

# Accepted Manuscript

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PII: S0006-291X(17)31567-X

DOI: [10.1016/j.bbrc.2017.08.022](https://doi.org/10.1016/j.bbrc.2017.08.022)

Reference: YBBRC 38297

To appear in: *Biochemical and Biophysical Research Communications*

Received Date: 26 June 2017

Revised Date: 0006-291X June 0006-291X

Accepted Date: 6 August 2017

Please cite this article as: A. Mukhuty, C. Fouzder, S. Mukherjee, C. Malick, S. Mukhopadhyay, S. Bhattacharya, R. Kundu, Palmitate induced Fetuin-A secretion from pancreatic  $\beta$ -cells adversely affects its function and elicits inflammation, *Biochemical and Biophysical Research Communications* (2017), doi: 10.1016/j.bbrc.2017.08.022.

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**Palmitate induced Fetuin-A secretion from pancreatic  $\beta$ -cells adversely affects its function and elicits inflammation**

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**ABSTRACT**

Islets of type 2 diabetes patients display inflammation, elevated levels of cytokines and macrophages. The master regulator of inflammation in the islets is free fatty acids (FFA). It has already been reported that FFA and TLR4 stimulation induces pro-inflammatory factors in the islets. In this report we demonstrate that excess lipid triggers Fetuin-A (FetA) secretion from the pancreatic  $\beta$ -cells. Palmitate treatment to MIN6 cells showed significantly elevated FetA levels in respect to their controls. Fatty acid induces the FetA gene and protein expression in the pancreatic  $\beta$ -cells via TLR4 and over-expression of NF- $\kappa$ B. In the NF- $\kappa$ B knocked down MIN6 cells palmitate could not trigger FetA release into the incubation medium. These results suggest that NF- $\kappa$ B mediates palmitate stimulated FetA secretion from the pancreatic  $\beta$ -cells. Blocking the activity of TLR4 by CLI-095 incubation or TLR4 siRNA restored insulin secretion which confirmed the role of TLR4 in FFA-FetA mediated pancreatic  $\beta$ -cell dysfunction. Palmitate mediated expression of NF- $\kappa$ B enhanced inflammatory response through expression of cytokines such as IL-1 $\beta$  and IL-6. These results suggest that FFA mediated FetA secretion from pancreatic  $\beta$ -cells lead to their dysfunction via FFA-TLR4 pathway. FetA thus creates an inflammatory environment in the pancreatic islets that can become a possible cause behind pancreatic  $\beta$ -cell dysfunction in chronic hyperlipidemic condition.

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