Podocyte as the Target for Aldosterone
Roles of Oxidative Stress and Sgk1

Shigeru Shibata, Miki Nagase, Shigetaka Yoshida, Hiroshi Kawachi, Toshiro Fujita

Abstract—Accumulating evidence suggests that mineralocorticoid receptor blockade effectively reduces proteinuria in hypertensive patients. However, the mechanism of the antiproteinuric effect remains elusive. In this study, we investigated the effects of aldosterone on podocyte, a key player of the glomerular filtration barrier. Uninephrectomized rats were continuously infused with aldosterone and fed a high-salt diet. Aldosterone induced proteinuria progressively, associated with blood pressure elevation. Notably, gene expressions of podocyte-associated molecules nephrin and podocin were markedly decreased in aldosterone-infused rats at 2 weeks, with a gradual decrease thereafter. Immunohistochemical studies and electron microscopy confirmed the podocyte damage. Podocyte injury was accompanied by renal reduced nicotinamide-adenine dinucleotide phosphate oxidase activation, increased oxidative stress, and enhanced expression of aldosterone effector kinase Sgk1. Treatment with eplerenone, a selective aldosterone receptor blocker, almost completely prevented podocyte damage and proteinuria, with normalization of elevated reduced nicotinamide-adenine dinucleotide phosphate oxidase activity. In addition, proteinuria, podocyte damage, and Sgk1 upregulation were significantly alleviated by tempol, a membrane-permeable superoxide dismutase, suggesting the pathogenic role of oxidative stress. Although hydralazine treatment almost normalized blood pressure, it failed to improve proteinuria and podocyte damage. In cultured podocytes with consistent expression of mineralocorticoid receptor, aldosterone stimulated membrane translocation of reduced nicotinamide-adenine dinucleotide phosphate oxidase cytosolic components and oxidative stress generation in podocytes. Furthermore, aldosterone enhanced the expression of Sgk1, which was inhibited by mineralocorticoid receptor antagonist and tempol. In conclusion, podocytes are injured at the early stage in aldosterone-infused rats, resulting in the occurrence of proteinuria. Aldosterone can directly modulate podocyte function, possibly through the induction of oxidative stress and Sgk1.

Key Words: aldosterone ▪ mineralocorticoid receptor ▪ podocytes ▪ oxidative stress ▪ Sgk1

Clinical studies have demonstrated that primary aldosteronism is associated with excessive albuminuria compared with essential hypertension.1,2 It is also shown that eplerenone, a selective mineralocorticoid receptor (MR) antagonist, reduces urinary albumin in patients with hypertension.3 In addition, we demonstrated previously that eplerenone successfully reduced proteinuria in Dahl salt-sensitive rats.4 These observations suggest that aldosterone, or the activation of MR, may cause dysfunction of the glomerular filtration barrier in hypertensive patients. In addition to the role in sodium transport, aldosterone is increasingly recognized as an important mediator of renal injury.5,6 Although precise mechanisms of aldosterone-induced kidney damage are still unclear, accumulating evidence indicates that aldosterone has direct effects on non-aldosterone-sensitive distal nephron cells and can modulate their functions via reactive oxygen species (ROS) generation, profibrotic action, or alteration of cell cycle regulators.7–9

Glomerular visceral epithelial cells, also called podocytes, cover the external surface of the glomerular basement membrane and contribute to various functions in the glomerulus. In particular, they constitute interdigitating foot processes, which are connected to each other by the slit diaphragms composed of nephrin, podocin, and other important molecules, and serve as the final filtration barrier to prevent the leak of plasma proteins.10 It has been shown that expression of the slit diaphragm components is affected in a variety of renal diseases that manifest proteinuria. Increasing evidence also suggests that podocyte injury and loss from glomerulus can be the key component of the process leading to glomerulosclerosis.11 Notably, genetic mutations resulting in a glomerulosclerotic phenotype occur in proteins that are expressed by podocytes.12

Hypertensive kidney damage is an important cause of end-stage renal disease, and proteinuria is the strong risk factor for the progression of chronic kidney disease.13 In our previous work, we have shown that the podocyte is involved in the glomerular damage of Dahl salt-sensitive rats and that MR blockade effectively ameliorates the podocyte injury and proteinuria.4 In this study, to further clarify the role of aldosterone

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in the glomerular epithelial cell injury, we analyzed podocyte damage in rats that received exogenous aldosterone infusion and a high-salt diet. We also examined the effects of eplerenone, hydralazine, and a superoxide dismutase mimetic tempol in this model to determine the involvement of MR, systemic blood pressure (BP), and ROS generation in aldosterone-modulated podocyte dysfunction. In addition, to prove that the podocyte is a direct target for aldosterone, we evaluated the expression of MR and MR effector mechanisms in podocytes using the cultured podocyte cell line.14

**Methods**

**Animal Experiments**

All of the animal procedures conducted were in accordance with the guideline for care and use of laboratory animals approved by our university hospital. Sprague–Dawley rats received a left uninephrectomy, and aldosterone (0.75 µg/h) was subcutaneously infused via an osmotic minipump (Alzet model 2004, Alza). The animals were fed a diet containing 8% NaCl. For control animals, our preliminarily study showed that high-salt diet (without aldosterone infusion) for 4 weeks did not cause significant BP elevation, proteinuria, and renal hypertrophy in uninephrectomized rats (Figure I, available online at http://hyper.ahajournals.org). Animals that do not receive a high-salt diet are commonly used as controls in similar models (eg, deoxycorticosterone acetate-salt rat15–16). In the following study, therefore, uninephrectomized rats with normal salt served as controls. Urine was collected for 24 hours using metabolic cages. Systolic BP was measured by the tail-cuff method. We also performed direct BP measurement for the accurate evaluation of BP17 (see online supplement).

**Protocol 1: Renal Injury in Aldosterone-Infused Rats at 2, 4, and 6 Weeks**

Uninephrectomized rats received continuous infusion of aldosterone and a high-salt diet ([ALDO], n=31) for 2 (n=8), 4 (n=15), and 6 weeks (n=8), respectively. Control rats received uninephrectomy and were fed a standard diet (n=24) for 2 (n=8), 4 (n=9), and 6 weeks (n=7). After BP measurement and urine collection, rats were anesthetized with ether, and kidneys were harvested.

**Protocol 2: Effects of Eplerenone, Tempol, and Hydralazine on Aldosterone-Induced Renal Damage**

ALDO rats were treated with the following drugs from 5 days before aldosterone infusion. For the effects of eplerenone treatment (n=28), ALDO rats were treated with eplerenone (1.25 g/kg of diet) for 4 weeks. For the effects of tempol (n=27), ALDO rats were treated with tempol (6 mmol/L in drinking water; Sigma) for 4 weeks. For the effects of hydralazine (n=26), hydralazine (0.5 mmol/L in drinking water; Sigma) was administered to ALDO rats for 2 weeks.

**Morphological Analysis and Immunohistochemistry**

Morphological analysis and immunohistochemistry were performed as described previously14–18 for details, see the online data supplement.

**Real-Time Quantitative RT-PCR**

Gene expression was quantitatively analyzed by real-time RT-PCR as described previously.20

**Western Blotting**

Western blotting was performed as described previously20 (see the online data supplement).

**Evaluation of Reduced Nicotinamide-Adenine Dinucleotide Phosphate Oxidase Activity**

Lucigenin chemiluminescence was used to measure reduced nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase activity in the kidney, as described previously21,22 (see the online data supplement).

**Analysis of Thiobarbituric Acid Reactive Substances**

The degree of lipid peroxidation was assessed using biochemical analysis of thiobarbituric acid reactive substances (TBARs). The urinary excretion rate of TBARS contents was determined using a TBARS assay kit (ZeptoMetrix Corporation), according to the manufacturer’s instruction.

**Cell Culture**

Murine cultured podocytes14 were grown and induced to differentiate as described previously.20 Treatment consisted of aldosterone (0.1 µmol/L)8,23 and aldosterone with spironolactone (10 µmol/L; Sigma) or tempol (10 µmol/L). Spironolactone or tempol was added 1 hour before aldosterone exposure.

**RT-PCR**

RT-PCR was performed as described previously.18 Primers used for MR were 5′-GTGGACAGTCTTTCTACCATCG-3′ (sense) and 5′-TGACACCCAGAAGCCTCATC-3′ (antisense).

**Immunocytochemistry**

Cells were fixed with 4% paraformaldehyde for 30 minutes, permealized with 0.1% Triton X-100, and saturated by 1% BSA for 30 minutes. MR and dihydrolidohistidium staining were performed as described previously.5

**Statistical Analysis**

Data are expressed as mean±SEM. For multiple comparisons, statistical analysis was performed by ANOVA and subsequent Tukey’s test. Unpaired t test was used for comparisons between 2 groups. Histological data were analyzed using nonparametric analysis with Kruskal–Wallis test, followed by Mann–Whitney U test.

**Results**

**Biological Parameters and Renal Morphology in Aldosterone-Infused Rats at 2, 4, and 6 Weeks**

Control rats did not develop hypertension and proteinuria at 2, 4, or 6 weeks (Table). Aldosterone-infused rats showed significant BP elevation and proteinuria already at 2 weeks, which further increased at 4 and 6 weeks. In the PAS-stained kidney sections (Figure 1A), histological damage was not prominent in aldosterone-infused rats at 2 weeks. At later stages, aldosterone-infused rats exhibited severe morphological changes that were identical to those reported previously in similar models.5–6 Glomeruli showed cell proliferation, tubulointerstitial damage, and sclerotic changes, which were accompanied by arteriolar hyalinosis and tubulointerstitial damage.

**Podocytes are Damaged in Aldosterone-Infused Rats**

We next analyzed glomerular expressions of nephrin and podocin. Interestingly, transcript levels of these molecules were markedly suppressed in aldosterone-infused rats at 2 weeks, with a gradual decrease thereafter (Figure 1B and 1C). We also found that desmin expression, a marker for podocyte injury,24 was enhanced in podocytes of aldosterone-infused rats (Figure 1D). Consistent with the results, transmission
electron microscopy analysis revealed the severe degenerative changes of podocytes and foot process retraction in aldosterone-infused rats at 2 weeks (Figure 1E). These results indicate that podocytes are involved at the early stage in aldosterone-induced renal injury.

### Biological Parameters in Control and Aldosterone-Infused Rats at 2, 4, and 6 Weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>2 Weeks</th>
<th></th>
<th>4 Weeks</th>
<th></th>
<th>6 Weeks</th>
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<tr>
<td></td>
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<td>Aldosterone (n=8)</td>
<td>Control (n=9)</td>
<td>Aldosterone (n=15)</td>
<td>Control (n=7)</td>
<td>Aldosterone (n=8)</td>
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<td>BW, g</td>
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<td>427±22</td>
<td>408±10</td>
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<td>BP, mm Hg</td>
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<td>214±5†</td>
<td>139±4</td>
<td>236±8‡</td>
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<tr>
<td>Upr, mg/day</td>
<td>10.9±1.6</td>
<td>37.1±12.0*</td>
<td>16.4±2.0</td>
<td>334.5±42.0†</td>
<td>16.8±2.3</td>
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<tr>
<td>K, mEq/L</td>
<td>4.91±0.19</td>
<td>3.79±0.11*</td>
<td>5.01±0.24</td>
<td>3.76±0.24†</td>
<td>4.84±0.21</td>
<td>3.66±0.23‡</td>
</tr>
</tbody>
</table>

BW indicates body weight; BP, blood pressure; Upr, urinary protein; K, serum potassium. Values are mean±SEM.

*P<0.01 vs control (2 weeks) rats. †P<0.01 vs control (4 weeks) rats. ‡P<0.01 vs control (6 weeks) rats.

### Effects of Eplerenone and Tempol in Aldosterone-Infused Rats

Next, we investigated the effects of eplerenone in aldosterone-infused rats (4 weeks, n=28). Eplerenone significantly reduced BP and almost nullified proteinuria observed in

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**Figure 1.** A, Periodic acid-Schiff (PAS)–stained kidney sections from control and aldosterone-infused rats. Ctrl indicates control; ALDO, aldosterone-infused rats; W, weeks. B and C, Quantitative analysis of nephrin (B) and podocin (C) gene expressions in the glomeruli. **P<0.01 vs Ctrl. D, Immunostaining for desmin. Left, Control rat glomeruli. Middle, Aldosterone-infused rats at 2 weeks. Desmin expression was increased in podocytes (arrows). Right, Staining was enhanced along the capillary loop at 4 weeks. E, Transmission electron micrographs of control (left) and aldosterone-infused rats at 2 weeks (right). Control rats showed normal structure of podocytes. In aldosterone-infused rats, podocytes exhibited degeneration of the cell body and retraction of the foot processes. Scale bars: A and D, 100 μm; E, 1 μm.
aldosterone-infused rats (Figure 2A and 2B). In direct BP measurement, mean arterial pressure was markedly elevated in aldosterone-infused rats (control rats: 102 ± 3 mm Hg; aldosterone-infused rats: 184 ± 9 mm Hg; P < 0.01). Eplerenone treatment partially reduced the mean arterial pressure (155 ± 16 mm Hg; P < 0.01 versus aldosterone-infused rats).

Histologically, glomerular damage was also ameliorated by eplerenone (Figure 2C and 2D). Furthermore, eplerenone prevented the decrease of nephrin and podocin gene expres-
sions in aldosterone-infused rats (Figure 2E). In immunofluorescent study, the nephrin staining score was reduced in aldosterone-infused rats, which was also prevented by eplerenone (Figure 2F and 2G).

We next evaluated NADPH oxidase activity. NADPH oxidase activity, as measured by superoxide generation in the presence of NADPH, was significantly augmented in the kidney of aldosterone-infused rats (Figure 3A and 3B), which was ameliorated by eplerenone. The NADPH oxidase is a multicomponent enzyme complex that consists of membrane-bound gp91phox and p22phox, the cytosolic subunits p67phox and p47phox, and the small GTPase Rac.25,26 We found that expressions of p67phox and Rac1 were upregulated in the membrane fraction in aldosterone-infused rats (Figure 3C). In addition, aldosterone-infused rats showed increased gene expressions of gp91phox and p47phox but not of p22phox (Figure 3D). Recent studies have identified a significant role of Sgk1 in the regulation of aldosterone action in glomerular cells, as well as aldosterone-sensitive distal nephron.27,28 The expression of Sgk1, an effector kinase of MR, was upregulated in aldosterone-infused rats, which was significantly inhibited in eplerenone-treated rats (Figure 3E).

To further clarify the role of ROS in our model, we investigated whether tempol may reduce oxidative stress,

Figure 3. A, NADPH oxidase activity was expressed as ROS production in response to the addition of its substrate NADPH. The source of ROS was confirmed by diphenyleneiodonium, a specific inhibitor of NADPH oxidase. B, NADPH oxidase activity in the kidney of Ctrl, ALDO, and ALDO+EPL. C, the expression of p67phox and Rac1 in the membrane fraction protein of the kidney. Top, representative blots. Bottom, result of densitometric analysis. D, Comparison of gp91phox, p47phox, and p22phox gene expressions among 3 groups. E, Sgk1 expression in aldosterone-infused rats.
proteinuria, and podocyte damage (n=27; Figure 4). Tempol actually reduced proteinuria by 79% (P<0.01 versus aldosterone-infused rats), along with partial BP decrement. BP was also evaluated by the direct measurement (mean BP: 131±9 mm Hg in the tempol-treated group; P<0.01 versus aldosterone-infused rats). Histological changes were clearly ameliorated by tempol (glomerulosclerosis score: 0.36±0.03; P<0.01). Consistent with the observations, reduced gene expression of nephrin in aldosterone-infused rats was significantly alleviated by tempol (Figure 4C). Podocin expression also tended to be higher in the treated group (Figure 4D; 0.05<P<0.1). We compared urinary excretion of TBARS among the 3 groups. Aldosterone-infused rats showed significant increase in the TBARS contents (P<0.01), which were suppressed by tempol treatment (P<0.05; Figure 4E). The Sgk1 induction in aldosterone-infused rats was also inhibited by tempol (Figure 4F).

Hydralazine Reduces BP but Not Urinary Protein and Podocyte Injury

Next, aldosterone-infused rats were treated with hydralazine (n=26). Rats were euthanized at 2 weeks. Although hydralazine almost normalized the BP elevation in aldosterone-infused rats (Figure 5A), proteinuria and reduced gene expressions of nephrin and podocin were not affected (Figure 5B and 5C). Consistent with the finding at 4 weeks, Sgk1 was upregulated in aldosterone-infused rats at 2 weeks as well (Figure 5D). Sgk1 was also significantly increased in the hydralazine-treated group (P<0.05 versus control), although the expression was partially reduced.

Aldosterone has Direct Effects on Podocytes

Other than its role in electrolyte and water homeostasis, aldosterone can exert diverse actions in multiple organs. Next, we analyzed MR expression in kidney and cultured podocytes. In control rat kidney, MR was localized not only to tubular cells but also to glomerular cells, including podocytes (Figure 6A). In cultured podocytes, MR was consistently present at both mRNA and protein levels (Figure 6B through 6D).

We next investigated Sgk1 expression in podocytes treated with aldosterone. Intriguingly, aldosterone significantly upregulated the Sgk1 mRNA expression at both 3 and 24 hours (Figure 7A). This induction was completely inhibited by spironolactone.
and partially blocked by tempol (Figure 7B). Finally, we analyzed the expression of NADPH oxidase subunit and superoxide production in podocytes in the presence of aldosterone. As shown in Figure 7C, aldosterone increased the protein expression of p67phox in the membrane fraction. Dihydroethidium staining revealed that aldosterone induced the intracellular superoxide production in podocytes, which was inhibited in the presence of spironolactone (Figure 7D).

Figure 5. Effects of hydralazine in aldosterone-infused rats at 2 weeks (controls: n=7; aldosterone-infused group: n=10; treatment group: n=9). A and B, Effects of hydralazine on BP (A) and urinary protein (B) in aldosterone-infused rats. C, Gene expressions of nephrin and podocin. D, Comparison of Sgk1 expression among 3 groups. ALDO+HYD, aldosterone-infused rats treated with hydralazine.

Figure 6. The presence of MR in glomeruli and cultured podocytes. A, Immunohistochemical analysis of MR in the rat tubules (left) and glomeruli (right) of control rats. MR was localized to glomerular cells (arrows). Scale bars, 50 μm. B, RT-PCR analysis of the MR. Glo, glomeruli; Pod, cultured podocytes. C, Western blotting analysis of MR in the glomeruli and podocytes. D, Immunocytochemistry of MR in podocytes. Scale bar, 100 μm.
Discussion

The present study demonstrates that aldosterone and a high-salt diet induce podocyte damage and proteinuria, which are almost completely blocked by eplerenone. NADPH oxidase activity and ROS generation are enhanced in aldosterone-infused rats, and tempol successfully ameliorates the podocyte damage along with the reduction of Sgk1 upregulation. Moreover, MR is consistently present in cultured podocytes, and Sgk1 expression and oxidative stress accumulation are enhanced in response to aldosterone treatment.

The important observation of our study was that podocytes were involved in early glomerular damage of aldosterone-infused rats. Other than its classical effects on renal sodium transport in aldosterone-sensitive distal nephron, recent studies suggest that aldosterone exerts deleterious effects on nonepithelial cells.23 In the kidney, mesangial cells and fibroblasts are the targets for the action of aldosterone.7,8 In addition, we showed for the first time that MR is present in podocytes, and Sgk1 expression and oxidative stress accumulation are enhanced in response to aldosterone treatment.

In the present study, tempol significantly reduced proteinuria and inhibited the decrease in nephrin and podocin expression in aldosterone-infused rats. Oxidative stress is regarded as an important mediator of podocyte damage.31 Oxidative stress can also play a pivotal role in our model, because aldosterone is a potent generator of ROS.22 We showed in this study that NADPH oxidase activity and TBARS contents were increased in aldosterone-infused rats. Amelioration of podocyte damage by tempol further supports an essential role for ROS in this model. The protective actions of tempol cannot be fully explained by the BP-lowering effect, because we demonstrated that hydralazine did not ameliorate the podocyte damage despite a reduction in BP. Moreover, we demonstrated that aldosterone stimulated membrane translocation of p67phox and ROS production in cultured podocytes. All of these results suggest that aldosterone can induce podocyte dysfunction via ROS accumulation.

We evaluated the effects of salt loading on the renal damage in our model and found that high-salt diet alone did not cause significant BP elevation and proteinuria. Indeed, the oxidative stress marker was significantly higher in aldosterone/high-salt–treated rats than control rats on a normal-salt or high-salt diet without aldosterone administration (data not shown). Thus, we consider that the protective effects of tempol can be mainly attributable to the reduction of oxidative stress augmented by aldosterone, not by the effects of high salt alone.

Figure 7. Sgk1 and oxidative stress induction in podocytes (n=7 or 8). A, Aldosterone increases Sgk1 gene expression in cultured podocytes. Aldosterone was added to the serum-free medium, and RNA was extracted at indicated times. *P<0.05, **P<0.01. B, Effects of spironolactone and tempol on aldosterone-induced Sgk1 expression. C, Aldosterone stimulates translocation of p67phox into the plasma membrane. D, Dihydroethidium staining of podocytes. Cells were treated with aldosterone for 3 hours in the presence or absence of spironolactone.
Another prominent finding of our study was that aldosterone-induced Sgg1 expression in the rat kidney, as well as in cultured podocytes. This upregulation was MR dependent, because it was completely inhibited by MR antagonist. Oxidative stress is known to induce Sgg1 expression. Aldosterone-induced upregulation of Sgg1 in podocytes might be partially attributable to overproduction of ROS, because tempol significantly blocked the Sgg1 induction. So far, the role of Sgg1 is best studied in aldosterone-sensitive distal nephron. Other than the distal nephron, Sgg1 mRNA is shown to be present in the glomeruli. Of note, Quinkler et al indicate a correlation between proteinuria and renal Sgg1 expression. They reported that Sgg1 mRNA expression was enhanced by 2- to 3.4-fold in chronic kidney disease patients with moderate-to-heavy proteinuria. Sgg1 upregulation is also observed in patients with diabetic nephropathy and glomerulonephritis. Sgg1 induction is mainly noted in the glomeruli, especially in the latter. These observations may indicate a pivotal role for Sgg1 in the glomerular function, particularly in the regulation of glomerular permeability. Of further note, Vallon et al reported an interesting finding using Sgg1 knockout mice: they showed that effects of deoxycorticosterone acetate-salt on proteinuria were significantly blunted in Sgg1 knockout mice, despite an identical increase in BP and creatinine clearance. Considering these observations together with our findings, it can be speculated that aldosterone mediates podocyte function through Sgg1 induction. Clearly, further studies are needed to elucidate the role of Sgg1 in podocyte and glomerular function.

We showed in this study that eplerenone nullified the podocyte damage and proteinuria, indicating the critical role of MR signaling in our model. Interestingly, recent studies indicate that MR activation is important in the pathogenesis of cardiovascular and renal damage not only in high-aldosterone status but also in low-aldosterone hypertension. Nagata et al demonstrated that, although plasma aldosterone levels were suppressed, MR antagonism improved the cardiac function in Dahl salt-sensitive rats that were fed a high-salt diet. Similarly, we have shown in our previous work that eplerenone ameliorates podocyte damage and proteinuria in that strain, suggesting that MR signaling can be involved in podocyte damage of low-aldosterone hypertension. It is noteworthy that Sgg1 is upregulated in the kidney of both Dahl salt-sensitive rats and aldosterone-infused animals. In this study, we described the upregulation of Sgg1 in vitro, as well as in the kidney of aldosterone-infused rats, as the effector mechanism of MR. Although the mechanisms modulating MR status may be different in Dahl salt-sensitive rats and in our model, it is possible that Sgg1 plays a key role as the common effector molecule of the MR signaling in podocytes.

**Disclosures**

None.

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