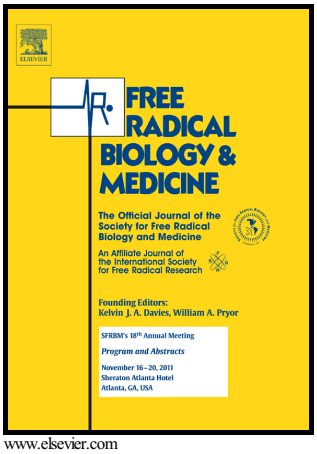

www.elsevier.com

Aspirin prevents TNF-α-induced endothelial cell dysfunction by regulating the NF-κB-dependent miR-155/eNOS pathway: Role of a miR-155/eNOS axis in preeclampsia

Joohwan Kim, Kyu-Sun Lee, Ji-Hee Kim, Dong-Keon Lee, Minsik Park, Seunghwan Choi, Wonjin Park, Suji Kim, Yoon Kyoung Choi, Jong Yun Hwang, Jongseon Choe, Moo-Ho Won, Dooil Jeoung, Hansoo Lee, Sungwoo Ryoo, Kwon-Soo Ha, Young-Guen Kwon, Young-Myeong Kim

PII: S0891-5849(17)30010-2
DOI: http://dx.doi.org/10.1016/j.freeradbiomed.2017.01.010
Reference: FRB13166

To appear in: *Free Radical Biology and Medicine*

Received date: 2 May 2016
Revised date: 28 December 2016
Accepted date: 6 January 2017

Cite this article as: Joohwan Kim, Kyu-Sun Lee, Ji-Hee Kim, Dong-Keon Lee Minsik Park, Seunghwan Choi, Wonjin Park, Suji Kim, Yoon Kyoung Choi, Jong Yun Hwang, Jongseon Choe, Moo-Ho Won, Dooil Jeoung, Hansoo Lee, Sungwoo Ryoo, Kwon-Soo Ha, Young-Guen Kwon and Young-Myeong Kim, Aspirin prevents TNF-α-induced endothelial cell dysfunction by regulating th NF-κB-dependent miR-155/eNOS pathway: Role of a miR-155/eNOS axis i preeclampsia, *Free Radical Biology and Medicine* http://dx.doi.org/10.1016/j.freeradbiomed.2017.01.010

Aspirin prevents TNF-α-induced endothelial cell dysfunction by regulating the NF-κB-dependent miR-155/eNOS pathway: Role of a miR-155/eNOS axis in preeclampsia

Joohwan Kim[a], Kyu-Sun Lee[a], Ji-Hee Kim[a], Dong-Keon Lee[a], Minsik Park[a], Seunghwan Choi[a], Wonjin Park[a], Suji Kim[a], Yoon Kyoung Choi[a], Jong Yun Hwang[b], Jongseon Choe[c], Moo-Ho Won[d], Dooil Jeoung[e], Hansoo Lee[f], Sungwoo Ryoo[f], Kwon-Soo Ha[a], Young-Guen Kwon[g], Young-Myeong Kim[a*]

[a]Departments of Molecular and Cellular Biochemistry, Kangwon National University School of Medicine, Chuncheon, Gangwon-do 24341, South Korea

[b]Departments of Obstetrics and Gynecology, Kangwon National University School of Medicine, Chuncheon, Gangwon-do 24341, South Korea

[c]Departments of Immunology, Kangwon National University School of Medicine, Chuncheon, Gangwon-do 24341, South Korea

[d]Departments of Neurobiology, Kangwon National University School of Medicine, Chuncheon, Gangwon-do 24341, South Korea

[e]Departments of Biochemistry, College of Natural Sciences, Kangwon National University, Chuncheon, Gangwon-do 24341, South Korea

[f]Departments of Biology, College of Natural Sciences, Kangwon National University, Chuncheon, Gangwon-do 24341, South Korea

[g]Department of Biochemistry, College of Life Science and Biotechnology, Yonsei University, Seoul 03722, South Korea

[*]Corresponding authors. ymkim@kangwon.ac.kr

Abstract

Preeclampsia is an inflammatory disease with endothelial cell dysfunction that occurs via decreased endothelial nitric oxide synthase/nitric oxide (eNOS/NO) activity. Aspirin reduces the incidence of hypertensive pregnancy complications. However, the underlying mechanism has not been clearly explained. Here, we found that tumor necrosis factor (TNF)-α, *microRNA (miR)-155*, and eNOS levels as well as endothelial redox phenotype were differentially regulated in preeclamptic patients, implying the involvement of TNF-α- and redox signal-mediated miR-155 biogenesis and eNOS downregulation in the pathogenesis of preeclampsia. Aspirin prevented the TNF-α-mediated increase in *miR-155* biogenesis and decreases in eNOS expression and NO/cGMP production in cultured human umbilical vein endothelial cells (HUVECs). Similar effects of aspirin were also observed in HUVECs treated with H_2O_2. The preventive effects of aspirin was associated with the inhibition of nuclear factor-κB (NF-κB)-dependent *MIR155HG* (*miR-155* host gene**)** expression. Aspirin recovered the TNF-α-mediated decrease in wild-type, but not mutant, eNOS 3′-untranslated region reporter activity, whose effect was blocked by miR-155 mimic. Moreover, aspirin prevented TNF-α-mediated endothelial cell dysfunction associated with impaired vasorelaxation, angiogenesis, and trophoblast invasion, and the preventive effects were blocked by miR-155 mimic or an eNOS inhibitor. Aspirin rescued TNF-α-mediated eNOS downregulation coupled with endothelial dysfunction by inhibiting NF-κB-dependent transcriptional *miR-155* biogenesis. Thus, the redox-sensitive NF-κB/*miR-155*/eNOS axis may be crucial in the pathogenesis of vascular disorders including preeclampsia.

Graphical abstract