Advances in pathogenesis and treatment of essential hypertension

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Hypertension is a significant risk factor for cardiovascular and cerebrovascular diseases and the leading cause of premature death worldwide. However, the pathogenesis of the hypertension, especially essential hypertension, is complex and requires in-depth studies. Recently, new findings about essential hypertension have emerged, and these may provide important theoretical bases and therapeutic tools to break through the existing bottleneck of essential hypertension. In this review, we demonstrated important advances in the different pathogenesis areas of essential hypertension, and highlighted new treatments proposed in these areas, hoping to provide insight for the prevention and treatment of the essential hypertension.

KEYWORDS

essential hypertension, arterial stiffness, salt-sensitive, sympathetic dysregulation, genetics - clinical

Introduction

Hypertension is characterized by a rise in systolic blood pressure (BP) and/or diastolic BP. The diagnostic criteria recommended in different guidelines for hypertension vary from each other in most major guidelines, it is recommended that hypertension be diagnosed when a person’s SBP in the office or in the clinic is \( \geq 140 \) mmHg and/or DBP is \( \geq 90 \) mmHg following repeated examinations (1). Hypertension is a significant risk factor for cardiovascular and cerebrovascular diseases (CVDs) and is the leading cause of premature death worldwide (2). The estimated prevalence of hypertension in the global adult population was 31.1% (1.39 billion) in 2010 and is still on the rise (2). Preventing and controlling hypertension is a major global public health strategy for reducing premature mortality from CVDs (3). Depending on whether a clear cause can be found, hypertension is divided into two categories: essential (primary) hypertension without a definite cause and secondary hypertension with a definite cause.

Essential hypertension accounts for more than 90% of all hypertensive patients (1), but the exact underlying mechanisms remain ambiguous. The present treatment of essential hypertension mainly based on long-term BP control but not curing the
Arterial stiffness

Arterial stiffness refers to a reduction in elasticity and distensibility of arteries, and pulse wave velocity (PWV) is often used to represent the degree of stiffness in large arteries. An increase in PWV indicates severe arterial stiffness and impaired in arterial dilatation capacity (8). Arterial stiffness has been closely associated with an increased risk of essential hypertension (9, 10), especially the isolated systolic hypertension (11). Vice versa, systolic BP is also associated with a clinically significant progression of arterial stiffness (12). It is still a “chicken and egg question” that elevated blood pressure and arterial stiffness which come first.

Arterial stiffness can be classified into functional arterial stiffness and structural arterial stiffness (13). Functional arterial stiffness is mainly related to the contractile function of vascular smooth muscle cells (VSMCs) which is influenced by a variety of factors (Figure 1). Among them, an increase in intracellular calcium ion (Ca^{2+}) concentration can directly influence VSMCs. And calcium channel blockers (CCBs), which are widely used in clinical settings, are to reduce intracellular calcium concentration in SMCs (14) and thus controlling BP. The nitric oxide (NO)-nitric oxide-sensitive guanylate cyclase (NOsGC)-cGMP pathway is also a well-studied pathway that is closely related to the contractile function of VSMCs. NO-NOsGC-cGMP pathway begins in vascular endothelial cells and regulates VSMCs contraction through a series of signaling (15–17). Injectable antihypertensive drugs, such as sodium nitroprusside and nitrates, all exert their vasodilatory effects through the NO-NOsGC-cGMP pathway.

Structural arterial stiffness is closely associated with age, hyperlipidemia, diabetes mellitus, and is characterized by elastin disruption, collagen deposition, and altered extracellular matrix composition (11, 13). However, unlike functional arterial stiffness, there is no effective treatment for structural arterial stiffness yet, since pathological changes in structural arterial stiffness are difficult to reverse. The phenotypic transition of VSMCs directly affects the structural arterial stiffness. Six phenotypes of VSMCs have been reported currently, out of which the contractile phenotype is rich in a-smooth muscle actin (a-SMA) and has the strongest contractile function. When VSMCs switch from contractile to other phenotypes (such as macrophage-like phenotype), the contractile function of the cells decreases significantly (18–20). Krüppel-Like Factor 4 (KLF4) is thought to be a key target in regulating the conversion of contractile VSMCs to other phenotypes (20). However, most of the current studies showed an important role of KLF4 in pulmonary hypertension (21–23), while it is not clear whether KLF4 in VSMCs is associated with essential hypertension.

Water-sodium retention and salt-sensitive

Water-sodium retention is a key cause of abnormal increases in intravascular fluid volume. Diuretics (especially thiazide diuretics) are important in the control of hypertension caused by water-sodium retention (24). Except secondary hypertension resulted from renal dysfunction, there is also a group of hypertensive patients related to water-sodium retention in essential hypertension, namely salt-sensitive hypertension.

High-salt intake is an important trigger in essential hypertension caused by water-sodium retention. Not all people will develop increased BP after consuming excessive salt. According to the blood pressure reactivity to salt-intake, patients are called salt-sensitive and salt-resistant, respectively (25). Multiple factors may contribute to the development of salt-sensitive hypertension, including age, obesity, genetic background, and maternal conditions during fetal life etc. (26), but the underlying mechanisms of salt-sensitive hypertension are not fully understood. Studies showed that low potassium activates (turns on) the system by hyperpolarizing the membrane, thereby driving Cl^- out of the cell and off.
FIGURE 1
Factors influencing the contractile function of smooth muscle cells. Ox-LDL, Oxidized low-density lipoprotein; TGs, Triglycerides; UPR, unfolded protein response; KLF4, Krüppel-Like Factor 4.

the inhibitory binding site on WNK (with no lysine [K]) kinases. Once disinhibited, WNK kinases phosphoactivate SPAK (STE20/SPS1-related proline/alanine–rich kinase), which in turn phosphoactivates nine–rich kinase co-transporter (NCC), and this called the Potassium Switch theory (27–29), which is one of the important theories on the pathogenesis of salt-sensitive hypertension. Recently, increasing evidence showed that intestinal flora is closely associated with salt-sensitive hypertension (30, 31) (Figure 2). The fecal microbiota of healthy rats could significantly lower BP in high-salt diet induced hypertensive (hSIH) rats, whereas the fecal microbiota of hSIH rats had opposite effects (32). Adoptive transfer of fecal material from conventionally housed high-salt diet–fed mice to germ-free mice predisposed them to increased inflammation and hypertension, the reason for this result may associated with an increase in Firmicutes, Proteobacteria, and genus Prevotella bacteria (33). The underlying mechanisms for intestinal flora to lead to increased BP are still under investigation. There is evidence that high-salt intake depleted Lactobacillus to induce T helper 17 cells and to promote hypertension (34). Another study demonstrated that high-salt dietary reduced the levels of B. fragilis and arachidonic acid in the intestine, which increased intestinal-derived corticosterone production and corticosterone levels in serum and intestine, thereby promoting BP elevation (32). In deoxycorticosterone acetate (DOCA)–salt mice model of hypertension, short-chain fatty acids released by the fermentation of fiber from the intestinal flora are associated with lower BP levels, and this may be closely related to the increase in Bacteroides acidifaciens (35). Notably, the intestinal flora is not only involved in salt sensitivity, it also participate in other underlying mechanisms of hypertension (36), including RAAS (37–39), vascular endothelium (40), and renal dysfunction (41) etc. A recent large intestinal flora sequencing study demonstrated the role of intestinal flora in human was extremely complex (42). Intestinal flora also has the potential to be an independent mechanism of essential hypertension.

Reducing sodium intake has been considered as an important way to reduce the incidence of hypertension (43–45). However, the benefits of using salt with low doses of sodium remain controversial, since low sodium intake is also associated with an increased risk of cardiovascular disease (46, 47). Great progress has been made in application of salt substitution recently. Excessive sodium intake leads to an increase in circulating fluid, which raises BP. While potassium intake has a diuretic effect, which reduces circulating fluid (48). Both dietary sodium reduction and dietary potassium supplementation have shown clear BP-lowering effects in clinical studies (45, 49).
In addition, according to the Potassium Switch theory, even high sodium intake, low dietary potassium still increases salt sensitivity (27). Salt substitution reduces sodium chloride and increases potassium chloride, thus exerting its antihypertension effects (50). There are two main types of salt substitution used in current clinical studies. One contains only sodium chloride and potassium chloride (51, 52), and the other one contains magnesium sulfate in addition to sodium chloride and potassium chloride (53, 54). Studies have demonstrated that both types of salt substitution not only lower BP but also reduce cardiovascular events in patients (51, 53–56). Additionally, the use of sodium and potassium salts (75% sodium chloride and 25% potassium chloride by mass) has therapeutic effects, as well as good economic benefits (55). Based on the results of these studies, it is very likely that salt recommendations for people 4, especially for hypertensive patients, will change in the near future. And to achieve the popularization of salt substitutes, the benefits of salt substitution need to be spread across the population (57).

**Renin-angiotensin-aldosterone system**

Renin-angiotensin-aldosterone system is a consecutive peptidergic system that functions in the control of the renal, adrenal, and cardiovascular systems. RAAS regulates BP mainly by affecting arterial constriction and water-sodium retention in the body. Both circulating RAAS and tissue RAAS (cardiac RAAS, vascular RAAS, intra-renal RAAS, brain RAAS and adipose tissue RAAS) have been involved in the pathogenesis of essential hypertension and related target organ damage (58). Several components of axis cascade have been identified in the RAAS, including angiotensinogen, renin, angiotensin-converting enzyme, angiotensins with various subtypes (Ang I, Ang II, Ang III, Ang IV, Ang 1-7), aldosterone and aldosterone receptors. Among these, angiotensinogen, produced by the liver, is the starting point of the system. Angiotensinogen is cleaved by renin secreted from the kidney to form angiotensin I. Angiotensin I (1-10) is then cleaved in the circulatory system by enzymes (e.g., Angiotensin converting enzyme) to form different peptides that eventually act in various organs (59). Among these cleavage peptides, the function of angiotensin II (1-8) has been elucidated the most. Angiotensin II binds to angiotensin II receptor (also classified as type 1, 2) in several organs and directly leads to vasoconstriction, water-sodium retention, and myocardial remodeling. In addition, when angiotensin II acts on the kidney, it further stimulates aldosterone secretion and exacerbates water-sodium retention (60).

RAAS inhibitors are one of the three cornerstones of existing antihypertension medications, and are also the drugs...
of first-line option for hypertensives with target organ damage (e.g., heart failure, mild-to-moderate renal failure). Clinical trials have demonstrated that RAAS blockades, including angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor (formally referred to as subtype-1 receptor, AT1R) blockers (ARBs), Angiotensin receptor-neprilysin inhibitor (ARNI), and mineralocorticoid receptor blockers (MRAs), contributes to the prevention of hypertension as well as the protection of target organs (1). In addition to oral drug therapies, hypertension vaccines developed for the RAAS system have become increasingly attractive in recent years (Table 1). The first hypertension vaccine has been studied for more than 30 years (61), and related studies are still ongoing. Compared with drug therapy, this immunotherapeutic approach to treating of hypertension have the potential to improve health outcomes, reduce healthcare costs, and increase medication adherence, since it can induce prolonged therapeutic effects and requires low frequency of administration. Currently, hypertension vaccines mainly target RAAS. Renin vaccines are the first vaccines developed. However, this vaccine has the risk of causing autoimmune diseases (61, 62), and in clinical studies, renin inhibitors do not provide long-term cardiovascular and renal protective effects despite their ability to lower BP (63, 64). Therefore, the future of renin vaccine to be used in clinic is not optimistic. Except for renin, other vaccines targeting Ang I, Ang II, AT1R, etc. have lowered BP at animal level without significant side effects. So far only CYT006-AngQb, an Ang II Vaccine, has obtained results in clinical phase II studies (65). However, it is worth mentioning that the clinical use of RAAS inhibitors is already very mature and painless, while vaccines may be cause pain and require repeated injections (65), which may discourage some patients from trying vaccine therapy. A recent study reported a non-RAAS-targeted vaccine, short peptide ADR-004 (cgiteagay), screened from α1D-AR, (1D-AR), not only effectively lowered BP, but also showed target organ protection after injection into spontaneous hypertension rats. This ADRQ1-004 vaccine targeting α1D-AR is expected to solve problems of low subtype selectivity and short half-life of α1-AR blockers in current clinical use (66).

### Sympathetic dysregulation

Sympathetic dysregulation is also an important cause of essential hypertension (67). The sympathetic overdrive leads to increased cardiac output, increased systemic vascular tone, and elevated plasma catecholamine levels. Patients with hypertension can manifest as greater muscle sympathetic nerve activity (MSNA) and lower baroreflex response (68).

Sympathetic hypertension varies widely among individuals and often associated with circadian patterns and mental status. MSNA plays a significant role in determining total peripheral resistance and vasoconstrictive function by controlling skeletal muscle (69). And MSNA may be a key cause of the huge individual variability in sympathetic hypertension, since studies have demonstrated that transduction of MSNA into vascular tone varies with age and sex (70, 71), and there is a close association of MSNA with attended (observed) and unattended (unobserved) BP levels in essential hypertension (72). The manifestations of BP changes in sympathetic hypertension are also complex, including morning hypertension, nocturnal hypertension, sleep apnea-related hypertension, orthostatic hypertension, resistant hypertension, etc., which may all be associated with autonomic dysregulation (73). Sympathetic overdrive not only contributes to the progression of BP elevation but also promotes hypertension-related target organ damage, such as left ventricular hypertrophy and dysfunction, congestive heart failure, renal insufficiency (73). Beta-blockers are drugs commonly used clinically for beta-adrenergic receptor action, which can inhibit the increase in BP and heart rate caused by sympathetic excitation. However, compared with other antihypertensive agents, such as diuretics, ACEi, ARB and CCBs, beta-blockers appear to be less protective against stroke and overall mortality, and are more often used as additional drugs for hypertensive patients (74). Exercise is an important way of controlling sympathetic hypertension, and studies have confirmed that high-intensity interval training (e.g., three 60-min exercise sessions per week for 4 months) can reduce BP by reducing MSNA (75, 76).

Renal denervation (RDN) has emerged as a potential treatment for resistant hypertension caused by sympathetic dysregulation. Renal sensory afferent nerve activity directly influences sympathetic outflow to the kidneys and other highly innervated organs involved in cardiovascular control. Abrogation of renal sensory afferent nerves reduces both BP and organ-specific damage caused by chronic sympathetic overactivity in various experimental models (77). Catheter-based radiofrequency denervation of the renal arteries is currently the most widely used technique for RDN, and RDN is gradually gaining recognition for its safety and antihypertensive effect (78–82), there are many RDN-related clinic trials ongoing (Table 2).

### Genetics

Hypertension is closely associated with genes, and our understanding of the relationship between genetics and BP has been well improved in recent years. More than 500 loci involved in the regulation of BP have been revealed by genome-wide association studies, taking the total number of BP genetic loci to over 1,000 (83–87). And BP is even discussed as a probable omnigenic trait (84). However, the identification of a true causal variant and its relevant gene product impacted is rarely straightforward. The lead single nucleotide polymorphism (SNP) typically indicates a chromosomal region usually with
TABLE 1  Hypertension vaccines.

| Target                  | Drug type                              | Studied subject          | Results                                                                 | Representative study |
|-------------------------|----------------------------------------|--------------------------|-------------------------------------------------------------------------|----------------------|
| Renin                   | Heterologous renin (antibodies are produced *in vivo*) | Monkeys                  | Reduced BP in monkeys, but induced renal autoimmune diseases.           | (61)                 |
|                         | Renin-derived Peptides (antibodies are produced *in vivo*) | Rats                     | Reduced BP in rats with no side effects.                               | (121)               |
| Angiotensin I (Ang I)   | Ang I-derived peptides                 | Rats                     | Reduced BP and Ang I levels in rats, with no effects on Ang II and no side effects. | (122)               |
| Angiotensin II (Ang II) | Ang II-derived active peptides         | Population (Phase I)     | Reduced Ang I levels but failed to reduce BP.                           | (123)               |
|                         | DNA fragment of Ang II (antibodies are produced *in vivo*) | Rats                     | Reduced BP with no side effects.                                        | (65)                 |
| Angiotensin II Type-1 Receptor (AT1R) | AT1R-derived peptides        | Rats                     | Reduced BP in rats with no side effects.                               | (124)               |
| α1-1D-Adrenergic Receptor (α1-AR) | α1-AR-derived peptides       | Rats                     | Reduced Ang II levels in rats but failed to reduce BP.                 | (125)               |

Other epigenetic modification, including post-translational histone modifications, non-coding RNAs and etc., also have been thought to be a promising study area for the development of novel future strategies for essential hypertension prevention and treatment (96, 97).

**Interactions between the pathogenesis of hypertension**

An updated Mosaic Theory has been proposed to explain the pathogenesis of hypertension, in which hypertension is considered as a response to different combinations of traits and stressors (98). In addition to vascular function, salt intake, sympathetic activation, genetics, microbiome, renal mechanisms, the new Mosaic Theory also highlights inflammation and oxidative stress (98). The interplay of these factors leads to a net-like pathogenesis of essential hypertension and increases the difficulty of the treatment.

In our opinion, the pathogenesis of hypertension is based on both decreased vasodilation and increased blood volume. Arterial stiffness directly causes a decrease in vasodilation, and water-sodium retention directly leads to an increase in blood volume. Additional factors such as RAAS, sympathetic system, and genes affect both vasodilation and blood volume (Figure 3A). Furthermore, there are complex interactions among those factors in the pathogenesis of hypertension. As a congenital factor, genes can simultaneously affect RAAS (59, 99–101), water-sodium retention (102), arterial stiffness (103), and sympathetic nerves (104). In the meantime, mutual effects also
TABLE 2  Ongoing clinical trial of RDN for hypertension.

| Identifier     | Participants number | Location                          | Conditions                          | Model description                                                                                             | Primary outcome measures                                                                                     | Status     |
|----------------|---------------------|-----------------------------------|-------------------------------------|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|------------|
| NCT04264403    | 80                  | Germany                           | Uncontrolled Hypertension with CKD stage3 | prospective, double-blind, multi-center, randomized                                                          | Change in systolic 24-h ambulatory BP                                                                         | Ongoing    |
| NCT04060641    | 30                  | United States, Texas              | Hypertension                        | retrospective, observational, cohort                                                                           | Correlation between genetic scoring and RDN effectiveness using office BP and AMBP                             | Ongoing    |
| NCT05234788    | 90                  | China                             | Uncontrolled Hypertension           | prospective, open label, parallel assignment, multi-center, randomized                                         | Reduction of office systolic blood pressure at 3 months.                                                    | Ongoing    |
| NCT05198674    | 1200                | United States, Georgia; Germany    | Uncontrolled Hypertension           | open label, single-group assignment                                                                          | Subgroup CKD: change in office SBP Subgroup isolated systolic hypertension: change in office systolic blood pressure change at 6 months Subgroup T2DM: change in office systolic blood pressure change at 6 months | Ongoing    |
| NCT05326230    | 154                 | Japan                             | Hypertension                        | double-blind, parallel assignment, randomized                                                                | Mean change in 24-hour systolic ABPM                                                                         | Ongoing    |
| NCT04314557    | 20                  | Spain                             | Hypertension with sympathetic dysautonomia etc. | prospective, observational                                                                                 | Change of SBP in orthostatism                                                                              | Ongoing    |
| NCT05027685    | 3000                | Germany                           | Hypertension                        | multi-center, observational                                                                                   | 1. Incidence of all-cause mortality, 2. Reduction in average home and office systolic/diastolic BP as compared to enrollment; 3. Reduction in average ambulatory systolic/diastolic BP (daytime, nighttime and 24-h); etc. | Ongoing    |
| NCT01673516    | 60                  | Norway                            | Uncontrolled Hypertension           | open label, parallel assignment, randomized                                                                  | Absolute change in office SBP                                                                               | Ongoing    |
| NCT02772939    | 80                  | Germany                           | Uncontrolled Hypertension           | open label, single-group assignment                                                                          | Predictive value of invasive PWV for BP response after renal denervation; Predictive value of non-invasive and invasive measures of in combination with clinical variables | Ongoing    |

RDN, Renal denervation; CKD, Chronic kidney disease; BP, Blood pressure; AMBP, Ambulatory blood pressure; T2DM, Diabetes mellitus type 2; SBP, systolic blood pressure; PWV, Pulse wave velocity.

exist between RAAS, water-sodium retention, arterial stiffness and sympathetic nerves (105–108, Figure 3B).

Circulating biomarkers

Biomarkers for patient classification, risk stratification and monitoring of response to therapy is an important integral component of diseases diagnosis and treatment. Several novel measurable circulating biomarkers have been identified as a possible screening method to define the risk of hypertension development in the last years. Study showed that administering Pentraxin 3 (PTX3) to wild-type mice induced endothelial dysfunction and increased blood pressure, while the effect was not observed in P-selectin–deficient mice (109). Moreover, compared with normotensive subjects, hypertensive patients have higher plasma levels of PTX3 and its mediators P-selectin and matrix metalloproteinase-1 (MMP1, regulated by PTX3) (109). This suggests that the combination of PTX3, P-selectin and MMP-1 may be a novel biomarker for predicting the onset of vascular dysfunction in hypertensive patients. Sortilin, a member of the vacuolar protein sorting 10 (VPS10P) family of receptors, has been positively correlated with vascular and metabolic disorders (110). A recent study demonstrated
that sortilin induced endothelial dysfunction of mesenteric arteries through NADPH oxidase 2 (NOX2) isoform activation, and the dysfunction could be prevented by knockdown of acid sphingomyelinase (ASMase) or sphingosine kinase 1 (111). Furthermore, plasma ASMase activity and plasma levels of sortilin increased in hypertensive subjects, especially in those with uncontrolled blood pressure (111). Therefore, the high levels of circulating sortilin may be helpful to explain the resistance to the anti-hypertensive pharmacological treatment. Some other biomarkers have also been reported in recent years, including Sphingosine-1-phosphate (112), bactericidal/permeability-increasing fold-containing family B member 4 (BPIFB4) (113), klotho (114), exosomal microRNAs (such as miR-130a, miR-195.) (115), SUV420H1 (116), etc., which are considered to have the potential in hypertension predicting or evaluating.

In addition to revealing the underlying mechanism or evaluating the state of hypertension, these markers also have the potential to classify essential hypertension due to biomarkers’ specificity. For instance, PTX3 or sortilin is related to vascular dysfunction, while SUV420H1 is identified as a potential biomarker for the early diagnosis of salt-sensitive hypertension. These specific sources of markers may provide guidance for targeted treatment of hypertension with different pathogenesis.
Summary

Hypertension is a disease named after its clinical features, which is doomed to the diversity of its pathogenesis. Unlike secondary hypertension with determined causes, the underlying mechanisms of essential hypertension have not been fully elucidated yet. The complicated mechanisms and poor understanding make it difficult to cure essential hypertension.

At present, there are two main research directions to further optimize the treatment of hypertension (Figure 4). One is to sort out this net and separate out the role of each individual factor. For example, recent studies have proposed new clinical indicators to estimate augmented MSNA in hypertensive subjects, independent of the volume of the conducting vessels (117, 118). The results, to some extent, dissociated the cross of arterial stiffness and sympathetic dysregulation. Besides, as mentioned above, taking advantage of circulating biomarkers may also guide a more precise treatment. Another direction is oriented toward lowering BP without exploring too deeply into the mechanisms. Several new approaches are being proposed, which have been shown to lower BP by a variety of mechanisms. Taking RDN as an example, it not only interrupts the sympathetic-mediated neurohormonal pathway, but may also reduce plasma renin activity and aldosterone levels to inhibited RAAS (119, 120). As the complicated mechanisms of essential hypertension are not likely to be sort out in the near future, it is also of great significance for clinicians to shift their focus to treatment efficacy to meet the clinical needs.

In summary, the reason why essential hypertension is difficult to cure is largely due to the pathogenesis which has not been fully elucidated and the factors leading to the pathogenesis of hypertension are intertwined. Continued in-depth mechanism study, especially the application of cutting-edge theories to the pathogenesis of hypertension, will be of great help in overcoming existing difficulties. On the other hand, optimizing the existing antihypertensive methods with blood pressure as the core goal is an important research direction for the clinical treatment of hypertension.

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JM was responsible for the conception and writing of the article. XC was responsible for critical revisions. Both authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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