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Editorial

Interplay between Saturated Free Fatty Acids and mmLDL Induces Inflammation in LPS-stimulated Macrophages

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We have followed an article titled "Nlrp3, Csf3, and Edn1 in Macrophage Response to Saturated Fatty Acids and Modified Low-Density Lipoprotein" by Lee *et al.*[1] with profound interest. The study showed that saturated fatty acids, palmitic acid (PA) in particular, and minimally modified low-density lipoprotein (mmLDL) induce the secretion of pro-inflammatory cytokines through activation of the extracellular signal-regulated kinase/mitogen-activated protein kinase pathway in lipopolysaccharide (LPS)-stimulated macrophages. Further, the authors identified several genes targeted by PA or mmLDL via RNA sequencing of LPS-stimulated macrophages. Although this study provides insights into the detailed molecular mechanism underlying the interplay between metabolic stress and inflammation, the insights from this study must be analyzed in the context of several concerns that have been discussed below.

NLR family pyrin domain containing 3 (NLRP3) is an essential regulator of adaptive immune response and its expression is induced by endogenous cytokines or microbial molecules through binding to Toll-like receptor (TLR), interleukin-1 receptor (IL-1R), and tumor necrosis factor receptor (TNFR).[2] Activation of NLRP3 via K^+ efflux, Ca^{2+} signaling, and mitochondrial reactive oxygen species (mtROS) triggers caspase-1 activation and subsequent secretion of IL-1β and IL-18.[2][3] As NLPR3 expression is known to be regulated by post-translational modifications (PTM),[2][4] the increase in NLRP3 messenger RNA (mRNA) level is not sufficient to promote its activation. However, this aspect has been overlooked in this study, with the authors only reporting an increase in NLRP3 at the mRNA level in LPS-stimulated macrophages treated with PA or mmLDL. Therefore, it is crucial to estimate the NLRP3 protein levels to gain comprehensive insights into the action of PA or mmLDL in LPS-stimulated macrophages.

Further, this study identified several genes (*Nlrp3*, *Csf3*, and *Edn1*) associated with inflammation in LPS-treated macrophages that are targeted by PA or mmLDL.[1] In this context, it must be noted that the activation of inflammatory responses is closely related with diverse sets of metabolic disease conditions, and the intricate interplay between inflammation and metabolic stress is mechanistically complex. In particular, PA, a free fatty

acid (FFA), has been widely reported to be a key regulator of insulin resistance and NLRP3 inflammasome formation in obesity models.[5][6] Recent research has highlighted the role of PA as a TLR agonist that leads to the direct activation of the NLRP3 inflammasome and onset of insulin resistance in obesity models.[7][8] Further, PA has been shown to induce insulin resistance through regulation of the nuclear factor (NF)-κB/insulin receptor substrate 1 axis in hepatocytes (Huh7 cells) and liver of high-fat diet-fed mouse.[5] Therefore, the interplay between FFA-mediated activation of inflammation and the pathophysiology of metabolic disease must be considered while interpreting results from the study under consideration.

mmLDL—a product of progressive low-density lipoprotein (LDL) oxidation—and oxidized LDL have been recognized as biomarkers of inflammation in human macrophages.[9]
The authors have previously reported that mmLDL induces the secretion of chemokines (including chemokine [C-X-C motif] ligand 2) and TNFα in LPS-treated macrophages in the presence of PA.[10] Here, they report the regulation of genes by mmLDL in LPS-stimulated macrophages and elucidate the detailed mechanism underlying mmLDL-mediated inflammatory response to LPS in macrophages. Taken together, these insights are expected to contribute to the development of approaches for the treatment of inflammatory diseases.[1]

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