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Brief Overview about Galectin-3 and its possible roles in Kidney Injury

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Abstract: It is typical for acute kidney injury (AKI) to develop and progress to chronic kidney disease (CKD), and both conditions are linked with high rates of morbidity and mortality. There is evidence that the profibrotic and inflammatory characteristics of the beta-galactoside binding protein gal3 (Gal3) contribute to the progression of both acute kidney injury (AKI) and chronic kidney disease (CKD). Patients with AKI and CKD have higher serum Gal3 levels, and this heightened level is linked to the worsening of CKD. Furthermore, AKI is more common in critically sick people who have Gal3 blocked, and both the prevalence and mortality of AKI in murine models of sepsis and ischemia-reperfusion injury are dramatically reduced. We discuss the possible therapeutic benefits of targeting Gal3 and its function in the pathogenesis of acute kidney injury (AKI) and chronic kidney disease (CKD).

Keywords: *Galectin-3, kidney injury*

Introduction

In spite of differences in economic status and geographic location, acute kidney injury (AKI) remains a leading cause of death and disability worldwide (Hoste et al., 2018). The impact of AKI on long-term health and medical costs is projected to exceed current projections, given the increasing incidence of AKI and the resulting rise in chronic kidney disease (CKD).

Cell proliferation, differentiation, inflammation, phagocytosis, exocytosis, and fibrosis are all regulated by the lectin galectin-3 (Gal3), which is expressed in many different organs and tissues (Chen and Kuo, 2016; Dong et al., 2018). According to Rabinovich et al. (2007), chimera-type Gal3 has a carbohydrate recognition domain (CRD) that is shared by all galectins and an N-terminal domain that enables the molecule to oligomerize and form pentamers. Among its several roles, Gal3 can regulate nucleus gene transcription and identify cytosolic and extracellular damage-and pathogen-associated molecular patterns (DAMPs and PAMPs, respectively) (Rabinovich et al., 2007; Dong et al., 2018). According to Rabinovich et al. (2007) and Dong et al. (2018), extracellular Gal3 has the ability to bind to receptors on cell surfaces, influence connections between cells, and bring in more lectin molecules to create lattice structures around cells, which can lead to inflammation and fibrosis.

There is evidence that Gal3 plays a role in inducing and exacerbating fibrosis and inflammation. It is likely involved in antigen presentation and mediates endocytosis and exocytosis (Lakshminarayan et al., 2014). According to research conducted by Burguillos et al. (2015), it was found that when exposed to lipopolysaccharide (LPS), Gal3 directly attaches to toll-like receptor 4 (TLR4), leading to an increase in inflammation. Furthermore, it was recently mentioned that Gal3 can enhance pyroptosis by binding to LPS glycan and activating cytosolic caspase-4/11 oligomers (Lo et al., 2021). Therefore, the fact that Gal3 interacts with these PRRs shows how Gal3 induces inflammation through intracellular and cell-surface pathways (Burguillos et al., 2015; Lo et al., 2021). Figure 1 shows potential pathways of Gal3-mediated inflammation.

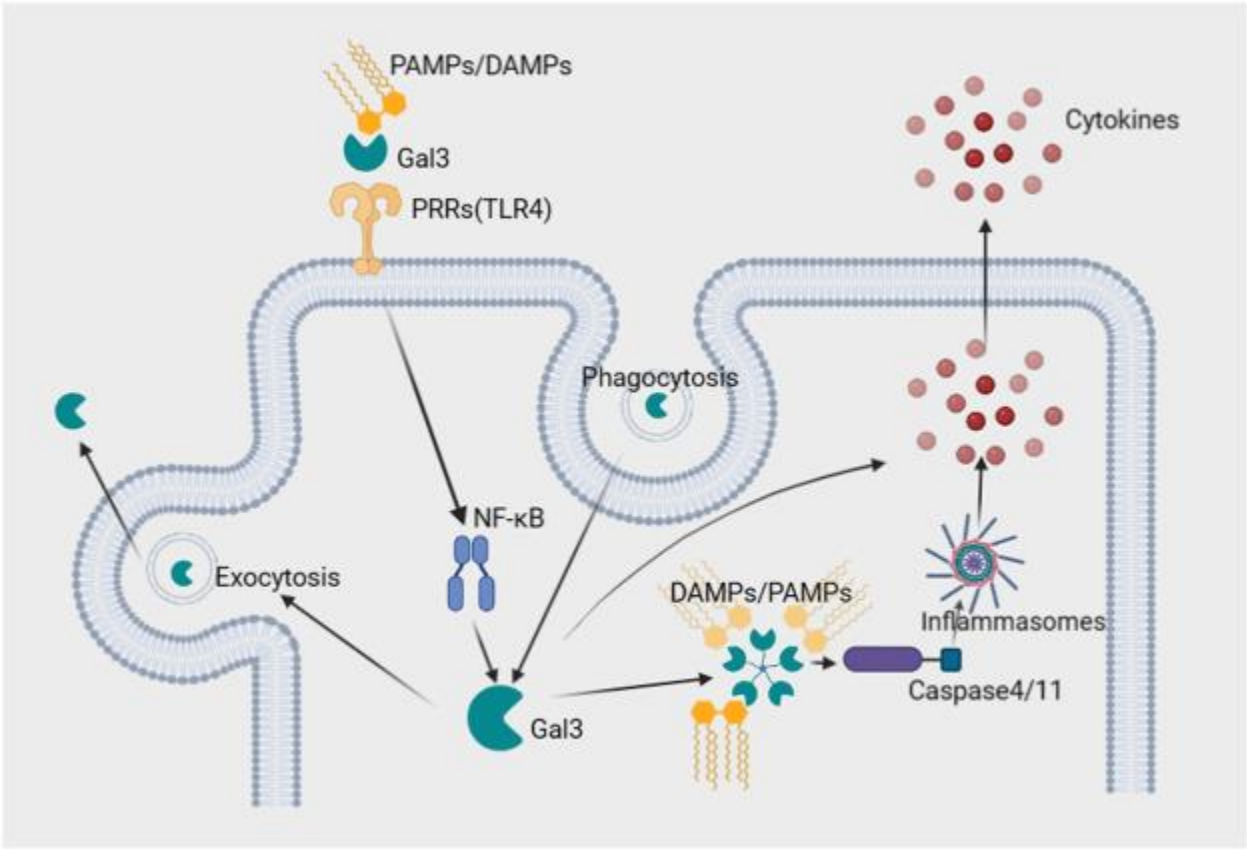

FIGURE 1
Potential roles of Gal3 in the inflammatory process. 1. Gal3 directly binds cell surface PRRs, such as TLR4, and PAMPs/DAMPs, which form a ternary complex and activate transcription factors such as NFkB, amplifying inflammation. 2. PAMPs/DAMPs in the cytosol are recognized by Gal3, which amplifies caspase-4/11 oligomerization and activates noncanonical inflammasomes, facilitating the secretion of cytokines. 3. Recycling of Gal3 mediates phagocytosis and exocytosis, facilitating antigen presentation and promoting inflammation. Abbreviations: DAMPs; damage-associated molecular patterns, Gal3; galectin-3, PAMPs; pathogen-associated molecular patterns, PRRs; pattern recognition receptors, TLR4; toll-like receptor 4.

Infections, autoimmune diseases, neurological disorders, cancers, and kidney and cardiovascular diseases may all have Gal3 as a possible biomarker (Dong et al., 2018; Hara et al., 2020). Also, Sun et al. (2021a), Boutin et al. (2022), and others have shown that Gal3 is involved in AKI development in both basic and clinical studies. Serum Gal3 concentrations have been linked to AKI and death in a number of critically ill patient investigations (Sun et al., 2021a; Sun et al., 2021b; Bootin et al., 2022). Animal studies have demonstrated that blocking Gal3 significantly reduces AKI and death rates in sepsis and ischemia-reperfusion damage models in mice (Sun et

al., 2021a; Sun et al., 2021b). These results point to Gal3 as a possible biomarker for AKI and to its possible involvement in the onset and progression of AKI and CKD. We summarize recent research that has shed light on Gal3's function in acute kidney injury (AKI) and chronic kidney disease (CKD), as well as its possible biomarker and therapeutic target roles.

Roles in renal ischemia-reperfusion injury (IRI) AKI

Renal ischemia-reperfusion injury (IRI) acute kidney damage (AKI) seems to include Gal3. The process most likely includes the generation of cytokines that promote inflammation and the activation of ROS (Fernandes Bertocchi et al., 2008). Through the use of bilateral renal pedicle clamping, Nishiyama et al. (2000) demonstrated that Gal3 mRNA started to rise 2 hours following IRI and increased by 6.2 times after 48 hours in a rat model of IRI AKI. Furthermore, a link was seen between Gal3 mRNA expression and renal injury, as evaluated by serum creatinine concentrations, after 48 hours after injury (Nishiyama et al., 2000). Gal3 deletion animals exhibited improved tubular regeneration and less severe acute tubular necrosis (ATN) in a mouse model of IRI that utilized bilateral renal pedicle blockage (Fernandes Bertocchi et al., 2008). Similarly, Sun et al. (2021a) found that modified citrus pectin (MCP) effectively reduced the increase in creatinine and blood urea nitrogen (BUN) and the degree of tubular injury in a rat IRI AKI model that utilized unilateral renal pedicle clamping. Overexpression of renal Gal3 was associated with fibrosis and inflammation in a mouse model, although MCP-induced Gal3 suppression reduced these outcomes (Martinez-Martinez et al., 2016).

In a study conducted by Dorai et al. (2011), rats were administered a reno-protective cocktail consisting of growth factors, mitochondria-protecting biochemicals, and manganese-porphyrin. The rats showed a marked reduction in serum concentrations of lipocalin-2, mucin-1, and Gal3, and they exhibited a remarkable reversal of histopathological changes when compared to the control group.In a rat model of IRI AKI, Cohen et al. (2013) also showed that a comparable reno-protective cocktail downregulated Gal3, which was linked to less oxidative stress and better protection of renal parenchymal function. The researchers Prud'homme et al. demonstrated that the cardiac damage caused by IRI AKI was Gal3-dependent and could be avoided by administering MCP, a Gal3 inhibitor, to mice with either Gal3 wild-type (WT) or Gal3 deficient bone marrow transplants (Prud'homme et al., 2019). The antiplatelet ticagrelor, like particular Gal3 inhibitors, was found to have a reno-protective effect in a mouse model of IRI by blocking the activities of Gal3 and caspase-3 (Mansour et al., 2022).

Roles in cisplatin-induced AKI

Overexpression of Gal3 caused renal cell cell cycle arrest and apoptosis, reducing their viability, according to a study by Li et al. (2018). In contrast, the harmful proapoptotic effects of cisplatin were considerably reduced when Gal3 was inhibited by MCP. Li et al. (2018) found that following cisplatin-induced AKI, mice treated with MCP had better kidney function and less renal fibrosis than controls. Volarevic et al. (2019) found that cisplatin-induced apoptosis was worse in Gal3 knockout mice and WT mice given a Gal3 inhibitor, but in Gal3 deficient mice with cisplatin-induced AKI, recombinant Gal3 reduced apoptosis. In addition, a recent study conducted by Al-Salam et al. (2021) found that cisplatin therapy in Gal3 knock-out mice resulted in higher levels of ATN and plasma urea, creatinine, cathepsin B, and cathepsin D when compared to wild-type animals. Further work is needed to determine the precise role of Gal3 in the pathophysiology of cisplatin-induced AKI, as there is minimal evidence and varying outcomes specifically related to this condition. These seemingly contradictory results could be due, in part, to the fact that different inhibitors had different effects and that Gal3 depletion or inhibition was more selective than Gal3 knockout.

Roles in folic-acid-induced AKI

Gal3 mRNA was found to be elevated in kidney tissue of rats modeled with folic acid-induced AKI at 2 hours following injury, and this upregulation persisted for a minimum of 7 days following injury (Nishiyama et al., 2000). Additionally, Kolatsi-Joannou et al. (2011) found that injured tubules showed increased Gal3 expression following folic acid injection, and that at 2 weeks post-injury, there was a decrease in proinflammatory cytokines, renal fibrosis, and apoptosis when Gal3 was inhibited. According to Kolatsi-Joannou et al. (2011), folic acid can cause AKI, however preventing or reducing Gal3 levels may help.

Roles in infection-associated AKI

According to various studies, including Ferreira et al. (2018), Wang et al. (2019), Chiu et al. (2020), Guo et al. (2021), and Humphries et al. (2021), myeloid cell-derived Gal3 is the driver of both chronic and acute inflammation, including inflammation caused by infections. Therefore, additional research into Gal3 as a potential therapeutic target is warranted. Median Gal3 concentrations were 1.4-fold and 2.7-fold higher in pneumonia and sepsis, respectively, in a clinical cohort research (Mueller et al., 2015). In addition, Sun et al. (2021b) showed that serum Gal3 concentrations were a predictor of AKI in sepsis patients. In a study conducted by Ferrer et al. (2018), it was found that in a mouse model of leptospirosis, macrophage depletion and Gal3 knockout animals had a higher bacterial load and worsened subacute nephritis compared to WT mice. Furthermore, Sun et al. (2021b) found that inhibiting Gal3 considerably decreased AKI incidence and death in a mouse sepsis model that utilized cecal ligation and puncture. As a result, a potential treatment strategy for sepsis and AKI caused by sepsis is Gal3 depletion or inhibition.

CKD progression

Increased blood Gal3 concentrations are associated with faster CKD progression after AKI, according to multiple studies. The blood creatinine (Cr) level and the urine protein-to-Cr ratio were found to be directly linked with the serum Gal3 concentration in 352 individuals with chronic kidney disease (Kim et al., 2021). Furthermore, those with impaired kidney function were found to have poor clinical outcomes when increased serum Gal3 concentrations were considered in a combined analysis of two clinical trials (Drechsler et al., 2015), in contrast to those with normal or near-normal renal function. According to Drechsler et al. (2015), patients with impaired kidney function were more likely to experience cardiovascular events, infections, and all-cause mortality when their mean Gal3 concentrations were higher. These concentrations were 12.8 ± 4.0 ng/ml for estimated glomerular filtration rate (eGFR) ≥90 ml/min, 15.6 ± 5.4 ng/ml for eGFR 60-89 ml/min, 23.1 ± 9.9 ng/ml for eGFR<60 ml/min, and 54.1 ± 19.6 ng/ml for dialysis patients. According to O'Seaghdha et al. (2013), a higher likelihood of eGFR decline and acute CKD was linked to elevated plasma concentrations of Gal3 among 2,450 participants in the Framingham Offspring Study. Furthermore, a study conducted by Rebholz et al. (2018) examined 9,148 patients in a community-based setting who did not have a history of chronic kidney disease (CKD) or heart failure. The patients with hypertension had the highest risk of incident CKD, and greater plasma Gal3 concentrations were also associated with this risk.

Mortality in CKD

According to Drechsler et al. (2015) and Alam et al. (2019), for CKD patients, higher Gal3 concentrations are linked to a higher risk of mortality. The area under the receiver operating characteristic curve (AUC-ROC) for serum Gal3 concentrations was higher than that of serum cystatin C and creatinine in a study evaluating 150 patients with CKD. The study found that Gal3 had a value of 0.89, cystatin C was 0.83, and creatinine was 0.85. (Ji et al., 2017). According to Ji et al. (2017), there was a significant difference in the 6-year kidney survival rates between the low Gal3 group (47.3%) and the high Gal3 group (22.8%). Tuegel et al. (2018) found that higher serum concentrations of Gal3, GDF-15, and sST2 were related with a larger chance of death in an observational cohort of 883 patients with CKD. Ostalska-Nowicka et al. (2009) used immunohistochemistry to show that children with diffuse mesangial proliferation and focal segmental glomerulosclerosis had higher glomerular and extraglomerular Gal3 immunoreactivity and did not respond to steroids.

Cardiovascular events in CKD and ESRD

In individuals with chronic kidney disease (CKD) and end-stage renal disease (ESRD), multiple studies have shown a correlation between Gal3 and cardiovascular events. Serum Gal3 was found to be associated with brain natriuretic protein (BNP) and high sensitivity troponin in CKD patients, according to a study that included 163 CKD patients and 105 healthy controls (Chan et al., 2020). Miljkovic et al. (2017) found that cardiovascular event risk was best predicted by combining Gal3, pentraxin-3, MMP-9, and eGFR measurements. Heart attacks and strokes were more common in hemodialysis patients whose Gal3 levels were high (Salib et al., 2021). Another research including hemodialysis patients indicated that Gal3 expression was linked to arteriovenous fistula stenosis (Ruan et al., 2021). Ruan et al. (2021) also found that serum Gal3 levels were positively

correlated with the development of neointima. The risk of cardiovascular mortality was shown to be higher in patients receiving continuous hemodialysis who had serum Gal3 concentrations higher (hazard ratio (HR) = 2.13, 95% CI 1.07-4.26) in a prospective cohort research (Liu et al., 2022). Also, Ghorbani et al. (2018) found that a cohort study included 2,477 participants linked an elevated risk of heart failure and all-cause death to a higher plasma Gal3 concentration that rose over time. There was a direct correlation between serum Gal3 concentrations and C-reactive protein (CRP) concentrations, an inverse correlation with estimated glomerular filtration rate (eGFR), and an association between higher serum Gal3 and CRP concentrations and vascular reactivity index, a measure of endothelial dysfunction, in a study of 130 patients with chronic kidney disease (Hsu et al., 2021).

Kidney transplant (KT)

There is some evidence linking Gal3 levels to the success or failure of kidney transplants in recent animal and human research. Research conducted by Henderson et al. (2008) examined 561 kidney transplant recipients and discovered that elevated serum Gal3 concentrations were linked to an increased probability of late graft failure. Furthermore, Dang et al. (2012) discovered that, in contrast to controls, Gal3 null animals showed far better preservation of renal tubules and lower interstitial fibrosis following kidney transplant in a mouse model of chronic allograft damage. Curiously, according to Tan et al. (2014), patients who underwent kidney transplantation exhibited noticeably lower Gal-3 concentrations three months after the operation, in contrast to patients who continued hemodialysis, who did not exhibit significantly different levels of Gal-3. Further exploration into Gal3-targeted treatments for the prevention of tubulointerstitial fibrosis following transplant is warranted in light of these findings.

Autoimmune nephropathy

According to Saccon et al. (2017), Gal3 plays a crucial role in autoimmune nephropathies by regulating the immune response, inflammation, and fibrosis. The interferon-regulated gene LGALS3, which encodes Gal3, was found to be directly associated with disease activity in kidney tissue from lupus nephritis patients (Almaani et al., 2019). According to Almaani et al. (2019), patients who managed to achieve a complete response also had reduced levels of LGALS3. According to Kang et al. (2009), patients with systemic lupus erythematosus (SLE) had higher amounts of blood Gal3 and higher levels of glomerular Gal3 expression when compared to healthy controls. Furthermore, there was a clear correlation between Gal-3 expression and anti-dsDNA levels, as well as an inverse correlation with complement 3 and 4 levels (Kang et al., 2009).

Diabetic nephropathy

The development of diabetic nephropathy may be influenced by Gal3. Gal3 reduces insulin sensitivity by binding directly to the insulin receptor and inhibiting downstream signaling; it also has a function in inflammation and fibrosis (Li et al., 2016). Gal3 inhibition, Gal3 heterozygous depletion, and Gal3 deletion improved insulin sensitivity and glucose tolerance in a diabetic mouse model relative to controls [72]. Patients with macroalbuminuria had considerably higher mean serum concentrations of Gal3 compared to those with microalbuminuria or without albuminuria, in a prospective investigation of diabetic nephropathy patients (Hodeib et al., 2019). An additional study conducted by Tan et al. (2018) found that elevated serum Gal3 concentrations were linked to the progression of renal disease in 1,320 patients with type 2 diabetes and an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m2 or above. Similarly, de Boer et al. (2017) found that individuals with type 1 diabetes had an increased serum Gal3 level, which was linked to a decreased estimated glomerular filtration rate (eGFR) and an increased urine albumin to creatinine ratio.

Hypertensive nephropathy

Higher blood Gal3 concentrations were found to be inversely linked with eGFR in hypertensive patients (Lau et al., 2021). Yao et al. (2016) found that serum Gal3 was linked to a higher likelihood of left ventricular remodeling in 107 hypertensive individuals, both before and after correcting for BMI and SBP (OR: 14.76; 95% CI, 5.39-27.76, $p < 0.001$). Reducing albuminuria, improving kidney function, and decreasing interstitial fibrosis, epithelial-mesenchymal transition, and inflammation on kidney biopsy were all signs that MCP-mediated Gal3 inhibition attenuated early kidney damage independent of blood pressure levels in a preclinical

study of spontaneously hypertensive rats (Martinez-Martinez et al., 2018).Additionally, Frenay et al. (2015) showed that blocking Gal3 reduced hypertensive nephropathy in rats, which was supported by better kidney function, less proteinuria, and less structural kidney damage (Frenay et al., 2015). Research conducted by Martinez-Martinez et al. (2015) in a different model of murine hypertension found that inhibiting Gal3 reduced inflammation and fibrosis in the kidneys under experimental hyperaldosteronism, regardless of blood pressure.

Renal fibrosis

According to recent research, Gal3 plays an essential role in fibrogenesis that impacts various organ systems, such as the heart, lungs, liver, and kidneys (Li et al., 2014). Plasma Gal3 concentrations were found to be inversely associated to estimated glomerular filtration rate (eGFR; $p = 0.005$) and directly related to interstitial fibrosis and tubular atrophy in a study of 249 CKD patients who underwent kidney biopsy (Ou et al., 2021). Similarly, Ou et al. (2022) found that interstitial fibrosis was more severe in patients with greater urine Gal3 concentrations who had kidney biopsies. The study included 280 patients.

Additionally, connections between Gal3 and renal fibrosis have been shown in murine models. According to Henderson et al. (2008), there was a notable increase in Gal3 expression in the renal interstitium and tubular epithelium in a mouse model of unilateral ureteral obstruction (UUO) compared to controls. The fibrotic phenotype was recovered in Gal3 knockout mice after adoptive transfer of WT Gal3-positive macrophages; furthermore, renal fibrosis was dramatically decreased in Gal3 knockout animals and after macrophage ablation (Henderson et al., 2008). According to Henderson et al. (2008), one of the key mechanisms that connects macrophages to renal fibrosis is the production of Gal3. Similarly, research by Calvier et al. (2015) found that genetic deletion of Gal3 or the Gal3 inhibitor MCP reduced cardiac and renal fibrosis linked with Gal3 expression in experimental hyperaldosteronism. Wu et al. (2022) found that in a different model of UUO in mice, macrophages lacking Twist1 showed less renal interstitial fibrosis and lower Gal3 expression compared to controls 14 days after UUO. Further evidence that Twist1/Gal3 signaling regulates macrophage plasticity and enhances renal fibrosis came from the fact that Twist1 directly activates Gal3 transcription and that Gal3 overexpression restored Twist1-mediated M2 macrophage polarization in Twist1-deficient macrophages (Wu et al., 2022). Gal3 expression was found to correlate with the degree of interstitial fibrosis in rat models of obesity and aortic stenosis. In a study conducted by Martinez-Martinez et al. (2016), it was found that inhibiting Gal-3 with MCP restored Gal3 levels and halted the advancement of renal fibrosis.

A variety of inflammatory and fibrotic diseases, such as AKI and CKD, are thought to be influenced by the pathophysiology of the carbohydrate-binding lectin Gal3. According to several studies (Drechsler et al., 2015; Ji et al., 2017; Alam et al., 2019; Sun et al., 2021b; Kim et al., 2021; Boutin et al., 2022). Gal3 inhibitors have been demonstrated to decrease inflammation and fibrosis in various diseases, and Gal3 concentrations are higher in AKI and CKD. (Supplementary Table S1). Experimental hyperaldosteronism, sepsis-associated acute kidney injury (AKI), hypertensive nephropathy, renal fibrosis, interstitial fibrosis after a transplant, and interstitial reticulointerstitial injury (RII) acute kidney injury (AKI) are among the conditions in which Gal3 inhibitors have been demonstrated to considerably reduce kidney injury in murine models. In light of these results, Gal3 inhibition or depletion deserves additional investigation as a possible therapeutic target in AKI and CKD.

Conclusion

Gal3 seems to be involved in the pathogenesis of AKI and CKD, as shown in the current literature. Impairment of kidney function, inflammation, and fibrosis can be achieved by inhibiting Gal3, a protein that is linked to the development and progression of AKI from multiple causes. The available data point to Gal3 as a promising biomarker and therapeutic target for AKI and CKD, highlighting the need for additional research in this area.

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