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www.elsevier.com

PII: S0891-5849(16)00005-8
DOI: http://dx.doi.org/10.1016/j.freeradbiomed.2016.01.004
Reference: FRB12715

To appear in: *Free Radical Biology and Medicine*

Received date: 29 July 2015
Revised date: 17 December 2015
Accepted date: 8 January 2016

Cite this article as: Deepika Awasthi, Sheela Nagarkoti, Amit Kumar, Megha Dubey, Abhishek Kumar Singh, Priya Pathak, Tulika Chandra, Manoj Kumar Barthwal and Madhu Dikshit, Oxidised LDL induced extracellular trap formation in human neutrophils via TLR-PKC-IRAK-MAPK and NADPH-oxidase activation, *Free Radical Biology and Medicine,* http://dx.doi.org/10.1016/j.freeradbiomed.2016.01.004

Oxidised LDL induced extracellular trap formation in human neutrophils via TLR-PKC-IRAK-MAPK and NADPH-oxidase activation

Deepika Awasthi[1], Sheela Nagarkoti[1], Amit Kumar[1], Megha Dubey[1], Abhishek Kumar Singh[1], Priya Pathak[1], Tulika Chandra[2], Manoj Kumar Barthwal[1] and Madhu Dikshit[1*]

[1]Pharmacology Division, CSIR-Central Drug Research Institute;

[2]Department of Transfusion Medicine, King George's Medical University, Lucknow, India.

***Corresponding author:** Madhu Dikshit, Director, CSIR-Central Drug Research Institute, B.S. 10/1, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow- 226031, India. Tel: +91522-2771940; Fax: +91522-2771941. E-mail: madhu_dikshit@cdri.res.in, madhudikshit@yahoo.com

Abstract

Neutrophil extracellular traps (NETs) formation was initially linked with host defence and extracellular killing of pathogens. However, recent studies have highlighted their inflammatory potential. Oxidized low density lipoprotein (oxLDL) has been implicated as an independent risk factor in various acute or chronic inflammatory diseases including systemic inflammatory response syndrome (SIRS). In the present study we investigated effect of oxLDL on NETs formation and elucidated the underlying signalling mechanism. Treatment of oxLDL to adhered PMNs led to a time and concentration dependent ROS generation and NETs formation. OxLDL induced free radical formation and NETs release were significantly prevented in presence of NADPH oxidase (NOX) inhibitors suggesting role of NOX activation in oxLDL induced NETs release. Blocking of both toll like receptor (TLR) -2 and 6 significantly reduced oxLDL induced NETs formation indicating requirement of both the receptors. We further identified Protein kinase C (PKC)-Interleukin-1 receptor associated kinase (IRAKs)-mitogen-activated protein kinase (MAPK) pathway as downstream intracellular signalling mediators involved in oxLDL induced NETs formation. OxLDL components such as oxidized phospholipids (lysophosphatidylcholine (LPC) and oxidized 1-palmitoyl-2-arachidonyl-sn- glycero-3-phosphorylcholine (oxPAPC)) were most potent NETs inducers and might be crucial for oxLDL mediating NETs release. Other components like, oxysterols, malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) were however less