Purple sweet potato color ameliorates kidney damage via inhibiting oxidative stress mediated NLRP3 inflammasome activation in high fat diet mice

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Abstract
Inflammation plays a crucial role in the pathogenesis of obesity. Purple sweet potato color (PSPC) has potential anti-inflammation efficacy. We evaluated the effect of PSPC on kidney injury induced by high fat diet (HFD) and explored the mechanism underlying these effects. The results showed that PSPC (700 mg/kg per day) reduced body weight, ratio of urine albumin to creatinine, inflammatory cell infiltration, and Collagen IV accumulation in mice fed an HFD (60% fat food) for 20 weeks. PSPC significantly reduced the expression level of kidney NLRP3 inflammasome including NLRP3 and ASC and Caspase-1, and resulted in decline of IL-1β. Moreover, PSPC inhibited the activation of IκB kinase β (IKKβ) and the nuclear translocation of nuclear factor kappa beta (NF-κB) in the upstream of NLRP3 inflammasome. These data imply that the beneficial effects of PSPC on HFD-induced kidney dysfunction and damage are mediated through NLRP3 signaling pathways, suggesting a potential target for the prevention of obesity.

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1. Introduction
Inflammation, as a major cause of organ damage, plays a crucial role in a variety of pathological processes of metabolic disorder diseases, such as gout, scurvy, and diabetic ketoacidosis. Emerging evidence suggests that inflammation-mediated kidney damage is involved in pathogenesis of obesity disease. Recently, several studies have shown chronic overfeeding, such as a high fat diet (HFD), leads to immune cell infiltration in different tissues, resulting in the production of inflammatory gene expression including cytokines, chemokines, and other mediators (Dong et al., 2014; Stemmer et al., 2012), which are implicated in oxidative stress and inflammatory response associated with obesity. HFD-induced activation of NOD-like receptor 3 (NLRP3) inflammasome and the alteration of its upstream or downstream signaling molecules, such as nuclear factor kappa beta (NF-κB) and the receptor of advanced glycation end products (RAGE), have also been demonstrated to be involved in obesity process, resulting in kidney injury and insulin resistance (Solini et al., 2013; Vandannagars et al., 2011; Harcourt et al., 2011). Furthermore, manipulation of inflammation-related genes can prevent and reverse kidney damage induced by HFD. For example, traditional fermented soybean products-doenjang and cheonggukjang blunted the kidney inflammatory response by suppressing NF-κB-related activities of inflammatory proteins in rats fed a HFD (Choi et al., 2011). Medical plant Magnolia extract (BL153) improved urine protein and kidney structure by reducing the expression of inflammation markers tumor necrosis factor-α (TNF-α) and plasminogen activator inhibitor-1 (PAI-1) in HFD-treated mice (Cui et al., 2013). Collectively, the natural...
productions contribute to attenuating kidney damage induced by HFD; however, the novel natural products and their protective mechanisms still need to be determined.

Purple sweet potato (Ipomoea batatas) color (PSPC), as a kind of anthocyanins, is a natural stable polyphenolic pigment and could be directly absorbed to the blood without cytotoxicity (Kano et al., 2005). Emerging studies demonstrate that PSPC possesses potential efficacy in the prevention of different inflammation-induced diseases via its in vivo effective anti-oxidant activities. The previous data in our lab have showed that PSPC could significantly ameliorate learning memory or liver injury by improving oxidative damage and inflammatory response of brain or liver in d-galactose-mediated aging mice (Shan et al., 2009; Zhang et al., 2009). Recently, PSPC is found to accelerate improvement in the prevention and treatment of HFD-mediated mouse obesity by reducing liver inflammation via AMPK signaling inhibition (Hwang et al., 2011a, 2011b) or by raising liver insulin sensitivity via blocking NF-κB signaling (Zhang et al., 2013). These results suggest that exploring the protective mechanism of PSPC on the metabolic tissues associated with obesity disease, such as kidney, may accelerate the progress in the treatment of obesity disease. In the present study, we studied kidney response of PSPC-administered mice to HFD feeding by testing oxidative stress and inflammatory response, and the regulatory mechanism of PSPC preventing kidney damage by measuring the role of NLRP3 inflammasome in the protective process.

2. Materials and methods

2.1. Animal and treatment

Eight-week-old male ICR strain mice (32.12 ± 2.14 g) were purchased from the Branch of National Breeder Center of Rodents (Beijing, China). The mice were housed in a room under the conditions of constant temperature (23 ± 1 °C) and humidity (60%), and a 12 h light/dark schedule (lights on 8:00–20:00). After one week of acclimatization to the conditions, mice were randomly divided into four groups including Control group, HFD, HFD/PSPC, PSPC. Mice were fed on either normal diet containing 11.4% fat, or HFD of 60% fat. In addition, mice were either administrated with PSPC [including two major components, cyanidin acyl glucosides and peonidin 340 (UV2501). The kidney sections were stained with hematoxylin and eosin, and measured by an expert in kidney pathology (S.M.) blinded to the type of treatment received by the animals.

Histological evaluations

The mice were perfused transcardially with 100 ml of 0.9% sterile saline, and kidney tissues were removed immediately and fixed in a fresh solution of 4% paraformaldehyde (PH 7.4) at 4 °C for 4 h, then incubated overnight at 4 °C in 100 mM sodium phosphate buffers (PH 7.4) containing 15%, 20%, and 30% sucrose, respectively; and embedded in optimal cutting temperature (OCT) compound (Leica, CA, Germany). 12 μm cryosections were collected on 3-animopropyl-trimethoxysilane-coated slides (Sigma–Aldrich). The kidney sections were stained with hematoxylin and eosin, and measured by an expert in kidney pathology (S.M.) blinded to the type of treatment received by the animals.

For biochemical analysis, mice were deeply anaesthetized and sacrificed. The kidney tissues were immediately separated and homogenized in ice cold 1/10 (w/v) 50 mM phosphate buffer saline solution (PBS, pH 7.2) with 10 strokes at 1200 rpm in a Potter homogenizer (Kontes, Vineland, NJ, USA). Homogenates were centrifuged at 12,000g for 10 min to obtain the supernatants for determining the level of advanced glycation end products (AGEs) and reactive oxygen species (ROS).

ROS assay.

For ROS assay, the kidney tissue homogenates were diluted at 1:20 (v/v) with ice-cold Locke's buffer (154 mM NaCl, 5.6 mM KCl, 3.6 mM NaHCO3, 2.0 mM CaCl2, 10 mM d-glucose, and 5 mM 4-(hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES, PH 7.4) to obtain the concentration of 5 mg tissue/ml.

Western blotting analysis.

For western blotting analysis, the kidneys were homogenized in 1/5 (w/v) ice-cold lysis buffer (25 mM HEPES, PH 7.4, 125 mM NaCl, 25 mM EDTA, 1 mM ethylene glycol tetraacetic acid, 1% NP-40, 1 mM Na3VO4, and the protease inhibitor mixture described above). The tissue homogenates were sonicated ten times for 10 s with 30 s intervals using a sonicator and centrifuged at 14,000g for 40 min at 4 °C, and then the supernatants were collected and stored at −70 °C for western blotting analysis. The expression levels of NF-κB p65 in cytoplasm and nuclear extracts of kidney tissues were assessed by western blotting, which was obtained by a nuclear/cytoplasm fractionation kit (BioVision, Inc., USA). Protein contents in the supernatants were detected by the bicinchoninic acid assay kit (Pierce Biotechnology, Inc., Rockford, IL, USA).

2.6. Determination of redox status

2.6.1. ROS assay

ROS was measured as described (Zhang et al., 2013). In brief, the reaction mixture (1 ml) containing Locke's buffer (PH 7.4; 0.2 ml of homogenate, and 10 μl of DCFH-DA (5 mM) was incubated for 15 min at room temperature to allow incorpo-ration of DCFH-DA into any membrane-bound vesicles and cleavage of the diacetate group by esterases. After 30 min of further incubation, the conversion of DCFH-DA to the fluorescent product DCF was measured using a spectrofluorometer with excitation at 484 nm and emission at 530 nm. Blanks were included to correct for background fluorescence (conversion of DCFH-DA in the absence of homogenate). ROS formation was quantified from a DCF standard curve. Data are expressed as pmol of DCF formed per minute per mg of protein.

2.6.2. AGEs assay

Advanced glycation end products (AGEs) are formed due to nonenzymatic glycation of macromolecules, especially proteins leading to their irreversible oxidation is increased under the hyperglycemia of diabetes mellitus and obesity. Therefore, AGEs content could reflect the degree of tissue oxidative damage. AGEs content was measured according to the protocols of AGEs assay kit (Lu et al., 2010).

2.7. Western blotting analysis

Western blotting analysis was performed as previously described (Shan et al., 2009). The supernatants were then separated using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS–PAGE) and analyzed by western blotting. For western blotting, samples (30 g protein) were separated by denaturing SDS–PAGE and transferred to a polyvinylidene fluoride membrane (Roche Diagnostics Corporation, Indianapolis, IN) by electrophoretic transfer. The membrane was blocked with 5% nonfat milk or 5% BSA and 0.1% Tween–20 in TBS and incubated overnight with one of the following primary antibodies: rabbit anti-RAGE and rabbit anti-NLRP3; rabbit anti-1 kappa B kinase β (IRB), rabbit anti-p-IRB and rabbit
anti-hBD2, rabbit anti-thioredoxin interacting protein (TXNIP), rabbit anti-pro-Caspase-1, rabbit anti-interleukin-1β (IL-1β), rabbit anti-apoptosis associated speck-like protein containing a CARD (ASC), rabbit anti-cyclooxygenase-2 (COX2), mouse anti-induce nitric oxide synthase (iNOS), and mouse anti-NF-κB. (Santa Cruz Biotechnology, Inc., California, USA; Cell Signaling Technology, Inc., Beverly, MA and Abcam, Cambridge, UK). Protein bands were detected using horseradish peroxidase–conjugated anti-rabbit, anti-goat, or anti-mouse secondary antibodies. The mean optical density (OD) values of detected bands were measured with Scion image analysis software (Scion Corp., Frederick, MD, USA) and were normalized to mouse anti-β-actin (Chemicon International Inc., Temecula, CA), or rabbit anti-β-tublin (Cell Signaling Technology, Inc.) as internal controls (OD detected protein/OD internal control).

2.8. Statistic analysis

All the data were analyzed by the software SPSS 15.0 statistically. ROS level, AGEs and western blotting results were analyzed with Newman–Keuls or Tukey's HSD post hoc test. Data are expressed as mean ± standard deviation (SD). Statistical significance is set at \( P < 0.05 \).

3. Results

3.1. PSPC ameliorates obesity, glucose intolerance and insulin resistance in HFD-treated mice

Chronic overfeeding such as a high fat diet leads to obesity, glucose metabolism dysregulation and insulin resistance. To identify the effect of PSPC on metabolism syndrome caused by HFD, we firstly tested the changes in body weight, blood glucose and insulin tolerance. We found that body weight significantly increased from the beginning of HFD treatment for 4 weeks \( [4 \text{ weeks}: F(3, 36) = 7.150, P < 0.001; 8 \text{ weeks}: F(3, 36) = 13.191, P < 0.001; 12 \text{ weeks}: F(3, 36) = 22.151, P < 0.001; 16 \text{ weeks}: F(3, 36) = 27.992, P < 0.001; 20 \text{ weeks}: F(3, 36) = 32.409, P < 0.001] \). And PSPC administration for HFD mice substantially inhibited the increase of body weight. Glucose and insulin tolerance tests are taken to evaluate glucose metabolism and insulin secretion in HFD treatment mice (Fig. 1). After 20-week dietary intervention, HFD treatment showed an obvious increase of fasting blood glucose value compared to Control group \( [F(3, 28) = 78.651, P < 0.001] \). Blood glucose level during glucose tolerance tests and insulin tolerance tests was found to be enhanced in HFD group compared to Control group. The data of glucose and insulin tolerance tests revealed that 20-week HFD treatment markedly impaired glucose tolerance and insulin sensitivity. However, PSPC administration for HFD mice significantly suppressed blood glucose level, improved glucose intolerance and insulin resistance. There were no difference among PSPC/HFD, PSPC and Control groups.

3.2. PSPC reduces urine albumin and kidney tissue damage in HFD-treated mice

Then, considering urine albumin-to-creatinine ratio (ACR) is an important marker of urine protein and associated with glomerular damage and progressive renal dysfunction in obesity and diabetes (Praga and Morales, 2010), we tested the changes of urine albumin-to-creatinine ratio and Collagen IV protein in the kidneys of PSPC treated HFD-mice. The results showed that HFD treatment dramatically enhanced the ACR ratio \( [F(3, 36) = 58.188, P < 0.001] \), while PSPC reduced the enhancement in urinary albumin caused by HFD (Fig. 2). Western blotting analysis and immunohistochemical staining also showed that HFD treatment exhibited higher extracellular matrix accumulation \( [F(3, 16) = 20.016, P < 0.001] \), and PSPC inhibited the accumulation of Collagen IV protein \( (P < 0.001 \text{ vs. HFD group}) \). Further, inflammatory cell infiltration and tissue damage were demonstrated by HE staining in the kidneys of HFD-treated mice. Comfortingly, PSPC treatment markedly

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**Fig. 1.** PSPC ameliorates obesity, glucose intolerance and insulin resistance in HFD-treated mice. (A) Weight body gain in different treatment groups at different time points \( (n = 10) \). (B) Effects of PSPC on fasting blood glucose of HFD mice after 20-week treatment \( (n = 8) \). (C) Data of glucose tolerance tests after oral gavage of 1.5 g/kg glucose in different treatment groups \( (n = 8) \). (D) Data of insulin tolerance tests after i.p. injection of 1 U/kg insulin in different treatment groups \( (n = 8) \). All values represent the mean ± SD. "\( P < 0.01 \), ""\( P < 0.001 \) vs. HFD group; "\( P < 0.05 \), """"\( P < 0.001 \) vs. control group.
ameliorated the histopathologic changes, however there was no significant among Control, HFD/PSPC and PSPC groups (See Fig. 2).

3.3. PSPC attenuates oxidative stress in the kidney of HFD-treated mice

To assess whether PSPC reduces oxidative stress which could induce inflammatory response, we measured the ROS level and the AGEs content. The results showed that ROS and AGEs significantly increased in HFD group ($F(3, 16) = 23.695, P < 0.001$; $F(3, 16) = 26.589, P < 0.001$) compared with Control group (Fig. 3). Our data showed that HFD induced oxidative stress in the kidneys of mice, while oral administration of PSPC to HFD mice significantly decreased the level of ROS ($P < 0.001$) and AGEs ($P < 0.001$). However, there were no notable difference among HFD/PSPC group, PSPC group and vehicle Control.

3.4. PSPC inhibits the activation of IKKβ/NF-κB signaling in the kidney of HFD-treated mice

To clarify the regulatory mechanism underlying the protective effect of PSPC on the mouse kidney damage induced by HFD treatment, we firstly analyzed the expression of IKKβ/NF-κB signaling, which plays a key role in the regulation of various genes involved in proliferation, apoptosis, immune and inflammatory response. The expression levels of IKKβ, IκBα, NF-κB, iNOS and COX-2 were measured by western blotting. As shown in Fig. 4, HFD treatment...
induced the activation of IKKβ/NF-κB pathway by enhancing the phosphorylation of IKKβ \( \text{p-IKKβ (Ser181)} \): \( F (3, 16) = 42.939, P < 0.001, \) vs. Control group], leading to the degradation of IκBα \( F (3, 16) = 20.255, P < 0.001, \) vs. Control group], accelerating NF-κB from the cytoplasm into the nucleus \( \text{cytoplasm NF-κB} \ F (3, 16) = 12.744, \text{nuclear NF-κB} \ F (3, 16) = 10.844, \) and increasing the expression of inflammatory markers COX-2 and iNOS \( F (3, 16) = 25.521, P < 0.001; F (3, 16) = 16.136, P < 0.001 \). Oral administration of PSPC to HFD mice for 20 weeks significantly reversed these changes \( P < 0.05, \) vs. the HFD group). There were no significant differences among Control group, PSPC group and HFD/PSPC group.

3.5. PSPC reduces the protein expression of NLRP3 inflammasome in the kidney of HFD-treated mice

The recent discoveries suggest a potential role of NOD-like receptors (NLRs) in innate immune triggered interest in the studies of chronic diseases such as obesity and type 2 diabetes (T2D) (Grant and Dixit, 2013). NLRP3, as one important component of NLRs, is a crucial protein of inflammasome complex including NLRP3, ASC, pro-Caspase-1. Activated NLRP3 interacts with ASC, and recruits pro-Caspase-1, resulting in the secretion of proinflammatory cytokines IL-1β. As shown in Fig. 5, compared with Control group, HFD treatment significantly increased the expression level of NLRP3 and ASC \( \text{[respectively} F (3, 16) = 12.155, P < 0.001; F (3, 16) = 12.526, P < 0.001] \), and activated Caspase-1 (cleaved Caspase-1: \( F (3, 16) = 11.988 \) and IL-1β \( F (3, 16) = 15.737, P < 0.001 \), while there was no significant change in the content of pro-caspase-1 among four groups. Our results showed that PSPC activated NLRP3 inflammasome pathway in the mouse kidney. Similarly, PSPC administration in the HFD-treated mice reversed these abnormal changes, made the above parameters restore to a near normal level \( \) (no significant vs. Control group). However, PSPC treatment did not substantially change these parameters in the kidneys of mice \( P > 0.05 \) vs. Control group).

3.6. PSPC decreases the protein expression of RAGE and TXNIP in the kidney of HFD-treated mice

TXNIP is ubiquitously expressed in a variety of cells, and acts an endogenous suppressor of ROS scavenging protein thioredoxin. TXNIP and RAGE are identified as the molecular nutrient sensors in the regulation of energy metabolism, linked oxidative stress and inflammation (Chutkow et al., 2010; Leuner et al., 2012). As shown in Fig. 6, HFD administration increased the expression level of TXNIP and RAGE in the kidneys of mice \( F (3, 16) = 18.185, P < 0.001; F (3, 16) = 10.612, P < 0.001 \), while PSPC suppressed the increase of renal TXNIP and RAGE induced by HFD-treatment, no significant change was found among Control group, PSPC group and PSPC/HFD group.

4. Discussion

The incidence of obesity has been climbing dramatically worldwide. It is a key risk factor for many metabolic diseases, including diabetes, hypertension, and heart disease. Recent studies indicate that obesity is accompanied by chronic inflammation in important metabolic tissues including adipose, liver and kidney, resulting in the release of pro-inflammatory cytokines and chemokines that contribute to the development of metabolic syndrome (Lu et al., 2012). The recent discoveries suggest a potential role of NOD-like receptors (NLRs) in innate immune triggered interest in the studies of chronic diseases such as obesity and type 2 diabetes (T2D) (Grant and Dixit, 2013). NLRP3, as one important component of NLRs, is a crucial protein of inflammasome complex including NLRP3, ASC, pro-Caspase-1. Activated NLRP3 interacts with ASC, and recruits pro-Caspase-1, resulting in the secretion of proinflammatory cytokines IL-1β. As shown in Fig. 5, compared with Control group, HFD treatment significantly increased the expression level of NLRP3 and ASC [respectively F (3, 16) = 12.155, P < 0.001; F (3, 16) = 12.526, P < 0.001], and activated Caspase-1 (cleaved Caspase-1: F (3, 16) = 11.988) and IL-1β [F (3, 16) = 15.737, P < 0.001], while there was no significant change in the content of pro-caspase-1 among four groups. Our results showed that PSPC activated NLRP3 inflammasome pathway in the mouse kidney. Similarly, PSPC administration in the HFD-treated mice reversed these abnormal changes, made the above parameters restore to a near normal level (no significant vs. Control group). However, PSPC treatment did not substantially change these parameters in the kidneys of mice (P > 0.05 vs. Control group).
The sustained oxidative stress is involved in many important signaling pathways, IKKβ/NF-κB and NLRP3/IL-1β are reportedly to be closely linked to the development of inflammatory response (Salminen et al., 2012). Consistently, we found kidney IKKβ was significantly activated after HFD administration, and this alteration was accompanied with the increase of nuclear NF-κB, a nuclear transcription factor. The result is in accord with the activated NF-κB in the kidneys of HFD-fed mice (Choi et al., 2011). In the present study, PSPC administration significantly reduced the activities of kidney NF-κB. Additionally, we previously found that PSPC also reduced activities of liver NF-κB in HFD-fed mice (Zhang et al., 2013). Because NF-κB regulates the expression of various genes, including cytokines, iNOS and COX-2, which are used to be major inflammatory mediators and pro-inflammatory markers, it plays a critical role in apoptosis, various autoimmune diseases and inflammation. Our data showed that HFD treatment increased the expression of iNOS and COX-2 in the kidneys, indicating PSPC’s effective preventive function for the kidney inflammation via NF-κB regulating the expression of iNOS and COX-2. Most recently, the NLRP3 inflammasome, which consists of NLRP3 molecule, adaptor protein ASC and pro-Caspase-1 that catalytically activates Caspase-1, causing the release of IL-1β and IL-18, was demonstrated to prevent obesity-induced inflammation and insulin resistance (Vandanmagsar et al., 2011). Consequently, NLRP3 inflammasome has emerged as an unexpected sensor for the pathogenesis of auto-inflammatory, metabolic danger and stress. Moreover, NLRP3 inflammasome is increasingly suspected of playing a major role in other human pathologies such as cancer, asbestosis and Alzheimer’s disease. NLRP3 is an important component of the inflammasome complex, and NLRP3 gene is activated by IKKβ/NF-κB. Deleting NLRP3 in mice can prevent inflammasome activation in adipose tissue and liver as well as increase insulin sensitivity (Stienstra et al., 2011), demonstrating that NLRP3 plays an important role in the development of obesity and T2D (Pejnovic et al., 2013). Interestingly, elevated ROS can activate NLRP3 inflammasome, resulting in the secretion of bioactive IL-1β, triggering the activation of NF-κB which in turn promotes the secretion of bioactive IL-1β (Grant and Dixit, 2013). We also found the related triggering regulatory results among ROS, NLRP3 inflammasome (NLRP3, ACS and Caspase-1), IKKβ and NF-κB in the kidneys of HFD-treated mice. However, PSPC reduced the production of ROS and AGEs; these changes are closely related to the alleviation of kidney oxidative damage and associated urine protein in PSPC-treated mice. Furthermore, PSPC reduced HFD-induced renal...
inflammation by dampening NLRP3/IL-1β and IKKβ/NF-κB pathways similar to recent reports (Dragano et al., 2013; Zhang et al., 2013).

NLRP3 inflammasome is also activated by TXNIP and RAGE and promotes the secretion of IL-1β (Zhou et al., 2010). The expression of TXNIP, as a hallmark of cell oxidative stress, is enhanced in obesity, T1D and T2D (Wang et al., 2013; Koenen et al., 2011). In the present study, HFD consumption was found to substantially stimulate the production of TXNIP, while, PSPC-treatment dampened the activation to ameliorate renal damage. Additionally, RAGE, a AGEs receptor, is promoted to express by the increase of AGEs under the condition of oxidative stress and hyperglycemia in obesity disease (Tomino et al., 2011). In contrary, deleted RAGE abolishes RAGE-induced IL-1β secretion (Shai et al., 2010), suggesting they may play the regulatory role in the development of obesity through mutually reinforcing expression. Combined our results with the previously reported ones, we speculated that PSPC prevented kidney damage by blocking endogenous oxidative cues and inflammatory reaction in HFD-induced obesity. This preventive pharmacologic efficacy is possibly obtained by PSPC inhibiting the expression of RAGE and of TXNIP, resulting in the inactivating of NLRP3 inflammasome, and causing the fall of NF-κB entranced into the nuclear.

Although we have clearly established the importance of PSPC’s protective function on the HFD-induced kidney injury during the development of obesity in animal models, additional studies focused on unraveling the importance of PSPC’s preventing against the inflammation induced by HFD diet in human kidney tissue are needed. In conclusion, PSPC showed a significant amelioration on kidney injury in HFD-fed mice by reducing the production of AGEs and ROS, and improving the sensitivity of insulation, this protection function on the kidney is played by suppressing the expression of TXNIP and RAGE, further inhibiting the activation of NLRP3 inflammasome and IKKβ/NF-κB pathways. Therefore, PSPC represents a potential natural product in the prevention of nephropathy induced by obesity.

Conflict of Interest
The authors declare there are no conflicts of interest.

Transparency Document
The Transparency document associated with this article can be found in the online version.

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