Gender-specific role of HDAC11 in kidney ischemia- and reperfusion-induced PAI-1 expression and injury

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Kim JI, Jung KJ, Jang HS, Park KM. Gender-specific role of HDAC11 in kidney ischemia- and reperfusion-induced PAI-1 expression and injury. Am J Physiol Renal Physiol 305: F61–F70, 2013.—Male gender and the male hormone testosterone increase susceptibility to kidney ischemia and reperfusion (I/R) injury, which is associated with inflammatory responses. Possible involvement of histone deacetylase (HDAC) in inflammatory responses has been suggested. We investigated the gender-specific role of HDACs in plasminogen activator inhibitor type-1 (PAI-1) expression and I/R injury. PAI-1 inhibition protected the kidney from I/R-induced inflammation and functional loss. Among HDACs, only HDAC11 negatively regulated PAI-1 expression in I/R-subjected kidney specifically and lipopolysaccharide (LPS)-stimulated mouse monocytes/macrophages. HDAC11 gene silencing increased PAI-1 expression. Chromatin immunoprecipitation assay confirmed binding of HDAC11 to the promoter region of PAI-1 and then release by I/R insult or LPS treatment. I/R-induced HDAC11 release was inhibited by orchietomy and reversed by dihydrotestosterone treatment. Release of HDAC11 increased acetylation of histone H3. In conclusion, male gender and male hormones accelerate I/R-induced decreases in expression and binding of HDAC11, resulting in an increase in PAI-1 expression. These data provide important insight into gender dimorphism offering HDAC11 as a novel target for I/R injury.

HDAC11; PAI-1; kidney ischemia and reperfusion; gender dimorphism

Gender dimorphism and the role of sex steroids in renal disease have been studied for decades with the expectation that potential therapies will be discovered through research. In addition to previously reported protective effect of estrogens, our group has reported that male hormones are responsible for increased susceptibility of males to renal injury such as ischemia and reperfusion (I/R) injury (18, 36, 37). Even though the effects of the male hormone on the oxidative stress and expression of inflammatory mediators were observed, the underlying mechanisms are largely unknown (37, 38, 41, 48), limiting the application. Thus elucidation of the mechanism underlying enhanced expression of inflammatory mediators will provide a more profound target.

Kidney I/R is a major cause of acute kidney injury, which is accompanied by histological damage, functional loss, and a high rate of mortality (42). Many inflammatory mediators and oxidative stress signals are known to be associated with I/R, and inhibition of these factors resulted in effective attenuation of I/R injury (10, 17). In addition, impaired reperfusion induced by endothelial cell swelling or capillary coagulation also plays a pivotal role in I/R injury. Anticoagulant therapy during warm ischemia inhibited inflammation and chronic kidney graft fibrosis with downregulation of plasminogen activator inhibitor type-1 (PAI-1) protein expression (11), indicating that regulation of PAI-1 expression would be a good strategy for treatment of I/R-induced inflammatory renal injury. Indeed, PAI-1 has a promigratory effect on macrophages (4) and increased expression of PAI-1 in an animal model of I/R has been reported (1). While the role of PAI-1 in chronic fibrosis induced by various sources such as diabetic nephropathy, ureteral obstructive-induced injury, glomerulonephritis, and I/R (1, 11, 19, 26, 32, 33), has well been studied, but the role of PAI-1 in acute kidney injury induced by I/R has not yet been reported.

The anti-inflammatory and antifibrotic effects of histone deacetylase (HDAC) inhibitors have recently been reported (15, 34), emerging as a novel therapeutic strategy for treatment of kidney dysfunction. However, because broad spectrum HDAC inhibitors were used in those in vivo experiments, current knowledge on the action of individual HDACs in kidney injury is very poor, limiting the clinical application. In addition, results of in vitro experiments using macrophage cells revealed differential effects of broad spectrum HDAC inhibitors on inflammatory gene expression by lipopolysaccharide (LPS) stimulation. Pan-HDAC inhibitor and HDAC1-specific inhibitor induced a decrease in other proinflammatory mediators, including endothelin-1 (Edn)-1, chemokine (C-C motif) ligand 7 (Ccl-7), monocyte chemotactic protein-3 (MCP-3), and IL12p40, whereas PAI-1 was rather increased in that setting (12). Therefore, for establishment of clinical application of HDAC inhibitors for inflammation, a specific isofrom of HDAC, and the underlying mechanism of expression of inflammatory factors such as PAI-1 should be verified. The result will be helpful in the effort to more effectively control I/R-induced inflammatory diseases.

In current study, we provide evidence of the male gender-specific role of HDAC11 and the underlying mechanism of the increase in I/R-induced PAI-1 expression and renal damage.

Materials and Methods

Animal preparation. All animal experiments were conducted in accordance with guidelines of the Institutional Animal Care and Use Committee at Kyungpook National University. Eight- to nine-week-old BALB/c mice were used in this study. Mice were subjected to either 30 min of bilateral renal ischemia or sham surgery, as described previously (35). In some male mice or female mice, orchietomy or ovariectomy was performed, respectively, 15 days before surgery, as described previously (37). Some mice were administered with dihydrotestosterone (DHT; 500 μg/kg of body wt; Sigma, St. Louis, MO) by subcutaneous injection every 4 days for 14 days before surgery. Some

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mice were administered with penta-O-galloyl-β-D-glucose (15 mg/kg of body wt, 2 h before and immediately after I/R, Sigma). Semi-quantitative RT-PCR. RNA was extracted using RNasy kit (Qiagen, Valencia, CA) followed by cDNA synthesis using ReverTraid First Strand cDNA Synthesis Kit (Fermentas, Glen Burnie, MD). PCR was performed using Taq DNA polymerase (Fermentas). PCR primer sequences were 5'-AGTCTAGAAGTGGTCCTT-3' and 5'-ACGTCATACTCGAGCCCATC-3' for PAI-1; 5'-ACAACAGCCTT-GCTTGAGGAAG-3' and 5'-TTTGGCTTCTGGCTTCTC-3' for HDAC3; 5'-AGGCTGTCATGGAGGAAATCTT-3' and 5'-CCGCCAATCTTCCGAGCTTGA-3' for HDAC5; 5'-AAGCTGTAGTGGCTACAGGAGTGA-3' and 5'-AGGCTGCTATGAGCAGGTGA-3' for HDAC6; 5'-GCTGAGAAGATG-GCTTGTGCTTG-3' and 5'-AATGGGAGATCTGCTGGCTT-3' for HDAC7; 5'-AGTTCCTGTAGATCGGGAAGTGA-3' and 5'-CGGCTAATAATTCTGCAGCA-3' for HDAC9; 5'-AGGATGATGTGGCTGTCATGTA-3' and 5'-TCTCTGATGGTCCTGGAGTTGT-3' for HDAC9; 5'-AAGGTGCCTGTGTTTCTCCTG-3' and 5'-ACAGTGCGTGGAGCTCCTCTTTAT-3' for HDAC10; 5'-TCTCAACG-AGCAGTGGTCTCT-3' and 5'-TTTGGCTTCTGGCTTCTCCT-3' for HDAC3; 5'-GTCAGCTTCTGCCGACGTTA-3' and 5'-TTCTGTAGACGAGCTGACACG-3' for HDAC2; 5'-TTCTCTGCTCCTGAGTGCTCGATTA-3' and 5'-TTTGTGTCAATAGCCCTTGTGCGG-3' for HDAC1; 5'-ACCCTGTAGTTCTCAATTTGGTGTTA-3' and 5'-TTTTCCTCCTCCCT-3' for HDAC5; 5'-GCCAAATACCTATTG-CGATAGCA-3' and 5'-ACATGAGCAGCTGGTGAATTG-3' for HDAC4; 5'-AACCCCTGACACAAAGATGCAGT-3' and 5'-TTGCTTCTGGCTTCTCCT-3' for HDAC1. Cell culture and small interfering RNA. Three to five passages of RAW264.7 cells (American Type Culture Collection, Manassas, VA) were transfected with 20 nM of HDAC11 small interfering RNA (Upstate Biotech, Millipore, Billerica, MA) following the manufacturer’s instructions. Briefly, RAW264.7 cells were transected with 20 nM of HDAC11 small interfering RNA (siRNA; Santa Cruz Biotechnology) or scrambled siRNA (5’-CUGAUGACUGAUGAUGTT-3’ and 5’-CAUUAUCACUGGUA-CAUGATTT-3’, duplicated) using Lipofectamine 2000. Histology. Kidneys were perfused with PLP solution (2% paraformaldehyde, 75 mM l-lysine and 10 mM sodium periodate; Sigma) for 15 min via the left ventricle. Kidneys were excised and placed in PLP solution at 4°C overnight, followed by embedding in paraffin, and cut into 2-μm thick sections. Sections were stained with periodic acid-Schiff. Micrographic pictures of 10 fields of outer medulla were taken using a Nikon Microphot-Fx (Nikon, Melville, NY). For scoring of tubular damage, 50 tubules per field were analyzed using the following scoring criteria: 0, no damage; 1, mild damage with the rounded epithelial cells and dilated tubular lumen; 2, moderate damage with flattened epithelial cells, dilated lumen, and congestion of lumen; and 3, severe damage with flat epithelial cells lacking nuclear staining and congestion of the lumen.

Statistics. The results are expressed as means ± SE. Statistical differences among groups were calculated using ANOVA and statistical differences between the groups were evaluated with an ANOVA using Student’s t-test. Differences between the groups were considered statistically significant with a P value of <0.05.

RESULTS

I/R-induced PAI-1 expression in the kidney was dependent on gender, particularly the male hormone. Our group previously reported that male gender is more susceptible to I/R injury than female gender and testosterone is responsible for enhanced susceptibility of males to ischemic renal injury (37). To elucidate the underlying mechanism of I/R-induced gender difference, we tested the effect of sex hormones on I/R-induced expression of PAI-1. PAI-1 mRNA levels were determined in male, orchietomized male, female, and ovarietomized female mice subjected to a sham operation or I/R. PAI-1 greatly increased in males with I/R than female gender and testosterone is responsible for enhanced susceptibility of males to ischemic renal injury (37). To elucidate the underlying mechanism of I/R-induced gender difference, we tested the effect of sex hormones on I/R-induced expression of PAI-1. PAI-1 mRNA levels were determined in male, orchietomized male, female, and ovarietomized female mice subjected to a sham operation or I/R. PAI-1 greatly increased in males with I/R (P<0.001 vs. male sham), and orchietomy significantly inhibited PAI-1 expression (P = 0.003 vs. intact male with I/R). I/R-induced PAI-1 was significantly lower in females (P < 0.001) than in males and ovarietomy did not change the PAI-1 level (Fig. 1, A and C), demonstrating the importance of the male hormone in I/R-induced PAI-1 expression. Then, intact males and orchietomized males were treated with DHT followed by I/R. Treatment with DHT tended to increase PAI-1 expression in intact males, but it was not statistically significant. DHT greatly increased PAI-1 expression in orchietomized males at the level of intact males (Fig. 1, B and D), confirming that I/R-induced PAI-1 expression is highly dependent on testos-
terone. Protein level of PAI-1 in intact males also greatly increased 24 h after I/R (P = 0.001 vs. sham). Orchiectomy inhibited PAI-1 expression (P = 0.005 vs. intact male I/R) and DHT reversed PAI-1 expression to the level of intact males (Fig. 1, E and F).

I/R-induced kidney damage was attenuated by the PAI-1 inhibitor via inhibition of inflammation. To investigate the role of PAI-1 in I/R injury, male mice were pretreated with PAI-1 inhibitor and subsequently subjected to I/R insult. Plasma creatinine (PCr) level and histological damage score were determined, and gross congestion of kidney was observed. Treatment with PAI-1 inhibitor resulted in significantly reduced loss of kidney function by I/R to 57% of vehicle-treated mice (Fig. 2A; P = 0.004 vs. vehicle). The PAI-1 inhibitor reduced I/R-induced histological damage (Fig. 2, B and C; P = 0.002 vs. vehicle) as well as kidney congestion significantly (Fig. 2D). Results of Western blot revealed that I/R-enhanced level of sham by orchiectomy, demonstrating that decrease in males (Fig. 3, 7 to the level of sham, HDAC11 negatively regulated PAI-1 expression in mouse macrophage/monocyte cell line RAW264.7. Because macrophage infiltration plays a key role in kidney I/R-induced inflammation (50), we used LPS-stimulated macrophage as a model of kidney response to I/R. PAI-1 is known to be expressed in the mouse macrophage/monocyte cell line RAW264.7 cell (12). We activated RAW264.7 cells with LPS and determined the mRNA levels of PAI-1 and five isotypes of HDACs. We included HDAC1 because treatment with specific HDAC1 inhibitor resulted in increased PAI-1 expression in RAW264.7 cells (12) and HDAC5, 8, 9, and 11 because they were changed in I/R-subjected kidney tissue (Fig. 3, A, F, I, J, and L). LPS stimulation increase PAI-1 over 10 times (Fig. 4, A and B) with a concomitant decrease in HDAC11 (Fig. 4, A and G),
suggesting negative regulation of PAI-1 expression by HDAC11. Expression of HDAC1, 5, 8, and 9 was not changed (Fig. 4, A and C–F). Further, to test the direct role of HDAC11 in expression of PAI-1, we silenced HDAC11 in RAW264.7 cells. Using siRNA for HDAC11, we knocked down HDAC11 mRNA to 30% of the control level (Fig. 5, A and B; \( P < 0.01 \) vs. control) and PAI-1 expression greatly increased to seven times upon silencing of HDAC11 (Fig. 5, A and C; \( P < 0.01 \) vs. control), indicating a negative but direct role of HDAC11 in PAI-1 expression. HDAC11 knockdown did not affect other types of HDACs (Fig. 5 D).

DHT reversed the effect of orchiectomy in I/R-induced decrease in HDAC 11 expression. To confirm that the effect of orchiectomy on sustenance of HDAC11 even after kidney I/R is due to the absence of the male hormone, we administered DHT to intact and orchiectomized male mice and performed I/R. After I/R, no change in HDAC11 was observed in orchiectomized male mice; however, HDAC11 in DHT-treated orchiectomized male mice showed a significant decrease (\( P < 0.001 \) vs. vehicle-treated I/R-subjected orchiectomized male). The level of decrease in HDAC11 in DHT-treated orchiectomized males was almost same as that in intact males (\( P <
0.158 vs. vehicle-treated I/R-subjected intact male). The effect of DHT on intact males was minimal (Fig. 6).

Male hormone-dependent I/R-induced release of HDAC11 from the specific PAI-1 promoter region is responsible for the increase in PAI-1 expression. We tested if HDAC11 binds to the PAI-1 promoter region in RAW264.7 cells and kidney tissue. As shown in Fig. 7B, results of the ChIP assay revealed binding of HDAC11 to PAI-1 pm2, 3, and 4 (named as described in MATERIALS AND METHODS). HDAC11 was then released upon LPS stimulation. The results of in vivo ChIP assay in intact and orchiectomized males also showed binding of HDAC11 to PAI-1 pm1, 2, and 4, which was released upon I/R insult in intact males. In orchiectomized males, HDAC11 bound to PAI-1 pm2 only and remained bound even after I/R insult (Fig. 7C), indicating the importance of release of HDAC11 from this region for I/R-induced PAI-1 expression and its dependence on the male hormone. In intact females and ovariectomized females, HDAC11 binding to this region was not affected by I/R (Fig. 7E), emphasizing the importance of the male hormone. Next, to evaluate the effect of release of HDAC11 from PAI-1 promoter on transcription of PAI-1, we assessed the level of acetylated histone H3. In I/R-subjected intact males, acetylation of histone H3 increased. By contrast, in orchiectomized males, intact females, and ovariectomized females it did not change (Fig. 7D and F), explaining the male hormone-dependent increase in PAI-1 transcription.

**DISCUSSION**

In the current study, upregulation of PAI-1 by release of HDAC11 from a specific region of the PAI-1 promoter was demonstrated. This event occurs in a male hormone-dependent manner, elucidating the mechanism of gender difference in kidney I/R injury, offering a novel and specific epigenetic target.

A vast amount of research on gender differences in cardiovascular disease, such as ischemic stroke, has been conducted, and significant clinical benefit has been obtained from those studies (30). Renal tissue also shows gender differences in anatomy, physiology, and pathophysiology, including renal...
One of the main pathways of injurious effect of testosterone is increased production of inflammatory mediators such as transforming growth factor-β1 (TGF-β1; Ref. 48), TNF-α (41), IL-1β, IL12 (38), and ICAM-1 (37). However, the underlying mechanism of the increased expression of these factors remained to be elucidated. Here, we found that kidney I/R-induced PAI-1 expression is greater in male mice than in orchiectomized males or females. Treatment with DHT reversed the expression of PAI-1, suggesting the role of the male hormone in the enhanced production. We showed that I/R ischemia, ureteral obstructive nephropathy, perioperative renal failure, and renal transplantation (6, 14, 16, 18, 29, 36, 37). Since gender dimorphism in kidney had been recognized decades ago, efforts have been made to elucidate the mechanism of the differential responses by males and females to lead to better therapy. As a result, with evidence of protective roles of estrogen, the harmful effects of testosterone in renal injury remained to be elucidated. Here, we found that kidney I/R-induced PAI-1 expression is greater in male mice than in orchiectomized males or females. Treatment with DHT reversed the expression of PAI-1, suggesting the role of the male hormone in the enhanced production. We showed that I/R

Fig. 6. Decrease in HDAC11 in I/R-subjected mouse kidney was dependent on the male hormone. A: electrophoresis of PCR product using primers for HDAC11. B: sham operation or I/R-induced HDAC11 mRNA level in mice kidney of intact and orchiectomized male with/without DHT treatment. Data are presented as means ± SE (n = 4). **P < 0.01 vs. its own sham. ^^P < 0.01 vs. vehicle-treated intact male with I/R. $$$P < 0.01 vs. vehicle-treated orchiectomized male with I/R.

Fig. 7. Binding and release of HDAC11 from PAI-1 promoter regulated acetylation of histone H3. A: analyzed promoter region of PAI-1. B and C: representative electrophoresis of ChIP PCR product using primers for specific regions of PAI-1 promoter from 2 independent ChIP assays. ChIP assay was performed against normal rabbit IgG or HDAC11 antibody. B: RAW264.7 cells treated with vehicle or LPS for 4 h. C: intact or orchiectomized male subjected to sham operation or I/R. D: representative electrophoresis of ChIP PCR product using primers for specific regions of the PAI-1 promoter from 2 independent ChIP assays. E: representative electrophoresis of ChIP PCR product using primers for specific regions of the PAI-1 promoter from 2 independent ChIP assays. ChIP assay was performed against normal rabbit IgG or acetylated histone H3 antibody in intact or orchiectomized males subjected to sham operation or I/R. E: representative electrophoresis of ChIP PCR product using primers for specific regions of the PAI-1 promoter from 2 independent ChIP assays. ChIP assay was performed against normal rabbit IgG or acetylated histone H3 antibody in intact or orchiectomized males subjected to sham operation or I/R. F: representative electrophoresis of ChIP PCR product using primers for specific regions of the PAI-1 promoter from 2 independent ChIP assays. ChIP assay was performed against normal rabbit IgG or acetylated histone H3 antibody in intact or orchiectomized males subjected to sham operation or I/R. ChIP assay was performed against normal rabbit IgG or acetylated histone H3 antibody.
induced inflammation and renal damage by increased PAI-1 within 24 h. Inhibition of PAI-1 using the novel PAI-1 inhibitor penta-O-galloyl-β-D-glucose, which works even in the presence of cofactor vitronectin (3), greatly attenuated acute kidney I/R injury at 24 h through inhibition of immune cell infiltration, such as macrophages and leukocytes. The PAI-1 inhibitor reduced I/R-induced congestion and damage of the tubules as well as functional loss. Our results emphasize the pivotal role of PAI-1 and the benefit of elucidation of its transcriptional regulation according to gender in acute kidney I/R injury.

HDAC inhibitors have emerged as a novel and effective therapeutic strategy for treatment of kidney inflammation and fibrosis induced in obstructive nephropathy (34), poly cystic kidney disease (5), diabetic nephropathy (21), and adriamycin-induced nephropathy (44), suggesting the expansion of HDAC inhibitors for treatment of inflammation-induced kidney injuries by I/R. Although the diseases mentioned above share inflammatory responses as a common cause of pathological consequence with I/R, the major type of HDACs, which plays a key role in each disease, and HDAC-regulated gene expression profiles would differ according to the sources of disease signals. Indeed, whereas ureteral obstruction increased HDAC1 and 2 expression (28), I/R decreased HDAC1 expression and did not affect HDAC2 expression in our results. Others have provided further evidence supporting this idea. The ATF-3 and HDAC1 complex is recruited to IL-6 and IL-12 promoters, inhibiting expression of IL-6 and IL-12, resulting in protection against acute kidney injury (22), which means that pan-HDAC inhibitors or the HDAC1 inhibitor may reverse this protection against I/R injury. In addition, the differential effects of the pan-HDAC inhibitor trichostatin A on macrophage-induced expressions of pro- and anti-inflammatory mediators depending on the concentrations have been demonstrated. (12). In addition, treatment with trichostatin A resulted in decreased expression of IL-6 and IL-1β, with simultaneously increased expression of CD36, TNF-α, and VCAM-1, exacerbating atherosclerosis in LDL receptor-deficient mice (7). These results suggest that application of HDAC inhibitors should be cautious and based on plentiful and profound data on the role of individual HDACs in specific signaling pathways.

Our results showed that, among 11 isotypes of HDACs, HDAC9 and 11 showed negative correlation with PAI-1 expression by I/R in a male hormone-dependent manner. Because HDAC9 decreased less than HDAC11 in an animal model and did not change in LPS-stimulated macrophage cells, which increased PAI-1 expression, we speculate that HDAC11 is primary regulator of I/R-induced PAI-1 expression through inflammatory response. While the function of HDAC11 has been reported in various pathophysiological events, including cancer (2), oligodendrocyte development (25), DNA replication (32), somatic cell growth (43), pancreatic β-cell function (27), tolerance induction in Kupffer cell (23), tolerance induction in antigen presenting cells (46), and neurological function of cocaine (13), its role or expression pattern in kidney physiology or pathology has not yet been reported. Our data revealed that HDAC11 decreased differentially in response to kidney I/R according to gender to increase acetylation of histone H3 and PAI-1 expression, presenting HDAC11 as a novel target for regulation of inflammation induced by I/R.

Our results of screening of HDACs in males and females with/without castration and with/without I/R insult will also inform and intrigue others to conduct further research on epigenetic regulation of various gender specific inflammatory diseases.

The PAI-1 gene is regulated in response to various signals, including cytokines, hormones, catecholamines, angiotensin II, glucose, cAMP, hypoxia, and many growth factors (9, 31). As mentioned in section 2.5, PAI-1 promoter (pm)1 contained TATA box, c-Ets, Elk-1, NFBK, and C/EBP; pm2 contained p300 and USF-2; pm3 contained C/EBP and AP-1; and pm4 contained c-Ets, NRF-2 binding site. It has been reported that EGF activates Ets binding site by phosphorylation of Elk1 (49); hypoxia activates C/EBP (24); oxidative stress activates AP-1 (47); EGF receptor activation activates NF-κB, steroid receptor coactivator-1 potentiates TGF-β/Smad signal, facilitating the functional link between Smad3 and p300/CFP (8); and TGF-β signal facilitates Smad/p53/USF-2 transcriptional complex (40), resulting in PAI-1 transcription (39). In addition, shRNA knock-down of Nrf2 and loss of Nrf2/Smad3/Smad4 complex resulted in increased transcription of PAI-1. The results of our ChIP assay revealed binding of HDAC11 to the PAI-1 pm2 promoter region results in negative regulation of PAI-1 transcription. Decreased binding or release of HDAC11 from this region resulted in increased acetylation of histone H3 in intact males but not orchietomized males, intact females, and ovariec tomized females, explaining the increase of PAI-1 only in intact males. In addition, regarding the presence of p300 and USF-2 binding sites in pm2 region, it is possible that release of HDAC11 may facilitate recruitment of p300 or USF-2 transcriptional complex to this region.

Taken together, I/R-induced downregulated expression and binding of HDAC11 to PAI-1 promoter resulted in enhanced expression of PAI1 in a male hormone-dependent manner. This finding explains the mechanism of increased susceptibility of males to kidney I/R injury, providing a novel and efficient target for epigenetic regulation of I/R injury.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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