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# NOS1-derived nitric oxide promotes NF-kB stability and transcriptional activity by inhibiting suppressor of cytokine signaling (SOCS-1) in response to TLR4 activation

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Nitric oxide synthases are a family of enzymes that catalyze the production of nitric oxide (NO) from L-arginine. NO is an important cellular signaling molecule, having essential roles in many biological processes including the control of blood pressure, regulation of neuronal activity and immune responses. $NOS_3$ (endothelial NOS or e NOS) and $NOS_2$ (inducible NOS or I NOS) have been appreciated as mediators of inflammatory processes. However, considerably less is known about the role of $NOS_1$ (neuronal NOS or n NOS) in inflammation. We have uncovered an important role for this enzyme in regulating TLR4 signaling. We demonstrate that in contrast to the enhanced susceptibility of $NOS_2^{-/-}$ and $NOS_3^{-/-}$ mice to LPS, $NOS_1^{-/-}$ mice are, in fact, more resistant to LPS-induced lethality and tissue injury. We demonstrate that the loss of $NOS_1$ attenuates TLR4-stimulated cytokine production and NF-κB activity *in vivo* and *in vitro*. Macrophages from $NOS_1^{-/-}$ animals demonstrate an LPS-induced decrease in protein levels of the p65 subunit of NF-κB. This decrease in p65 protein correlates with an increase in protein levels of suppressor of cytokine signaling-1 (SOCS1) and increased physical association between SOCS1 and p65. On studying the mechanism of NOS1-regulation of inflammation we found that an early pulse of $NOS_1$-derived NO was required to stabilize p65 in the nucleus of macrophages via the inhibitory S-nitrosation of suppressor of Cytokine Signaling-1 (SOCS1). $NOS_1$-derived NO through nitrosation of Cys147 and Cys179 on SOCS1 permits p65-mediated pro-inflammatory gene transcription and is essential for the mechanism of inflammation. Taken together, our results demonstrate that $NOS_1$ is a fundamental early regulator of gene transcription of the inflammatory response thereby heavily impacting the course, type and duration of the inflammatory process.

## Biography

Mirza Saqib Baig has a research background in innate immunity and inflammation. Presently, he is working as a Scientist at the Department of Bioscience and Bioengineering, Indian Institute of Technology (IIT), India. Dr. Baig earned his Ph.D. from Central Drug Research Institute, India in 2009. Further, he underwent his postdoctoral training at the Department of Medicine, University of Illinois at Chicago and Mayo Clinic, Rochester, MN, USA. Dr. Baig has been honored with various international and national awards. He has published several research articles in peer-reviewed international Journals, including his recent cutting-edge findings in the Journal of Experimental Medicine (JEM).

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