs regulate tumor development by modifying various oncogenes and tumor suppressor genes to influence signal transduction of numerous signaling pathways such as those involved in the cell cycle, proliferation, and apoptosis pathways.

Epidemiological studies have shown that melanoma patients are prone to subsequent renal cell carcinoma. Much evidence has indicated that a genetic susceptibility exists between these 2 conditions. The microphthalmia-associated transcription factor (MITF) is a familial transcription factor that plays an important role in the maintenance of melanocyte growth and differentiation and melanoma development. MITF has a periodic missense substitution mutation, Mi-E318K. Its glutamine at the 318th site is replaced by lysine; therefore, the original SUMOylation IKQE sequence is changed to IKKQ. Thus, SUMOylation of MITF is blocked, ubiquitin-mediated MITF degradation is promoted, melanin synthesis is affected, and tumor development is promoted. In addition, MITF (Mi-E318K) can activate transcription of the hypoxia-inducible factor HIF-1A. This factor can increase the ability of tumors to tolerate hypoxia and promote tumor proliferation.

Von Hippel-Lindau (VHL) syndrome is an autosomal dominant hereditary disease involving multiple organ lesions caused by mutations in the tumor suppressor gene VHL. Its main manifestations are central nervous system disease, retinoblastoma, renal hemangioma, renal cell carcinoma, and pheochromocytoma. The VHL gene is located in the chromosome 3p25–26 region. Its mutations cause expression disorders of the tumor suppressor protein pVHL and induce the development of tumors of multiple systems. SUMO-1 and SUMO-2 bind to the K171 site of pVHL to induce SUMOylation and inhibit pVHL degradation. In addition, the RWDD3 gene-encoded product RWD domain-containing protein SUMO Enhancer (RSUME) can promote SUMOylation of pVHL to block its binding to Elongins and Cullins (ECV) to form the ubiquitin-proteasome complex, thus inhibiting HIF-1 degradation and promoting tumor development.

In total, these studies only initially involved the various kidney diseases regulated by in SUMOs, and some questions and modified mechanism in kidney are still controversial. The regulation of SUMO modification in the progression of kidney disease and SUMOylation site still needs further to research and confirm.

**Discussion and perspective**

Research on SUMO constantly updates people’s understanding of its regulatory effects. SUMO has been established as a modifier to regulate cell function. By combining different substrate proteins, the degradation of the protease system is prevented, increasing the stability and promoting the expression of a series of signal molecules, thus regulating various physiological functions of the cells. Moreover, many studies have found sumo is closely involved in the development of cardiac disease, neurodegenerative disease, cancer, and innate immunity. SUMO is closely associated with the pathogenesis of kidney disease. SUMO participates in the activation of NF-κB inflammatory signaling pathway, playing a central regulatory role in the inflammation and progression of DN, and the secretion of various chemokines in AKI. SUMO involves in the regulation of TG2 and Nrf2 antioxidant stress, affecting renal tubular injury in AKI. SUMO affects the MAPK/ERK pathway, regulating intracellular signal transduction, modulating the transcription and expression of effector molecules in DN. SUMO contributes to the TGF-β/Smad pathway, leading to fibrosis of the kidney. SUMO interacts with HIF-1, participating in chronic hypoxia-induced renal injury. The conjugate combination of SUMO and p53 regulates cell proliferation and apoptosis, and participates in the regulation of tumorigenesis. In addition, SUMOylation of MITF modulates renal tumors secondary to melanoma. Similarly, SUMOylation of tumor suppressor gene VHL regulates the occurrence of renal cell carcinoma in VHL syndrome [Figure 2A–2D]

In addition to the pathways above, the close relationship between SUMOylation and autophagy should be concerned. Autophagy is a conserved multistep pathway that degrades and recycles damaged organelles to maintain intracellular homeostasis. The autophagy pathway is upregulated under stress conditions including cell starvation, hypoxia injury, nutrient deprivation, endoplasmic reticulum stress, and oxidant stress, which are involved in the pathogenesis of kidney disease. Thus, regarding SUMOylation and kidney disease, it is reasonable to anticipate that SUMOylation may contribute to the autophagy mechanism of kidney disease. Moreover, protein modification with the SUMO can affect protein function, protein stability protein interactions, and protein targeting localization. SUMOylation plays a key role in nutrient and metabolic mechanisms that influence cellular metabolism. There is increasing evidence that SUMO is a key component of the regulation of the fundamental metabolic processes, including energy and nucleotide metabolism. Therefore, we must also emphasize the potential role of SUMO in metabolic regulation in renal injury. However, there are currently few researches about the pathway and specific molecules of regulating metabolism under conditions of metabolic stress in renal. Further research is needed by the majority of nephropathy researchers to understand the relationship between SUMO and metabolism in the kidney’s physiological and pathological environment.

Although few researches regarding the treatment of kidney disease in SUMO, there are still some studies indicating the
hydrolyzing enzymes and SENP have been applied to the pathological changes in kidney disease. For example, the above mentioned that SENP1 can inhibit the degradation of HIF-1α by SUMOylation, promoting the expression of HIF-1 in the nucleus of podocytes, thus increasing the secretion of VEGF by podocytes and improve the ability of endothelial cells against hypoxia injury. Ginkgolic acid, a SUMO inhibitor, was used to reduce apoptosis by p53.

Figure 2: The major mechanisms regulated by SUMO and SUMOylation in kidney disease. (A) SUMO participates in the activation of NF-κB inflammatory signaling pathway. (B) SUMO contributes to the TGF-β/Smad pathway. (C) SUMO conjugated with p53 modulate cell proliferation and apoptosis. (D) SUMO and SENP regulate HIF-1 in hypoxia-induced renal injury.
SUMOylation.\textsuperscript{36} SUMO also plays an important role in the development of renal tumors caused by genetic diseases. SENP and SUMO inhibitors may also be applied in targeted therapy of kidney tumors, with the development of SUMOylation and the discovery of novel SUMO inhibitors, new therapeutic methods and strategies based on SUMOylation will be discovered in the near future.

Conclusions

In summary, PTM of substrates by SUMOs is an indispensable process by which proteins participate in life-sustaining activities. The dynamic balance between SUMOylation and ubiquitination regulates the expression of corresponding substrate proteins to further activate signaling pathways in which each molecule is located, induce a series of pathological responses, and eventually cause the development of various diseases. Regulation of the SUMOylation modification also plays an indispensable role in kidney diseases. Tissue injury, inflammatory responses, fibrosis, apoptosis, and tumor proliferation in kidney diseases all involve SUMOs. We have reasons to believe that with the continuous in-depth studies on substrate SUMOylation and continuous increases in the understanding on the regulatory mechanisms of SUMO in kidney diseases in the near future, new treatment measures and strategies targeting kidney diseases will be developed.

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Conflicts of interest

None.

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