Growth hormone-releasing peptides, CD36, and stimulation of cholesterol efflux: cyclooxygenase-2 is the link

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This editorial refers to ‘CD36-mediated cholesterol efflux is associated with PPARγ activation via a MAPK-dependent COX-2 pathway in macrophages’ by K. Bujord et al., pp. 457–464, this issue.

Atherosclerosis, a chronic inflammatory disease of the vasculature, is the primary cause of morbidity and mortality in industrialized countries. Endothelial dysfunction/activation is a major initiating event in atherosclerosis, which leads to the recruitment of circulating monocytes, their differentiation into macrophages, and their subsequent transformation into lipid-loaded foam cells through the uptake of modified lipoproteins, particularly oxidized LDL (oxLDL). Foam cells play a key role in this disease by stimulating the production of inflammatory cytokines, chemokines, and reactive oxygen species at the vessel wall. Foam cell formation can be regarded as a balance between the uptake of modified lipoproteins, through scavenger receptors such as CD36, and the efflux of cholesterol, primarily via ATP-binding cassette transporters (ABC) A1 and G1. Several factors are known to control macrophage cholesterol uptake and efflux, including cytokines, bioactive peptides and activators of nuclear receptors, particularly peroxisome proliferator-activated receptors (PPARs).

PPARs are ligand-activated transcription factors that regulate glucose and lipid homeostasis along with inflammatory responses, thereby representing excellent therapeutic targets for limiting atherosclerosis. PPARs are activated by several fatty acids and fatty acid-derived products along with synthetic agonists, including fibrates (PPARα) and thiazolidinediones (PPARγ) used in the treatment of dyslipidaemia and type 2 diabetes, respectively. Activation of PPARα and γ inhibits foam cell formation by suppressing lipid uptake and storage and stimulating cholesterol trafficking and efflux. A major pathway for the PPARα/γ-mediated cholesterol efflux involves the expression of liver-X-receptor (LXR)-α, which then induces the transcription of the ABCA1 gene.

Bujord et al. provide insight into the mechanisms underlying the promotion of macrophage cholesterol efflux by a peptide ligand of CD36 through this PPAR-LXR-ABCA1 pathway. The study relates to EP 80317, an analogue of growth hormone releasing-peptides (GHRPs), which stimulate growth hormone (GH) release via binding to the GH secretagogue-receptor 1a (GHS-R1a), a G protein-coupled receptor whose endogenous ligand is now recognized to be ghrelin. Several studies have shown that GHRPs have GH-independent cardioprotective properties, and the identification that they serve as ligands for CD36 suggested that interference with oxLDL binding might represent a potential mechanism. Subsequent studies showed that hexarelin, a synthetic GHRP, enhances macrophage cholesterol efflux and the expression of ABCA1 and ABCG1 genes through the activation of PPARγ, and this requires its binding to both CD36 and GHS-R1a. To dissociate between the two receptor-binding activities, EP 80317, a GHRP analogue with CD36-binding activity but devoid of GHS-R1a interaction and GH-releasing activity, has been used in several studies in relation to atherosclerosis. Administration of EP 80317 was found to protect apolipoprotein E (apoE)-deficient mice, but not apoE/CD36 double knockout mice, from developing atherosclerotic lesions through a reduction of oxLDL internalization and the activation of the PPARγ-LXRα-ABCA1 pathway in macrophages.

The current study describes the molecular mechanisms underlying the EP 80317-mediated cholesterol efflux. Using peritoneal macrophages from apoE-deficient mice along with the murine J774 cell line, which expresses low levels of apoE, the authors show that EP 80317 activates PPARγ and stimulates cholesterol and phospholipid efflux in an ABCA1- and ABCG1-dependent manner. More interestingly, using a combination of biochemical and pharmacological approaches, they demonstrate that EP 80317 mediates its actions through the activation of extracellular signal-regulated kinase (ERK)1/2. This leads to increased expression of cyclooxygenase-2 (COX-2), which converts arachidonic acid to several bioactive lipids such as...
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cations in the light of two recent publications that also
atherosclerosis will need to be thoroughly investigated.
Furthermore, as this and several previous studies have
used synthetic GHRPs (EP 80317 and hexarelin), the exact
roles and mechanism of action of endogenous GHRPs in
atherosclerosis will need to be thoroughly investigated.
Despite these limitations, the findings have wider
implications in the light of two recent publications that also
show a key role for this ERK1/2-COX-2-15d-PGJ2-PPAR
pathway in other settings, thereby suggesting that it might
represent a common anti-atherogenic mechanism.10,11
First, the pathway (with an additional requirement for p38
mitogen-activated protein kinase, p38 MAPK) was found
to be necessary for statin-mediated attenuation of
lipopolysaccharide-induced inflammatory responses in
macrophages.10 Because EP 80317 has recently been found
to also reduce the expression of several inflammatory
markers in apoE, but not apoE and CD36 double knockout
mice,12 it would be of interest to determine whether such
an action is also mediated through this pathway. In addition,
it is possible that the complex and conflicting function of
CD36 in vivo13 could be in part due to the anti-atherogenic
actions of ligands such as GHRPs. Secondly, oxLDL has been
shown to activate PPARα/γ in macrophages through
intracellular 15d-PGJ2 production via ERK1/2-dependent
COX-2 expression, and it was speculated that these effects
might represent a potential protective mechanism to
control excess atherosclerotic progression.11 Taken
together, these studies suggest that several factors that
induce COX-2 expression might also act protectively, at
least in part, through the activation of PPARs. Indeed, selec-
tive COX-2 inhibitors are associated with enhanced cardio-
vascular events in humans,14 and COX inhibitors have been
found to promote macrophage foam cell formation and to
inhibit the expression of key genes implicated in cholesterol
efflux.15
In summary, a cross-talk mechanism involving MAPK-
dependent activation of COX-2 and leading to the pro-
duction of an endogenous PPAR ligand has now been
identified to attenuate two key atherogenic actions in
macrophages: the inflammatory response and foam cell
formation. More research needs to be carried out on this
signalling pathway, given its potential for the treatment of
atherosclerosis.

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