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Review

Role of cytochrome P450 epoxygenase-dependent arachidonic acid metabolites in kidney physiology and diseases

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Abstract: Kidney diseases are important causes of mortality world widely. Renal microvascular dysfunction plays a pivotal role in the development of kidney diseases. Pharmacological and biochemical tools have been used to conduct detailed studies on the metabolization of arachidonic acid by cytochrome P450 (CYP450) in renal microvasculature. CYP450 epoxygenase metabolites epoxyeicosatrienoic acids (EETs) are mainly produced in renal microvessels. EETs exhibit renoprotective effects through vasodilation, antihypertension, anti-apoptosis and anti-inflammation, and were reported as therapeutic targets of renal diseases. However, the ability of the kidney in generating EETs is reduced in renal diseases. Recently, the studies from transgenic animal overexpressing CYP450 epoxygenases and application of soluble epoxide hydrolase inhibitors revealed that increasing of EETs exhibits renoprotective effects *in vivo*. The present review focuses on the protective mechanisms of EETs in kidney physiology and diseases.

Key words: cytochrome P450 (CYP450) epoxygenase; epoxyeicosatrienoic acid (EET); kidney disease

花生四烯酸细胞色素P450代谢物在肾脏生理和疾病中的作用

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摘 要：肾脏疾病在全球范围内都是导致死亡的重要原因。肾脏微血管功能失调在肾病的发生与发展中发挥着不可忽视的作用。药理学和生物化学等领域的许多实验方法已被用来研究花生四烯酸的细胞色素P450 (cytochrome P450, CYP450)代谢物对肾脏微血管功能的调控作用。在肾脏中，CYP450表氧化酶代谢物环氧二十碳三烯酸(epoxyeicosatrienoic acids, EETs)主要在肾脏微血管产生。EETs可以通过舒张血管、降低血压、抗细胞凋亡、抗炎等多个方面发挥肾脏保护作用。CYP450表氧化酶代谢物EETs可作为肾脏疾病的治疗靶点。然而，在肾脏发生疾病时，肾脏微血管产生EETs的能力会显著降低。近来，用转基因动物过表达CYP450表氧化酶或用可溶性环氧化物水解酶(soluble epoxide hydrolase, sEH)抑制剂也均证实增加EETs水平具有明显的肾脏保护作用。本综述将重点讨论花生四烯酸的CYP450代谢物EETs在肾脏生理及疾病状态下具体的调控机制。

关键词：细胞色素P450代谢物；环氧二十碳三烯酸；肾脏疾病
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1 Introduction

Substantial evidence indicates that cytochrome P450 (CYP450) metabolites of arachidonic acid play a key role in the regulation of epithelial transport and vascular function[1, 2]. Arachidonic acid is metabolized to eicosanoid mediators by the cyclooxygenase (COX), lipoxygenase (LOX), and CYP450 monooxygenase pathways. The CYP450 pathway produces two types of eicosanoid products, epoxyeicosatrienoic acids (EETs), formed by CYP450 epoxygenases, and hydroxyeicosatetraenoic acids (HETEs), formed by CYP450 ω-hydroxylase[3] (Fig. 1). EETs are produced by the vascular endothelium in responses to various stimuli such as the agonists of acetylcholine or bradykinin or shear stress, which activates phospholipase A2 to release arachidonic acid. However, EETs can be further metabolized to their corresponding dihydroxyeicosatrienoic acids (DHETs) by soluble epoxide hydrolase (sEH), and this metabolism limits many of the biological actions of EETs.

It was reported that CYP450 eicosanoids have a role in the pathogenesis of polycystic kidney disease[4]. CYP450 ω-hydroxylase metabolite 20-HETE plays an important role in renal regulatory mechanisms by modulating the activities of the Na^+-K^+-ATPase, Na^+-K^+-$2Cl^-$ cotransporter, and K^+ channels in various segments of kidney nephrons[5–7]. However, CYP450 epoxygenase metabolites EETs regulate kidney function by directly affecting tubular ionic transport, vascular tone, and cellular proliferation[8, 9]. Furthermore, the action of 11, 12-EET on the renal microcirculation and its ability to activate K^+ channels in vascular smooth muscle cells supported that it acts as an endothelium-derived hyperpolarizing factor (EDHF)[10].

Impaired renal function can occur as a consequence of cardiovascular diseases and often progress to end-stage renal disease (ESRD)[11]. ESRD is characterized by extensive albuminuria, increased level of inflammatory cytokines, severe decline in renal function, and elevation in blood pressure leading to increased risk of

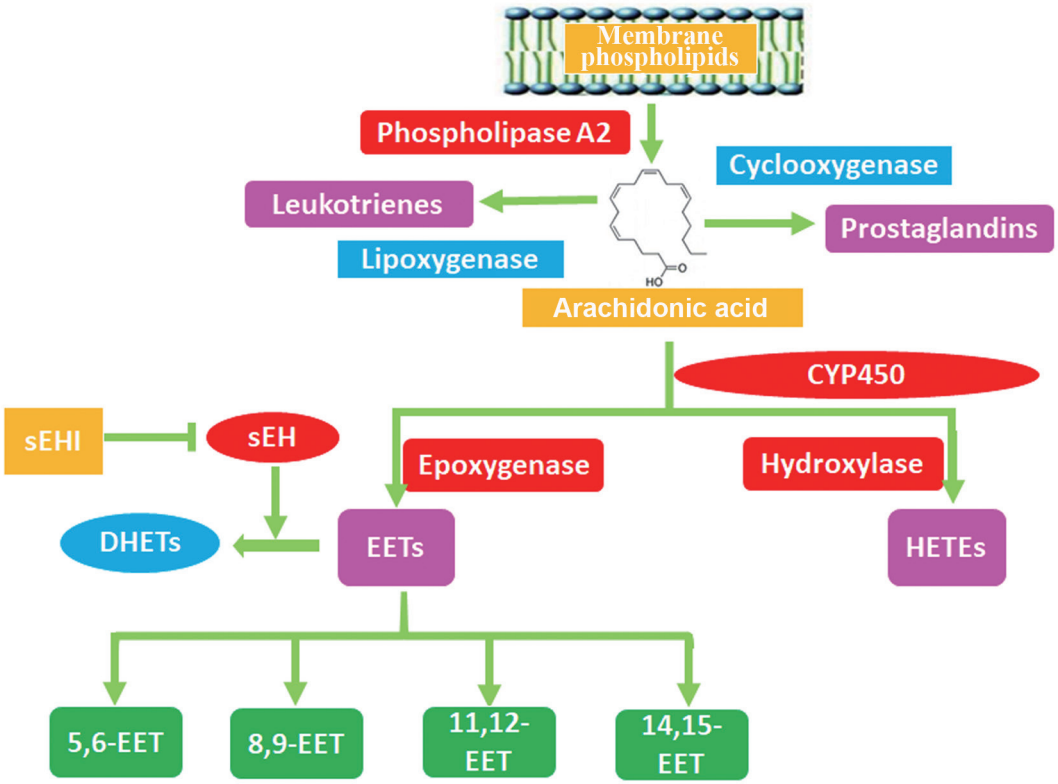

Fig. 1. The metabolites of arachidonic acid from three independent enzymes. Arachidonic acid esterified into membrane phospholipids is released via phospholipase A2 after membrane stretch or via the action of hormones and autacoids. Free arachidonic acid is metabolized to eicosanoid mediators by the cyclooxygenase, lipoxygenase, and CYP450 monooxygenase pathways. The CYP pathway produces two types of eicosanoid products, epoxyeicosatrienoic acids (EETs), formed by CYP450 epoxygenases, and hydroxyeicosatetraenoic acids (HETEs), formed by CYP450 ω-hydroxylase. EETs are hydrolyzed to dihydroxyeicosatrienoic acids (DHETs) by soluble epoxide hydrolase (sEH).

cardiovascular death[11]. The pathophysiology of ESRD is multifactorial, such as, endothelial dysfunction and vascular inflammation, which also can be independently associated with mortality[12, 13]. Over the past two decades, it has become increasingly evident that EETs exert many protective effects on the kidney. This review will focus on EETs and their contribution to hypertension from the aspects of renal microvascular actions and kidney diseases. It also discusses the therapeutic potential of EETs.

2 Molecular and cellular mechanisms of EETs

2.1 EETs and signaling

2.1.1 EETs as EDHF

CYP450 epoxygenase metabolites EETs produced by the vascular endothelium, was the most likely candidate as a putative EDHF, which has received considerable support from several investigations[14]. EETs serve as EDHF largely through their ability to activate endothelial NO synthase (eNOS) and NO release[15]. However, Quilley *et al*. has reported that among the epoxides, 5, 6-EET was the most likely mediator of vasodilation independent of NO in the rat. In addition, CYP450-dependent coronary vasodilation was in response to bradykinin[16]. Previous reports suggested that 11, 12-EET was an important EDHF in human left internal mammary arteries[17]. The mechanism of inducing hyperpolarization and relaxation in smooth muscle cells of human left internal mammary arteries was through large conductance Ca^{2+}-activated K^+ channels[17]. It showed that CYP450 inhibitors could attenuate endothelium-dependent vasodilation[18]. For example, 14, 15-epoxyeicosa-5(Z)-enoic acid (14, 15-EEZE), an EET-specific antagonist, alone could inhibit the EDHF component of methacholine, bradykinin and arachidonic acid-induced relaxations, and inhibit the smooth muscle hyperpolarization response to bradykinin by against EET[19]. Another study showed that 14, 15-EEZE could inhibit acetylcholine-induced relaxation by (29 ± 3)% in renal afferent arteriole[20]. EETs plays a very important role in vasodilation as EDHF.

2.1.2 EETs as ligands of G-protein coupled receptors (GPCR)

Multiple lines of evidence suggested that the actions of EETs were partly mediated via GPCR signaling[21]. It has been suggested that 14, 15-EET exerted its vasodilator effect via Gs-coupled signaling, leading to increased cAMP[21, 22]. Additional reports showed that the mechanism involving GPCR was provided by the observation that 11, 12-EET induced activation of large-conductance Ca^{2+} activated K^+ channels and that tissue plasminogen activator expression was mediated by the Gs component of a heterotrimeric GTP binding protein[23, 24].

2.2 EETs and mitogenesis

EETs could stimulate mitogenesis in kidney mesangial cells. For example, 8, 9-EET and 14, 15-EET could stimulate mitogenesis by activation of Na^+/H^+ exchange in cultured rat glomerular mesangial cells[25]. Furthermore, 14, 15-EET mediated signal transduction by selective incorporation into cellular lipids, which extended the potential biologic roles of arachidonate metabolites to stimulate cell proliferation[25]. Epidermal growth factor has been reported to increase EET levels in proximal tubule and 5, 6-EET, but not 8, 9-, 11, 12-, or 14, 15-EET, may be a modulator of epidermal growth factor induced [Ca^{2+}] increases and involved in mitogenesis[26]. The mitogenic effects of the EETs were mediated by activation of Src kinase and initiation of a tyrosine kinase phosphorylation cascade partly[27]. Moreover, 14, 15-EET stimulated tyrosine phosphorylation of the specific pp60 substrate p120 and c-Src association with epidermal growth factor receptor was indicated by immunoblotting[27]. Recent study showed that upregulation of G-protein-coupled receptor 40 (GPR40) expression enhances the mitogenic response to EETs and a relatively high expression level of GPR40 was detected in a subset of tubules including cortical collecting ducts in the mammalian kidney[28].

3 EETs, kidney function and diseases

3.1 Vascular effect of EETs: vasodilation

The production rates of EETs increased 3 folds from fetus to 9 weeks of age, whereas epoxygenase activity demonstrated no differences between the two strains at any age group tested, although the amount of EET and DHET in a given age was significantly different. Moreover, CYP450 eicosanoids were reported as vasodilatory, largely through their ability to activate eNOS and NO release[15]. It has been reported that the COX dependent vasoactivity of 5, 6-EET in the rabbit kidney has two components such as releasing of vasodilator prostaglandins, prostaglandin E2 (PGE2) and prostacyclin

(PGI2), and metabolism of 5, 6-EET to a prostaglandin analog, 5, 6-epoxy-PGE[29]. However, another study showed that in the blood perfused rat kidney, 5, 6-EET could cause COX dependent renal vasoconstriction, whereas in the rat isolated kidney 5, 6-EET produced dose-dependent vasodilation through perfusing with a physiological buffer. The reason that platelet COX could metabolize 5, 6-EET to vasoconstrictor products might contribute to the *in vivo* vasoconstrictor effect of this eicosanoid[30]. Pre-glomerular vasoconstriction to 5, 6-EET was COX dependent and required an intact endothelium, whereas the vasodilation to 11, 12-EET was stereo-selective and was the result of direct action of the epoxide on the pre-glomerular vascular smooth muscle[31]. In the spontaneously hypertensive rats (SHRs), 5, 6-EET- and 11, 12-EET-induced renal vasodilatation was more than two folds greater than that registered in Wistar Kyoto rats (WKYs). Thus, the augmented vasodilator responses to arachidonic acid in the SHRs was through activation of K^+ channels, and 5, 6-EET was the most likely mediator[32]. Activation of protein kinase A was an important mechanism responsible for the afferent arteriolar vasodilation elicited by the sulfonimide analog of 11, 12-EET[33]. Activation of adenosine 2A (A2A) receptors coupled to *de novo* EET stimulation might represent an important mechanism in regulating preglomerular microvascular tone[34]. 11, 12-EET has been reported to be the likely mediator of A2A-induced dilation of rat preglomerular microvessels. In rat pre-glomerular microvessels, activation of A2A receptors was coupled to EET release upstream of adenylyl cyclase activation and EETs stimulate mono-ADP-ribosyltransferase, resulting in Gsalpha protein activation[35]. The mechanism of afferent arteriolar dilation to 11, 12-EET analogs involved phosphoprotein phosphatase 2A activity and Ca^{2+}-activated K^+ channels[36]. 14, 15-EET also could induce afferent arteriolar relaxation depending strongly on NO acting via blocking Ca^{2+}-activated K^+ channels[20]. It has been reported that the greater vasodilator response to 2-chloroadenosine seen in kidneys obtained from high salt fed rats was mediated by increased EET release. As EETs are renal vasodilator and natriuretic eicosanoids, interactions between adenosine and EETs may contribute to the adaptive response to high salt intake[37]. It also showed that EETs acted through TRPV4-TRPC1-KCa1.1 complex to induce smooth muscle membrane hyperpolarization and relaxation in human internal mammary arteries[17].

3.2 EETs and the regulation of blood pressure

The rAAV-CYP2J2 gene delivery increased EET generation *in vivo* and then attenuated the rise in blood pressure[38]. An orally active analog of 14, 15-EET, PVPA, obviously prevented the development of hypertension and mitigated kidney injury in cyclosporine-treated rats[39]. Since EETs have a wide spectrum of biological and renal effects, they may influence not only renal hemodynamics and salt and water balance but also antihypertensive mechanisms in SHRs[40]. Overexpression of endothelial CYP450 epoxygenase attenuated afferent arteriolar constrictor reactivity and renal injury in mice by reducing blood pressure[41]. Another study indicated that overexpression of CYP450 epoxygenases attenuated the development of hypertension mediated partly by ANP via activating epidermal growth factor receptor[42]. EET-B also has been reported to have anti-hypertensive properties, improve vascular function, and decrease renal inflammation and injury in angiotensin II (Ang II)-induced hypertension[43]. While the orally active EET-A attenuated the development of experimental Ang II-dependent malignant hypertension, likely via suppression of the hypertensiogenic axis and augmentation of the vasodilatory/natriuretic axis of renin-angiotensin system[44]. Furthermore, sEH was reported to play an important role in the regulation of blood pressure, and blood pressure could be reduced by inhibition of sEH during Ang II-induced hypertension[45]. Study also demonstrated that the fenofibrate-induced increase of CYP450 epoxygenase expression and the 12-(3-adamantane-1-yl-ureido)dodecanoic acid (AUDA)-induced stabilization of EET production in the kidneys could cause renal vascular dilation and reduce sodium retention, contributing to the improvement of abnormal renal hemodynamics and hypertension in high-fat diet rats[46]. However, another study showed that EETs increased portal resistance and mediated the pressure response to ET-1 in the portal circulation that might be involved in pathophysiology of portal hypertension in part[47].

3.3 EETs and apoptosis

Previous study demonstrated that EET analogs attenuated nephrotoxicity by decreasing apoptosis which was associated with reduction in caspase-12 expression and caspase-3 activity in kidney. Moreover, they further demonstrated that the protective activity of EET analogs

did not compromise the anticancer effects of cisplatin *in vitro*[48]. Our previous study indicated that rAAV-CYP2J2 gene delivery could protect remnant kidney against renal injury in 5/6-nephrectomized rats by inhibiting apoptosis and fibrosis via regulation of protein expression including transforming growth factor-β1 (TGF-β1)/SMADs, MMPs, MAPKs, and apoptosis-related proteins[38]. Increasing exogenous 11, 12-EET or endogenous EETs with Ad-CMV-CYP2C23-EGFP transfection could decrease apoptosis of inner medulla collecting duct cells induced by hypotonic stress. Moreover, up-regulation of γ-epithelial sodium channel (γ-ENaC) induced by hypotonic stress was abolished by elevation of exogenous or endogenous EETs. EETs attenuated hypotonic-induced apoptosis of inner medulla collecting duct cells, and that regulation of γ-ENaC might be a possible mechanism contributing to the anti-apoptotic effect of EETs in response to hypotonic stress[9]. EET-A could mitigate elevated renal parenchymal apoptosis by acting on the p53/Fas/FasL (Fas ligand) pathway in total body irradiation rats[49]. Another study showed that PVPA, a novel, orally active analog of 14, 15-EET, reduced tubular epithelial cell apoptosis, attenuated the generation of reactive oxygen species, and modulated the unfolded protein response that was associated with endoplasmic reticulum stress. Consistent with the *in vivo* data, PVPA attenuated cyclosporine-induced apoptosis of NRK-52E cells *in vitro*[39]. 14, 15-EET has been reported to mitigate ischemia reperfusion kidney injury[50]. Manipulation of the endogenous 14, 15-EET by changing their biosynthesis or degradation with selective inhibitors resulted in anticipated effects. For example, firstly, 14, 15-EET significantly reversed the ischemia-reperfusion-caused reduction in glycogen synthase kinase 3β (GSK3β) phosphorylation in murine kidney. Secondly, 14, 15-EET dose-dependently inhibited the hypoxia/reoxygenation-induced apoptosis of murine renal tubular epithelial cells. Thirdly, 14, 15-EET reversed the hypoxia/reoxygenation caused reduction in GSK3β phosphorylation in murine renal tubular epithelial cells. In addition, our previous study showed that the sEH-deficient diabetic mice also had decreased renal tubular apoptosis that coincided with increased levels of anti-apoptotic bcl-2 and bcl-xl by decreasing levels of the pro-apoptotic bax from activation of the PI3K-Akt-NOS3 and AMPK signaling cascades. Furthermore, sEH gene inhibition and exogenous EETs significantly protected HK-2 cells from TNFα-induced apoptosis *in vitro*[51].

3.4 EETs and inflammation

It was reported that 14, 15-EET analog treatment alleviated proteinuria and renal dysfunction induced by cyclosporine, inhibited inflammatory cell infiltration into the kidney and decreased renal fibrosis[39]. Loss of sEH promoted anti-inflammatory and fibro-protective effects in unilateral ureteral obstruction kidneys via activation of peroxisome proliferator-activated receptor (PPAR) isoforms and downregulation of NF-κB, TGF-β1/Smad3, and inflammatory signaling pathways[52]. Previous study showed that genetic ablation of sEH prevented renal tubulointerstitial fibrosis and inflammation in experimental mouse models of chronic kidney disease. Inhibition of sEH enhanced levels of EET regioisomers and abolished tubulointerstitial fibrosis by reducing collagen deposition and myofibroblast formation after unilateral ureteral obstruction. EETs could mitigate inflammatory response by decreasing influx of neutrophils and macrophages, decreasing expression of inflammatory cytokines, macrophage inflammatory protein-2, monocyte chemotactic protein-1, TNF-α, and ICAM-1 in kidneys. Furthermore, EETs reduced unilateral ureteral obstruction-upregulated TGF-β1/Smad3 signaling and induced NF-κB activation, oxidative stress, tubular injury, and apoptosis. In addition, EETs downregulated antifibrotic factors, including PPAR isoforms[53].

3.5 EETs and renoprotection

EET analogs have been shown to attenuate cisplatin-induced nephrotoxicity by reducing these renal injury markers by 40%–80% along with a 50%–70% reduction in oxidative stress, inflammation, and endoplasmic reticulum stress evident from reduction in related biomarkers in renal tubular cast formation[48]. Our previous study showed that overexpression of CYP2J2 gene protected renal function by preventing renal injury[38]. Consistent with the ability of EETs to interfere with NF-κB signaling, the observed renoprotection was associated with attenuation of renal NF-κB activity and corresponding decreases in the expression of tumor necrosis factors TNF-α, TNF receptor-1, TNF receptor-2, and intercellular adhesive molecule-1 before the detection of tubular injury. As EETs are renal vasodilators and natriuretic eicosanoids, the antipressor response to salt loading may operate through A2A receptors-EET mechanism to protect renal function[54]. EETs have been

reported to regulate renal blood flow which might influence renal function in Midkine deficient mice[14]. CYP450/EET system also was shown to offer a novel therapeutic strategy to treat or prevent calcineurin inhibitors-induced nephrotoxicity[39]. Other study also showed that 5/6 renal mass reduction Ren-2 transgenic rats exhibited a profound deficiency of intrarenal availability of active EETs, which probably contributed to the progression of chronic kidney disease in this model of Ang II-dependent hypertension, and that restoration of intrarenal availability of EETs using long-term c-AUCB treatment exhibited substantial renoprotective actions[55]. sEH inhibition protected against renal fibrosis by ameliorating proteinuria-induced renal tubular epithelialto-mesenchymal transition through regulating the PI3K-Akt-GSK-3β signaling pathway[56]. In addition, our previous study showed that streptozotocin-induced diabetic manifestations were attenuated in sEH-deficient mice relative to wild-type controls, with significantly decreased levels of glycated hemoglobin A1c, creatinine, blood urea nitrogen and urinary microalbumin excretion[51]. sEH inhibitor, t-AUCB, has been reported to have the ability to reduce renal fibrosis, renal macrophage infiltration, IL-17 expression and monocyte chemotactic protein 1 levels in diabetic SHR by inducing heme oxygenase 1 [57]. Another study suggested that EETs, other fatty acid epoxides and sEH inhibition could attenuate cisplatin-induced kidney injury[58]. However, Zhu *et al*. indicated that contrary to previous hypothesis, renal function declined more severely in sEH-knockout (KO) mice as demonstrated by higher serum creatinine and urea levels[59]. The sEH-KO mice also featured stronger tubular lesion scores, tubular apoptosis, and inflammatory cell infiltration. Plasma and renal EET/DHET-ratios were higher in sEH-KO than wild type (WT) mice. Furthermore, CYP-eicosanoid profiling also revealed that renal, but not plasma and hepatic, 20-HETE levels were significantly increased in sEH-KO mice compared with WT mice. In line with this finding, renal expression of Cyp4a12a, the murine 20-HETE-generating CYP-enzyme, was up-regulated both at the mRNA and protein levels, and Cyp4a12a immunostaining was more intense in the renal arterioles of sEH-KO mice compared with WT mice. So they thought that the potential beneficial effects of reducing EET degradation were obliterated by a thus far unknown mechanism leading to kidney-specific up- regulation of 20-HETE formation in sEH-KO mice[59].

4 Summary

Over the past decades, considerable interest has been focused on the arachidonic acid CYP450 pathway. A lot of evidence has been accumulated and demonstrated that CYP450 metabolites are involved in the regulation of renal epithelial transport and vascular smooth muscle cell function. EETs are reported as autocrine and paracrine lipid mediators. EETs were always thought as an EDHF and activator of large-conductance Ca^{2+} activated K^+ channels. More and more evidence indicates that EETs have effects on other ion channels and signal transduction pathways. EETs also have relationship with angiogenesis, mitogenesis, apoptosis, and PPAR-transactivated gene expression. Furthermore, sEH inhibitors have also been studied in the blood pressure regulation. The functions of EETs are also involved in the regulation of the pathophysiology of hypertension, diabetic nephropathy, and inflammation or toxic glomerular injury and so on. Those signaling pathways would provide fruitful targets for intervention in the pharmacologic treatment of renal diseases.

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