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Original Research Article

Nicotinamide phosphoribosyltransferase inhibitor is a potential therapeutic target in LPS-induced human trophoblast cell injury

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Abstract

Purpose: *To investigate the role of nicotinamide phosphoribosyltransferase (NAMPT) in lipopolysaccharide (LPS)-induced damage in trophoblastic HTR-8/SVneo cells (HTR8 cells), with the aim of ultimately providing new therapeutic targets of preeclampsia (PE).*
Methods: *Trophoblastic HTR-8/SVneo was cultured and treated with LPS to mimic PE in vitro, while FK866, an antagonist of NAMPT, was used to establish an inflammatory model of HTR8 cells. Western blot, enzyme-linked immunosorbent assay (ELISA) and quantitative real-time-polymerase chain reaction (qRT-PCR) were used to evaluate inflammatory response in HTR8 cells, and cell counting kit-8 (CCK8) and oxidative stress kits were performed to quantify cell activity in HTR cells.*
Results: *Compared with the control group, the administration of LPS significantly increased the expression levels of NAMPT in HTR8 cells. FK866 suppressed the expression levels of pro-inflammatory factors IL-1β, TNF-α and IL-6, and alleviated inflammation by inhibiting NAMPT-mediated NF-κB pathway. The antioxidant effect of FK866 was achieved via activation of antioxidant proteins, catalase (CAT) and glutathione (GSH).*
Conclusion: *FK866 protects HTR8 cells from LPS-induced inflammation and oxidative stress through the inhibition of NAMPT-NF-κB signaling pathway. Thus, NAMPT is a potential therapeutic target for preeclampsia (PE).*

Keywords: *HTR8/SVneo cells, Nicotinamide phosphoribosyltransferase, FK866, Inflammation, Pre-eclampsia*

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INTRODUCTION

Preeclampsia (PE), a serious disorder of pregnancy, is characterized by proteinuria and hypertension [1]. Despite the unclear pathophysiology of PE, it is well accepted that abnormal placenta development is associated with the dysregulation of the antioxidant defence system and the production of proinflammatory cytokines [2]. The pro-inflammatory environment at the maternal-fetal interface is crucial for the placentation and implantation stage, in which inflammatory factors are involved in regulating the differentiation, proliferation and invasion of trophoblast cells during placental formation [3]. Patients with preeclampsia exhibit a higher

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inflammatory state due to the release of abnormal pro-inflammatory cytokine such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [4]. This abnormal inflammatory response leads to the activation of the nuclear factor-κB (NF-κB) signaling pathway and excessive oxidative stress [3].

Nicotinamide phosphoribosyltransferase (NAMPT) was originally regarded as a cytokine that enhances the amplification and differentiation of pro-B cells, but it is also considered to be a ubiquitous evolutionarily conserved protein which is constitutionally expressed in the fetal membrane, with its largest expression being in the amniotic membrane [5]. The pro-inflammatory effect is achieved by promoting the release of IL-1β, TNF-α, IL-6 and other pro-inflammatory factors, which play important roles in the diagnosis and evaluation of inflammatory diseases. In addition, as a stress response gene, NAMPT is up-regulated under the intervention of hypoxia and inflammation [6]. Interestingly, NAMPT has been shown to promote inflammation by increasing the expression of pro-inflammatory mediators through the NF-κB pathway [7]. Another study also proved that NAMPT promotes endothelial cell angiogenesis, and enhances the permeability of the human placental amniotic membrane [5]. Therefore, NAMPT is likely to plays a key role in placental inflammation and oxidative stress during the pathogenesis of PE.

Increasing evidence indicates that FK866, a specific noncompetitive nicotinamide phosphoribosyl transferase inhibitor, exhibits an anti-inflammatory and antioxidant effect. In addition, FK866, which leads to the inhibition of the NF-κB pathway, has been proven to be protective in acute lung injury. However, there are few reports on whether FK866 affects the inflammation of human trophoblasts (HTR8 cells). Therefore, this study is aimed to assess the potential of NAMPT as a therapeutic target for preeclampsia, and the protective mechanism of FK866 against inflammation in HTR8 cells.

EXPERIMENTAL

Chemicals and reagents

Fetal bovine serum (FBS), Lipopolysaccharide (LPS), FK866, RPMI 1640 Medium and dimethyl sulfoxide (DMSO) were purchased from Sigma (St. Louis, MO, USA). Phosphate-buffered saline (PBS), penicillin-streptomycin and 0.25 % trypsin-EDTA were purchased from New Cell in China.

Cell culture and group intervention

The human trophoblast HTR8/SVneo cell line (HTR8 cells) was purchased from Nanfang Hospital Clinical Research Center (Guangzhou, China). The cells were cultured in 1640 medium supplemented with 10 % fetal bovine serum and 1 % penicillin-streptomycin, and maintained in a humidified incubator containing 5 % CO_2 and 95 % air at 37 °C. Before being treated with LPS and FK866, the cells were starved for 12 h in FBS without medium. For the treatment experiments, the cells were treated with LPS (5 μg/ml) alone for 24 h or FK866 (2 nM) 2 h before LPS treatment. After 24 h of co-culture, various indices were determined.

Cell viability assay

Cell viability was determined using a cell counting kit-8 assay (Proteintech, Rosemont, IL, USA). Following treatment with FK866 or LPS, HTR8 cells (2×10^4 cells/well) were cultured in 96-well culture plates for 24 h. Then, after treatment for 24 h, a total of 10 μL CCK-8 reagent was added in and incubated for 2 h in a 5 % CO_2 incubator at 37 °C. Finally, the optical density values were acquired with a microplate reader at 450 nm.

ELISA assay

The inflammatory factors, IL-6 and IL-1β, and sFit, released in cell supernatant, were determined using ELISA kit (R&D Systems, Minneapolis, MN, USA) based on the kit manufacturer's instructions, and the absorbance obtained with a microplate reader at 450 nm.

Western blotting analysis

After washing the cells with PBS 2 times, the total protein was extracted using a mixture of radioimmunoprecipitation assay (RIPA) lysis buffer (New cell, China) and protease inhibitor (New cell, China). Then, protein concentration was determined by a bicinchoninic acid (BCA) kit (New cell, China). Equal amounts of proteins were separated on 10 % sodium dodecyl sulfate-polyacrylamide gel electrophoresis, and then transferred onto polyvinylidene difluoride membranes (New cell, China). The membranes were blocked with 5 % non-fat milk for 1 h at room temperature, and then incubated overnight at 4 °C with primary antibodies of NAMPT (Santa Cruz, 52 KDa, Santa Cruz, CA, USA), p-NF-κB antibody (1 : 1000, 65 KDa, Affinity, Santa Clara, CA,USA), p-IKK-α antibody (1 : 1000, 85 KDa, Wanleibio, Shenyang, China), TNF-a antibody (1 : 1000, 35 KDa, Affinity, Santa Clara, CA,USA),

β-actin (1 : 5000, 42 KDa, ABMART, Shanghai, China). After washing with PBS-T three times, the membranes were incubated with horseradish peroxidase-conjugated secondary antibodies (New cell, China) at room temperature for 1 h. Finally, the bands were visualized by ECL luminescent solution (New cell, China) using a Chemiluminescence imaging system (Biolight, China) and quantified by using ImageJ software (National Institutes of Health, USA).

Quantitative real time-polymerase reaction (qRT-PCR)

The NAMPT mRNA level was determined by using qRT-PCR technology. After the treatments, the cells were washed twice with cold PBS. Total RNA was extracted from the cells using RNA extraction kit (New cell, China), while cDNA synthesis was performed by reverse transcription kit (TaKaKa, Tokyo, Japan), and amplification carried out using RT synthesis kit (TaKaKa, Tokyo, Japan). Primer sets were obtained from Huada Gene (Beijing, China). The endogenous housekeeping gene, GAPDH, was used as an internal control. The primer sequences used are shown in Table 1. The level of mRNA expression was calculated using the $2^{-\Delta\Delta Ct}$ method.

Table 1: Primer sequences of NAMPT and GAPDH used in PCR

Gene	Primer sequences (5'-3')
GAPDH	Forward: 5'-GAAGGTGAAGGTCGGAGTC-3'
	Reverse: 5'-GAAGATGGTGATGGGATTTC-3'
NAMPT	Forward: 5'-AATGTTCTCTTCACGGTGGAAAA-3'
	Reverse: 5'-ACTGTGATTGGATACCAGGACT-3'

Measurement of oxidative stress

After experimental treatment, cells were lysed with RIPA lysis buffer and centrifugated at 14,000× g for 10 min at 4 ◦C. Protein quantification was performed using a Bicinchoninic acid (BCA) protein assay kit. The activities of catalase (CAT) and glutathione (GSH) were determined using the corresponding assay kits (Nangjing Jiancheng, China). Operate according to the instructions of the kit. All results are normalized to the protein concentration of each sample.

Statistical analysis

The data were analyzed using GraphPad Prism 8 (La Jolla, CA, USA), and presented as mean ± SD. Student's t-test was used to compare the differences between the two groups, with $p < 0.05$ considered statistically significant.

RESULTS

LPS induced up-regulation of NAMPT in HTR8 cells

The expression of NAMPT increased with the increase in LPS dose, but the difference was not statistically significant when LPS concentration was greater than 5 ug/ml (Figure 1 A). Treatment with LPS at a dose of 5 ug/ml also significantly increased NAMPT protein level at different time points, but there was no statistically significant increase in expression at 48 h compared with 24 h (Figure 1 C). Therefore, in this study, HTR8 cells were incubated with LPS (5 ug/ml) for 24 h to establish the inflammation model.

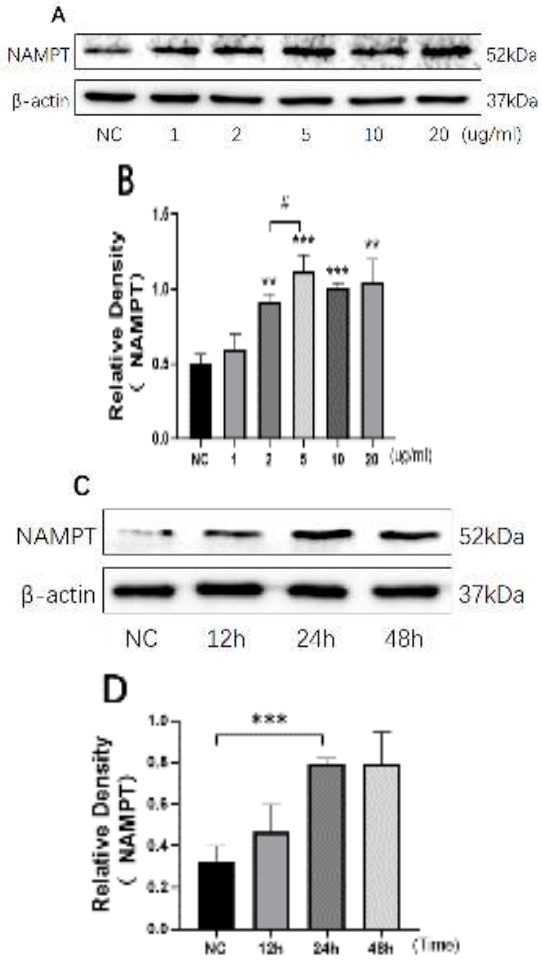

Figure 1: LPS induced the up-regulation of NAMPT in HTR8 cells. LPS increased the protein expression of NAMPT in a concentration-dependent (A) and time-dependent manner (C). B and D: Relative density of the bands corresponding to Figure 1A and C. Data are expressed as mean ± SEM (n = 3, $p < 0.05$)

FK866 reduced the expression of pro-inflammatory cytokines in HTR8 cells

Results from ELISA test showed that IL-6, IL-1β and sFit were up-regulated 0.68-fold, 1.2-fold, and 0.52-fold respectively in the LPS-treated HTR8 cells, compared to those of the control cells. However, the administration of FK866 significantly attenuated the expression of IL-6, IL-1β and sFit by 47.2, 64, and 33.4 %, respectively, in FK866+LPS group. Besides, there was no statistical significance between FK866+PBS and NC groups (Figure 2).

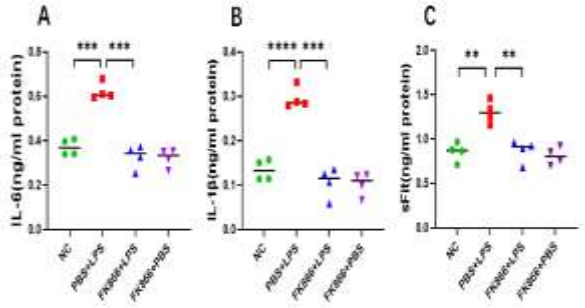

Figure 2: FK866 inhibited LPS-induced inflammation in HTR8 cells. IL-6, IL-1β and sFit levels were determined by ELISA with four samples in each group (A-C). Data are expressed as mean ± SEM (n=4, $p < 0.05$)

FK866 inhibited the LPS-induced NF-κB pathway activation in HTR8 cells

Western blot results showed that p-IKKα, p-NF-κB, and TNF-α were significantly up-regulated 1.58-fold, 0.5-fold, and 0.85-fold respectively in the LPS-treated group compared to those of the NC group (Figure 3). FK866 significantly reduced the increase of p-IKKα, p-NF-κB, and TNF-α in HTR8 cells to 51.5 %, 46.9 %, and 41 %, respectively, when compared to those with the LPS-treated group. Interestingly, WB results showed that the overexpression of NAMPT in inflammation response was inhibited by the intervention of FK866, and reduced by 69.8 %. Additionally, the total RNA expression level of NAMPT was upregulated 2.42-fold due to treatment with LPS when compared to that in the control group, but also reduced by 61.3 % after pretreatment with FK866 (Figure 4). FK866 alone had no effect on the expression of NAMPT.

FK866 attenuated the LPS-induced oxidative stress injury and improved cell viability in HTR8 cells

After treatment with LPS, the levels of GSF and CAT indicators related to oxidative stress were reduced to 47.8 and 44.3 %, respectively, but significantly increased in the FK866+LPS group. To further determine whether the inhibition of NAMPT expression alleviates LPS-induced cell damage, the activity of HTR8 cells was measured. The results showed that cell viability was decreased by 38.4 % in the LPS group compared to that of control group. However, administration of FK866 improved cell viability, as the level was 38.2 % higher than the PBS+LPS group (Figure 6). These results indicate that FK866 improved oxidative stress damage induced by LPS and cell viability. In addition, there was no statistical significance between the NC group and the PBS+FK866 group.

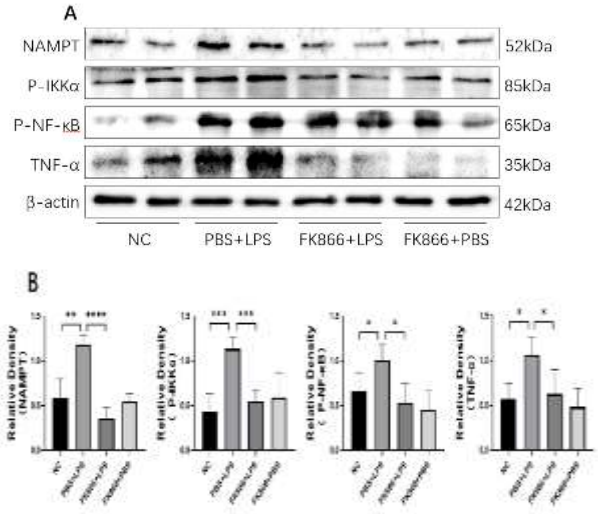

Figure 3: Effect of FK866 on NMPT-NF-κB pathway protein in HTR8 cells. (A) Western blot results showed the levels of NAMPT, p-IKKα, p-NF-κB, and TNF-α in HTR8 cells from each group. (B) Relative densities of NAMPT, p-IKKα, p-NF-κB, and TNF-α, based on statistical analysis of the results of 2 independently repeated experiments. Data are based on expressed as the mean ± SEM (n=4, $p < 0.05$)

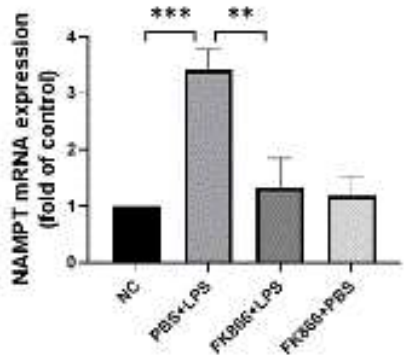

Figure 4: MRNA expression levels of NAMPT following treatment with FK866. Relative expression of NAMPT in HTR8 cells. Data are expressed as mean ± SEM (n = 3, $p < 0.05$)

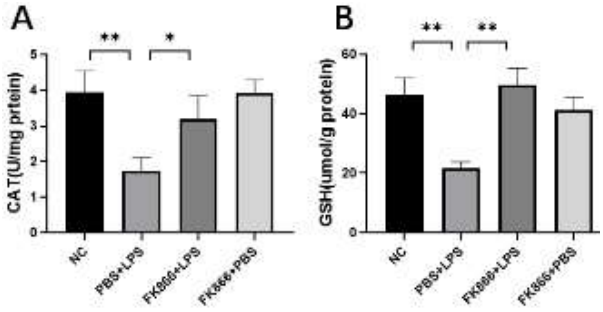

Figure 5: FK866 attenuated LPS-induced oxidative stress in HTR8 cells. CAT (A) and GSH (B) levels. Data are expressed as the mean ± SEM (n = 4, $p < 0.05$).

DISCUSSION

Preeclampsia is usually associated with elevated expression levels of pro-inflammatory cytokines and excessive oxidative stress, leading to abnormal development of placental blood vessels and interstitium [8,9]. Increased levels of inflammation caused by infection is one of the most common factors in PE, which affects the safety of the mother and offspring [9]. However, the specific pathogenesis of PE is still unclear. In this study, FK866, as a non-specific inhibitor of NAMPT with anti-inflammatory effects actions, ameliorated LPS-induced inflammation and oxidative stress in HTR8 cells by antagonizing NAMPT-mediated NF-κB signaling pathway.

Lipopolysaccharide (LPS) is secreted by the cell wall of *Gram*-negative bacilli, which causes inflammatory responses in various organ systems of the human body [10]. The NF-κB pathway plays an important role in both normal and pathological processes, including inflammation, apoptosis and oxidative stress. In addition, NF-κB pathway, an important regulatory route, is involved in placental development and vascular remodeling during pregnancy [3,11]. NF-κB activation is reportedly significantly increased in preeclamptic placentae compared with that in normal placentae. The activation of NF-κB pathway leads to the phosphorylation of NF-κB subunit and the binding of target genes, thus promoting the expressions and release of inflammatory cytokines and regulating the inflammatory response. What's more, P-NF-κB and p-IKKα are important phosphorylated products after activation of NF-κB pathway [12,13]. In this study, LPS significantly increased the expression of p-NF-κB, p-IKKα, TNF-α, IL-1 IL-1β, and IL-6 after LPS stimulation of placental trophoblast cells, which results were consistent with the results of Guanlin Li [14].

Activation of NF-κB pathway was involved in the LPS-induced inflammatory response in HTR8 cells. Besides, one study has shown that NAMPT was also associated with placental angiogenesis [5]. Therefore, this study also explored the expression of angiogenesis-related sFit factor, one of the markers of elevated expression in PE, which blocks angiogenesis by antagonizing VEGF expression [15,16]. Results showed that the expression of sFit was significantly increased in LPS-induced placental trophoblast inflammation, indicating that placental angiogenesis was limited in inflammatory environments.

The mechanism of action of NAMPT is mainly manifested in two forms: intracellular and extracellular. NAMPT is involved in cellular NAD synthesis related to oxidative stress. NAMPT also enhanced the expression and release of extracellular inflammatory cytokines such as TNF-a, IL-1, and IL-6. Another study has shown that the terminal promoter of NAMPT contains NF-κB binding sites, and may regulate inflammatory responses by activating the NF-κB pathway [7].

Current studies on NAMPT mainly focus on human umbilical vein endothelial cells and alveolar type II epithelial cells, and few studies on placental trophoblast. FK866 is an important nonspecific inhibitor of NAMPT, which can effectively restrain the activation of NAMPT pathway [17]. In the present study, treatment with FK866, the expression levels of phosphorylated proteins associated with NF-κB pathway were inhibited in the inflammatory model of HTR8 cells, and the expression levels of downstream proteins such as TNF-a, IL-1β and IL-6 cytokine, were down-regulated significantly. These results indicate that NAMPT, as the upstream protein of the NF-κB pathway, is involved in the regulation of inflammation in HTR8 cells. Moreover, the expression of sFit was decreased by FK866, implying that antagonizing NAMPT may protect the formation of placental blood vessel. Interestingly, this study found that FK866, an NAMPT antagonist, inhibited the expression of NAMPT. There is a hypothesis that FK866 inhibited the inflammatory cascade amplification effect by inhibiting the release of pro-inflammatory factors, leading to the decreased expression of NAMPT. However, the specific mechanism of action needs to be investigated in further experiments.

Numerous studies have reported that oxidative stress and inflammation are mutually reinforcing, and the elevated levels of inflammation and oxidative stress in the placenta are also major

features of PE [2,18,19]. The cells are known to have antioxidant defense mechanisms to protect against oxidative stress. This system is comprised of antioxidants, such as glutathione (GSH) and superoxide dismutase (SOD), which scavenge ROS to prevent possible cell damage [20]. In this study, GSH and CAT were selected as indices of intracellular oxidative stress. Expression of CAT and GSH decreased after suppressing the function of NAMPT, and this improved the antioxidant capacity of the cells. Therefore, FK866 exerted an antioxidant effect on scavenging free radicals, which is consistent with the findings of a previous study [21]. Besides, flow cytometry studies confirmed that FK866 improved cell viability in HTR8 cells treated with LPS. Thus, overall, the results indicate that by inhibiting the activation of NAMPT pathway, oxidative stress damage in the inflammatory response of HTR8 cells were reduced, suggesting that NAMPT could be a new target for the treatment of preeclampsia.

Limitations of the study

However, there are some limitations in this study. Firstly, Human placental trophoblast cells have the limitation to fully simulate human placental function. It is necessary to ascertain whether NAMPT is involved in the pathological process of PE through regulating NF-κB pathway *in vivo*. It also needs to be verified whether NAMPT is involved in PE through Toll-R4, P38-MAPK and other classical inflammatory pathways, and whether NF-κB is involved in these pathways.

CONCLUSION

The findings of this study demonstrate that FK866 alleviates LPS-induced inflammation of HTR8 cells by enhancing antioxidant capacity and antagonizing NAMPT-NF-κB signaling pathway. Furthermore, NAMPT is a potential new therapeutic target for preeclampsia, but this needs to be further investigated *in vivo.*

DECLARATIONS

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Funding

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Zuoman Zhang and Lijun Tang contributed equally to this work.

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