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REGULAR ARTICLE

Inhibition of the receptor for advanced glycation end-products (RAGE) protects from secondhand smoke (SHS)-induced intrauterine growth restriction IUGR in mice

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Abstract Intrauterine growth restriction (IUGR) is a disease affecting 10% of all pregnancies. IUGR is associated with maternal, fetal, or placental abnormalities. Studies investigating the effects of secondhand smoke (SHS) exposure and IUGR are limited. The receptor for advanced glycation end-products (RAGE) is a pro-inflammatory transmembrane receptor increased by SHS in the placenta. We tested the hypothesis that inhibition of RAGE during SHS exposure protects from smoke-induced IUGR. C57BL/6 mice were exposed to SHS or SHS + semi-synthetic glycosaminoglycan ethers (SAGEs) known to inhibit RAGE signaling. Trophoblast cells were treated with cigarette smoke extract (CSE) with or without SAGEs in order to address the effects of RAGE inhibition during trophoblast invasion in vitro. SHS-treated mice demonstrated a significant reduction in fetal weight (7.35-fold, $P \leq 0.0001$) and placental weight (1.13-fold, $P \leq 0.0001$) compared with controls. Mice co-treated with SHS and SAGEs were protected from SHS-induced fetal weights decreases. SHS treatment of C57BL/6 mice activated placental extracellular signal-regulated kinase (ERK) (3.0-fold, $P \leq 0.05$), JNK (2.4-fold, $P \leq 0.05$) and p38 (2.1-fold, $P \leq 0.05$) and the expression of inflammatory mediators including TNF-α (1.34-fold, $P \leq 0.05$) and IL-1β (1.03-fold, $P \leq 0.05$). SHS-mediated activation of these molecules was reduced to basal levels when SAGE was co-administered. Invasion of trophoblast cells decreased 92% ($P < 0.002$) when

treated with CSE and CSE-mediated invasion was completely reversed by SAGEs. We conclude that RAGE inhibition protects against fetal weight loss during SHS-induced IUGR. These studies provide insight into tobacco-mediated IUGR development and clarify avenues that may be helpful in the alleviation of placental complications.

Keywords Secondhand smoke · IUGR · RAGE · Placenta · Trophoblast invasion

Introduction

Human pregnancy is characterized by complex temporal and spatial signaling processes that culminate in the creation of a healthy newborn. Disruption of these carefully orchestrated events occurs in obstetric complications such as intrauterine growth restriction (IUGR), that regularly impacts fetal and neonatal morbidity and mortality. Many complications have been associated with restricted fetal growth such as perinatal hypoxia and asphyxia, cerebral palsy and persistent pulmonary hypertension of the newborn (Brar and Rutherford 1988; Gray et al. 1999; Pollack and Divon 1992). Furthermore, several studies have reported long-term sequelae of IUGR complications including adult hypertension, heart disease, stroke and diabetes (Barker 1993; Smith et al. 2016; Barker et al. 1993; Holemans et al. 1993; Phipps et al. 1993; Reusens-Billen et al. 1989). Placental abnormalities associated with the IUGR placenta include reduced syncytiotrophoblast surface area (DiFederico et al. 1999), increased thickness of the exchange barrier formed

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by the trophoblast and fetal capillary endothelium (Ishihara et al. 2002), decreased trophoblast invasion (Mayhew et al. 2003; Pijnenborg et al. 1991), increased mTOR protein (Roos et al. 2007) and an increase in placental trophoblast apoptosis (Allaire et al. 2000; Hung et al. 2002). Although research has discovered many processes that contribute to the development of these pathologies, much more research is required to fully elucidate the underlying mechanisms associated with placental insufficiency in the context of IUGR.

Cigarette smoking during pregnancy has been a subject of intense study for decades (Arffin et al. 2012). In fact, many researchers have posited that smoking cigarettes throughout pregnancy may be the single most important avoidable cause of adverse pregnancy outcomes (Bickerstaff et al. 2012; Akkar et al. 2015). Indeed, even exposure to low levels of nicotine, the primary addictive chemical compound found in cigarettes, has been demonstrated to affect normal brain development, increase infant mortality rates and lead to the development of IUGR (Guan et al. 2009; Wahabi et al. 2013). Overall, exposure to cigarettes has been shown to have devastating effects on the developing fetus; however, reports detailing the consequences of passive secondhand smoke (SHS) exposure have yet to produce conclusive findings. Evidence suggests that mothers who are exposed to SHS may experience an increase in the risk of newborn orofacial clefting, (Kummet et al. 2016), elevated risks of wheeze development in newborns (Vardavas et al. 2016) and even learning difficulties (Jorge et al. 2016). While data continue to demonstrate the deleterious effects of tobacco smoke, there are conflicting reports as to its correlation with IUGR. A study by Wahabi et al. (2013) found a link between SHS and the induction of IUGR (Wahabi et al. 2013), yet, in contrast, Subramoney et al. (2010) reported no correlation between IUGR incidence and pregnant women exposed to smoke (Subramoney et al. 2010). Despite the conflicting reports, studies have suggested that SHS significantly increases the risk for spontaneous abortion, preterm delivery, sudden infant death syndrome and still births (Dempsey and Benowitz 2001; Engel et al. 2013; Khader et al. 2011; Lee et al. 2012a, b). More research is needed to fully understand the relationship between placental dysfunction and SHS exposure. Furthermore, an investigation into the possible mechanisms that may be contributing to the development of these adverse outcomes is warranted, as it may lead to pioneering insights and possible therapeutic improvements.

The receptor for advanced glycation end-products (RAGE) is a pattern recognition cell surface receptor increased during SHS exposure (Winden et al. 2014; Robinson et al. 2012). RAGE is capable of binding a host of ligands such as advanced glycation end-products (AGEs), HMGB1, S100/calgranulins and an additional variety of substances

(Morbini et al. 2006). RAGE signaling is implicated in the pathogenesis of many inflammatory diseases such as Alzheimer's (Lubitz et al. 2016), diabetes (Nelson et al. 2015), atherosclerosis (Belmokhtar et al. 2016), COPD (Reynolds et al. 2011) and diverse rheumatological disorders (Wu et al. 2016). Some products generated via RAGE signaling include NF-kB, Cox-2, IL-1ß and TNF-a, thus RAGE signaling likely influences apoptosis and the mediating of potent pro-inflammatory responses found in many chronic inflammatory pathologies (Bianchi et al. 2010). RAGE has been discovered in many cell types including smooth muscle, endothelium, macrophages and epithelium but has its highest expression in the lung and the placenta (Buckley and Ehrhardt 2010; Holmlund et al. 2007). Because the RAGE signaling axis has been linked with pro-inflammatory cascade events, novel drug therapies that target RAGE or its family of ligands are currently being investigated. One such recent modality with promise is semi-synthetic glycosaminoglycan ethers (SAGEs). SAGEs are partially lipophilic sulfated polysaccharide derivatives that modulate inflammation via the abrogation of RAGE signaling (Zhang et al. 2011). In this research endeavor, we examine the potential protective effects of SAGEs, specifically through blocking RAGE signaling in the lessening of downstream pro-inflammatory targets that contribute to the development of IUGR.

Materials and methods

Animals and tissue preparation

C57 Black 6 (C57BL/6) mice were obtained from Charles River Laboratories (Wilmington, MA, USA). Mice were housed in a conventional animal facility, supplied with food and water ad libitum and maintained on a 12-h light:dark cycle. Animals were separated into three groups: wild-type room air (RA; WT + RA), wild-type and SHS (WT + SHS) and wild-type, SHS and SAGEs injections (WT + SHS + SAGEs). To obtain timed pregnancies, females were caged with males overnight. Mice were allowed to undergo normal gestational development until embryonic day 14.5 (E14.5) at which time mice were either restrained and exposed to room air, or restrained and exposed to SHS. On E14.5, pregnant mice were then given either PBS or SAGEs injections until E18.5, at which time they were euthanized. Only live birth animals were considered for the study and any mice with absorbed fetuses were noted and excluded from the datasets. The first five conceptuses proximal to the ovaries from each uterine horn were collected and placentae and fetuses were weighed at this stage of pregnancy. Placental tissues were then snap-frozen in liquid nitrogen for protein analysis. For immunohistochemistry analysis, whole conceptuses were frozen in dry ice-cooled heptane. Mice were housed and utilized in

accordance with protocols approved by the IACUC at Brigham Young University.

Secondhand smoke (SHS) exposure

Mice were exposed to SHS generated from 3R4F research cigarettes from Kentucky Tobacco Research and Development Center, University of Kentucky, via a nose-only exposure system (InExpose System; Scireq, Montreal, Canada). Mice were individually placed in soft restraints and connected to an exposure tower, wherein a computer-controlled puff of smoke generated every minute resulted in 10 s of SHS followed by 50 s of fresh air. Six mice in each group where exposed to SHS from six cigarettes over 10 min. This procedure was repeated from E14.5 to E18.5 at which time the mice were euthanized. To generate RA controls, mice were similarly restrained for a period of 10 min but were only exposed to RA. The SHS challenge was determined to be acceptable and was tolerated without evidence of toxicity. Furthermore, this nose-only model of smoke exposure yielded chronic blood carboxyhemoglobin levels of ~5%, a value similarly observed in human smokers (Wright et al. 2008).

SAGEs treatment

SAGEs (GM-111) were used in these studies, kindly gifted by Dr. Glenn D. Prestwich from the University of Utah Medical Center. All animal groups were administered an intraperitoneal injection (IP) with 20 μg/day (Zhang et al. 2011) of either SAGEs or saline (PBS) from E13.5 to E18.5 and exposed to either SHS or RA as previously explained.

Immunoblotting

Western blot analysis was used to assess the expression of a collection of cell signaling proteins in both control, control + SHS exposed and control + SHS + SAGEs treated animals. Briefly, tissues were homogenized in protein lysis buffer (RIPA; Fisher Scientific, Pittsburg, PA, USA). Protein lysates (20 μg) were separated on Mini-PROTEAN® TGX™ Precast gel (Bio-Rad Laboratories) by electrophoresis and transferred to nitrocellulose membranes. Membranes were incubated overnight with antibodies for RAGE, TNF-α, IL-1β, phospho and total extracellular signal-regulated kinase (ERK), JNK, or p38 (all from Cell Signaling, Danvers, MA, USA). A secondary horseradish peroxidase antibody (1:1000; Santa Cruz Biotechnology) was incubated in 5% milk for 1 h at room temperature. The membranes were incubated with chemiluminescent substrate (Pierce, Rockford, IL, USA) for 5 min and the emission of light was digitally recorded using a C-DiGit® Blot Scanner (LI-COR, Lincoln, NE,

USA). Quantification of proteins was performed by densitometry and normalization with actin provided comparisons between treated and control samples.

Invasive trophoblast cell culture, cigarette smoke extract (CSE) and SAGEs

A first-trimester cytotrophoblast cell line Swan71 (SW71; n = 9) was used for invasive cytotrophoblast studies. SW71 cells were maintained and cultured in RPMI medium (Mediatech, Manassas, VA, USA). Cell medium was supplemented with 10% fetal bovine serum (FBS) and 1% penicillin and streptomycin. Cigarette smoke extract (CSE) was generated as previously described by Reynolds et al. (2006, 2008). Briefly, two 2RF4 research cigarettes (University of Kentucky, Lexington, KY, USA) were continuously smoked with a vacuum pump into 20 ml of DMEM medium (Mediatech). The smoke-bubbled medium was filtered through a 0.22-μm filter to remove large particles. The resulting medium was defined as 100% CSE. Dilutions were made using DMEM medium to a stock concentration of 10% CSE.

Cell treatments

SW71 cells were detached and 20,000 cells/ml were incubated in 2% FBS medium alone, medium supplemented with 0.5% CSE or 0.5% CSE and 50 μg/ml SAGEs. All treatments were carried out for 24 h. Real-time cell invasion was determined following these treatments.

Real-time cell invasion determination

An xCELLigence was utilized to determine real-time invasion of trophoblast cells. Protocol was followed as suggested by the manufacturer. Briefly, invasion was assessed in 16-well CIM-Plates (n = 9). The top wells were coated with a 1:40 matrigel concentration and trophoblast cells were plated in the top chamber at a concentration of 20,000 cells/well in 2% FBS RPMI in a total volume of 100 μL, in the presence or absence of CSE or CSE and SAGEs. The bottom chamber wells were filled with 160 μL of 10% FBS RPMI. The cells were then placed in the RTCA DP instrument and invasion readings were carried out every 15 min for 24 h.

Statistical analysis

Data were assessed by one- or two-way analysis of variance (ANOVA). When ANOVA indicated significant differences, Student's t test was used with the Bonferroni correction for multiple comparisons. Results were checked for normality and data were shown as means ±
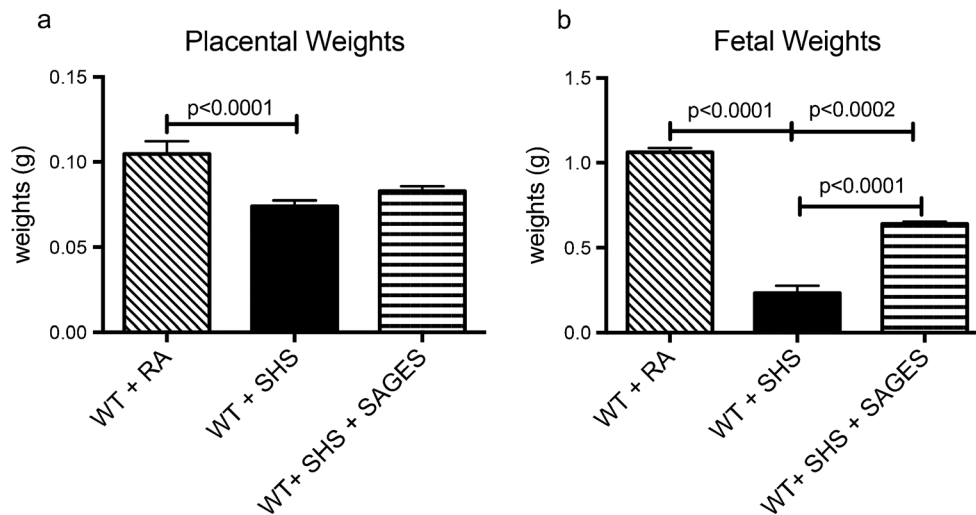
Fig. 1 Placental and fetal weight differences during secondhand smoke (*SHS*) exposure. A significant decrease in placental (**a** 1.4-fold, $P \le 0.0003$) and fetal weights (-: 2.3-fold, $P \le 0.0002$) was observed in SHS-treated wild-type (*WT*) animals compared to room air (*RA*) controls. No significant recovery was observed in placental weights when comparing placenta from animals co-treated with SHS and SAGEs to those exposed to SHS alone (**a**). A significant recovery in fetal weights (4.22-fold, $P \le 0.0001$) was observed in SHS-exposed mice with SAGEs when compared with animals treated with SHS alone (**b**)
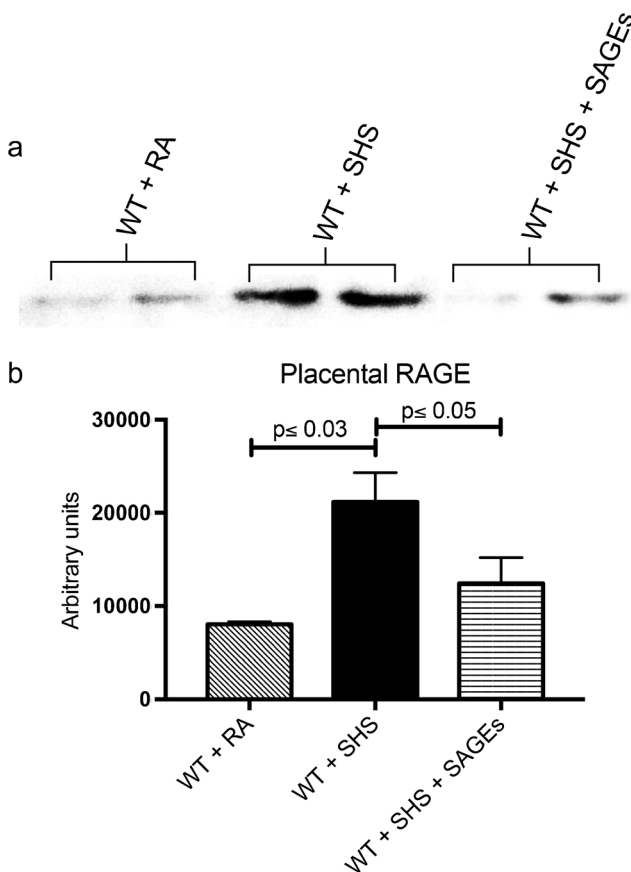

Fig. 2 Placental RAGE expression during SHS-induced IUGR. A characteristic RAGE western blot is shown in (a). RAGE was increased (1.13-fold, $P \le 0.05$) with SHS in the placenta of treated animals when compared to room air (*RA*) controls. This increase was reversed when animals were treated with SHS and SAGEs
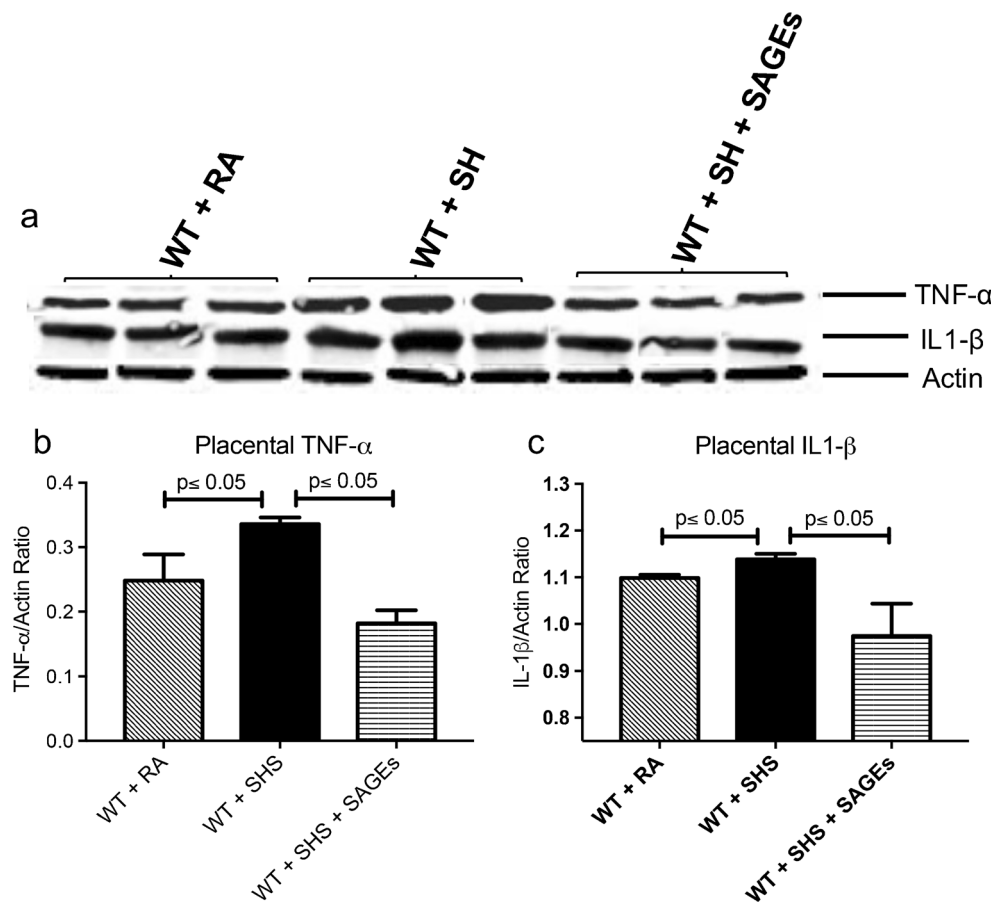
SE. Significant differences between groups were noted at $P < 0.05$.

Results

Inhibition of RAGE by SAGEs and placental and fetal weights

We first conducted in vivo studies in order to investigate the effects of SHS on fetal and placental weights. Compared to RA-exposed controls, animals treated with SHS developed significantly lighter placentas (1.13-fold, $P \le 0.0001$) and fetal weights were significantly less (7.35-fold, $P \le 0.0001$) following 4 days of SHS treatment (Fig. 1a, b).

We next sought to inhibit RAGE in wild-type mice during SHS exposure. This round of in vivo studies involved the treatment of mice with SAGEs, recently developed sulfated polysaccharide derivatives shown to significantly inhibit RAGE signaling. There was no significant recovery in placental weights from animals co-treated with SHS and SAGEs when compared to those exposed to SHS alone (Fig. 1a). However, treatment of SHS-exposed mice with SAGEs caused a significant increase in fetal weights (4.22-fold, $P \le 0.0001$) when compared with animals treated with SHS alone (Fig. 1b). Despite significant protection, fetal weights were not completely restored by SAGEs treatment when compared to RA-exposed controls (1.74-fold, $P \le 0.0001$; Fig. 1b). Importantly, no weight changes were observed when room-air control animals were treated with SAGEs when compared to non-treated controls (not shown).

RAGE expression and influence of IUGR following SHS exposure and SAGEs treatment

After examining placental and fetal weight changes stemming from SHS exposure, RAGE expression was evaluated to determine whether maternal SHS exposure elicited changes in placental protein expression. RAGE protein levels were elevated (1.13-fold, $P \leq 0.05$) with the addition of SHS when compared to RA controls (Fig. 2). This elevation was reduced when animals were treated with SHS and SAGEs (Fig. 2).

RAGE signaling molecules in the placenta of SHS exposed animals with or without SAGEs treatment

To further characterize the effects of SAGEs in the placenta, we studied cell signaling molecules associated with RAGE activation. Increased TNF-α and IL-1β expression is known to be controlled, at least in part, by RAGE signaling (Xian et al. 2015; Li et al. 2015). A characteristic western blot for TNF-α and IL-1β is shown in Fig. 3a. SHS treatment increased both TNF-α (1.34-fold, $P \leq 0.05$) and IL-1β (1.03-fold, $P \leq 0.05$) in the placenta of SHS-treated animals when compared to RA controls

(Fig. 3b, c). Interestingly, treatment with SAGEs decreased both TNF-α (1.84-fold, $P \leq 0.05$) and IL-1β (1.16-fold $P \leq 0.05$) in the SH- exposed animals when compared with the animals treated with SHS alone (Fig. 3b, c). To further investigate RAGE signal transduction in the placenta, we next looked at phosphorylated levels of ERK, JNK and p38. A characteristic western blot for ERK, JNK and p38 is shown in Fig. 4a. An increase in p-ERK activation (3.0-fold, $P \leq 0.05$) was observed in the placenta from animals treated with SHS when compared to RA controls (Fig. 4b). When SAGEs were added to the SHS animals, activated ERK was significantly diminished (3.1-fold, $P \leq 0.05$) when compared to animals treated with SHS alone (Fig. 4b). Similarly, increased activation of JNK (2.4-fold, $P \leq 0.05$) occurred following SHS exposure and treatment with SAGEs was sufficient to significantly inhibit SHS-mediated p-JNK levels (2.3-fold, $P \leq 0.05$) (Fig. 4c). In our analysis of p-P38, we observed a significant increase in p-P38 levels in SHS-exposed placentas compared to RA-exposed controls (2.1-fold, $P \leq 0.05$) and a significant restoration of p-P38 to unexposed baseline when SHS and SAGEs were co-administered (1.8-fold, $P \leq 0.05$) (Fig. 4d).
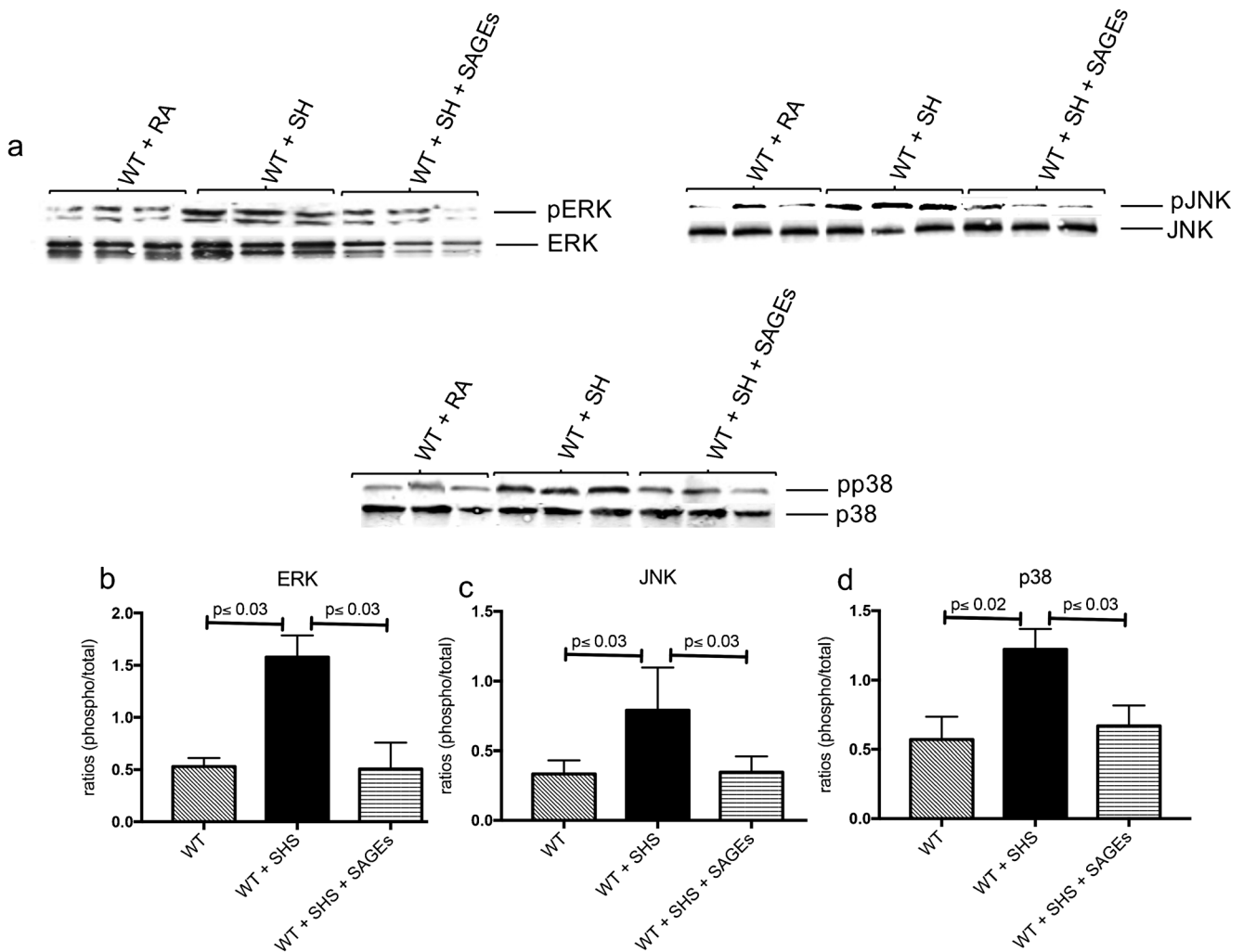
Fig. 4 Placental pERK (**a**), pJNK (**b**) and pP38 (**c**) expression during SHS-induced IUGR. A characteristic western blot is presented for each molecule in (**a**). A significant increase in pERK activation (2.61-fold, $P \leq 0.05$) was observed in placentas from animals treated with SHS when compared to RA controls. In contrast, when SAGEs were added to the SHS animals, activated ERK was significantly decreased (2.26-fold, $P \leq 0.05$) when compared to animals treated with SHS alone (**a**). A significant increase in JNK activation (1.79-fold, $P \leq 0.05$) occurred following SHS exposure when compared to RA controls. When SHS animals were co-treated with SAGEs, a significant decrease in pJNK levels (1.45-fold, $P \leq 0.05$) was observed (**b**). Similarly, a significant increase in pP38 levels in SHS exposed placentas was observed compared to RA-exposed controls (2.44-fold, $P \leq 0.05$) and a significant restoration of pP38 (1.55-fold, $P \leq 0.05$) was observed in the SHS and SAGEs-treated animals when compared to animals treated with SHS alone (**c**)

Trophoblast invasion

A cellular hallmark of diminished placental weights observed in IUGR is decreased trophoblast invasion (Arroyo and Winn 2008). Previous reports from our laboratory have already demonstrated decreased cell invasion by trophoblast cells following exposure to CSE (Mejia et al. 2016). We therefore sought to quantitatively determine the plausible protective effects of SAGEs on cultured trophoblast invasion treated with CSE. As expected, CSE treatment decreased trophoblast invasion (7.4-fold, $P < 0.02$) in culture (Fig. 5a). Diminished invasion orchestrated by CSE was completely reversed when SAGEs and CSE were concomitantly added to the media of cultured trophoblasts (Fig. 5b).

Discussion

RAGE signaling has been a major focal point in inflammatory research over the past several years. Numerous early studies sought to elucidate roles for RAGE signaling in the pulmonary apparatus (Stogsdill et al. 2013; Winden et al. 2013; Barton et al. 2014); however, roles are not clearly understood in terms of systemic expression and RAGE's relationship to non-pulmonary-related pathologies. In regards to pregnancy, recent research has demonstrated that RAGE activation may play an important role in normal placentation (Konishi et al. 2004) as RAGE is localized to the developing human trophoblast. Furthermore, current research has confirmed that increased RAGE levels are found in preeclamptic (PE) placentas
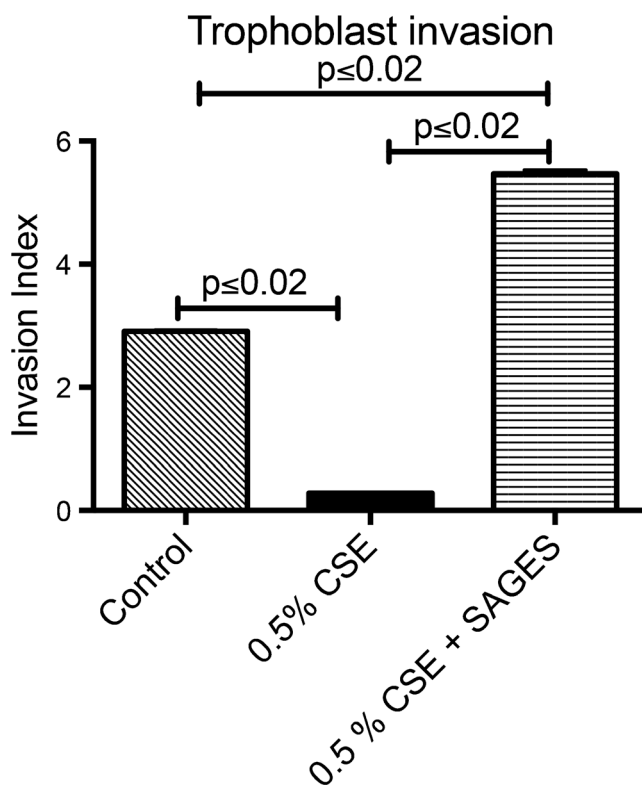
Trophoblast invasion

Fig. 5 CSE and SAGEs treatment and trophoblast invasion. Cell invasion of cultured trophoblast cells was decreased (7.4-fold, $P \leq 0.02$) during exposure to 0.5% CSE. Inhibited invasion mediated by CSE was completely reversed in trophoblasts co treated with SAGEs and CSE

(Alexander et al. 2016). Because one of the primary activators of the RAGE signaling axis is tobacco smoke exposure, we sought to examine the possible effects of SHS exposure during pregnancy. Our initial investigation revealed that the addition of SHS during embryogenesis was sufficient to cause decreased placental and fetal weights. Unsurprisingly, RAGE expression was demonstrated to be elevated by SHS. These data corroborate recent findings that the addition of SHS increases RAGE protein in a variety of tissues (Winden et al. 2014; Prasad et al. 2015).

To further confirm that RAGE signaling may be implicated in IUGR, we tested a newly developed compound that inhibits RAGE signaling. The addition of SAGEs into SHS-exposed animals during pregnancy resulted in significant protection against fetal weight loss. This positive outcome suggests that more research is needed to further evaluate the possible therapeutic benefits of RAGE targeting in the placenta. Indeed, although our data only revealed significant protection, it remains possible that a more robust study that involves a broad dose curve may reveal complete protection against fetal and placental weight loss in the context of smoke exposure.

Because our in vivo studies implicated RAGE signaling as a modulator of IUGR, we sought to characterize additional RAGE-mediated targets. ERK is a protein usually associated with proliferation. Previous studies have demonstrated that

p-ERK is elevated in patients with PE and IUGR (Bahr et al. 2014). Consistent with this data, our research demonstrated increased levels of p-ERK when animals were exposed to SHS. Furthermore, as ERK is at least partially mediated through the RAGE signaling axis, when SAGEs was administered in conjunction with SHS exposure, active ERK protein levels were significantly blocked. The p38 MAPK and JNK belong to the MAPK family of intracellular signal transducers involved in mammalian growth. In the RAGE signaling pathway, these downstream mediators activate NF-kB, which then in turn influences transcriptional regulation. Studies have demonstrated that p38 and JNK protein levels remain unchanged in IUGR; however, phosphorylated p38 and JNK levels are decreased in placental disease (Laviola et al. 2005). Our own data showed increases in overall p-P38 and p-JNK protein when control and SHS groups were compared. When SHS smoke animals were given SAGEs treatment, these animals decreased both p-P38 and p-JNK. These data suggest that these potent intermediates of inflammation and their subsequent activation are at least partially enabled through the RAGE signaling pathway. Furthermore, this assertion supports previous reports that implicates RAGE signaling in the activation of these proteins in patients with PE, IUGR and gestational diabetes (Alexander et al. 2016).

Endothelial cell dysfunction is believed to largely contribute to the pathogenesis of PE/IUGR. Inflammatory cytokines such as IL-1β and TNF-α have been shown to induce functional alterations in endothelial cells (Daneva et al. 2016) and have been found elevated in PE patients (Xian et al. 2015). It has been well documented that SHS increases TNF-α and IL-1B levels. Furthermore, research has demonstrated that RAGE signaling increases both of these pro-inflammatory cytokines, thus propagating the ability of RAGE to affect systemic inflammation. Our western blot analyses demonstrated elevated levels of TNF-α and IL-1β with the addition of SHS. However, TNF-α and IL-1β were both diminished to below the control levels when SAGEs were introduced, suggesting that this potential therapeutic may be influencing IUGR by decreasing inflammation.

A hallmark of IUGR/PE is shallow invasion of trophoblast cells (Harmon et al. 2016). Diminished invasion ultimately results in a high-resistance, low-capacity perfusion system, creating large-scale nutrient and oxygen deficiencies. Using an in vitro system, we demonstrated that the addition of SHS was sufficient to drastically decrease trophoblast cell invasion and that SAGEs treatment notably restored invasion.

We conclude that inhibition of RAGE protects against fetal and placental weight loss during SHS-induced IUGR. This conclusion is notably supported by the discovery that hindered trophoblast invasion was reversed by SAGEs treatment. Our results further suggest that there is a direct correlation between RAGE activation and the development of IUGR during SHS exposure. These studies provide insight into tobacco-mediated

IUGR progression and clarify possible avenues for alleviating placental complications during SHS exposure.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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