Myocardial 15-Epi-lipoxin A₄ Generation Provides a New Mechanism for the Immunomodulatory Effects of Statins and Thiazolidinediones

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“In matters of observation, chance favors only the prepared mind.”

his famous maxim of Louis Pasteur, spoken in 1854 during his inaugural lecture as Professor and Dean at the University of Lille, can be applied today to the fortuitous observation that hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors, in addition to their designed lipid-lowering effects, display a fascinating array of antiinflammatory properties. Post hoc analyses of the West of Scotland Coronary Prevention Study (WOSCOPS) population, and more recently the Cholesterol and Recurrent Events (CARE), Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL), Long-term Intervention With Pravastatin in Ischemic Disease (LIPID), and Heart Protection Study (HPS) trials, have all found benefits conferred by statins that are independent of low-density lipoprotein cholesterol–lowering alone.¹ Only through careful analyses of early clinical trials of statins administered for lowering cholesterol and cardiovascular events did scientists uncover additional benefit for these agents in cardiac protection beyond their ability to reduce cholesterol synthesis. Inflammation and immune responses are now appreciated to play pivotal roles in the pathobiology of atherosclerosis,² and recent clinical and basic investigations have uncovered important immunomodulatory roles for statins.³ Of interest, the peroxisome proliferator–activated receptor family of transcription factors is activated by and cooperates with statins in their antiinflammatory actions. In this issue of Circulation, Birnbaum and colleagues⁴ now show evidence for 15-epi-lipoxin (LX)₄₄ generation from rat liver that is further induced by concomitant aspirin ingestion by 128 healthy subjects, plasma aspirin-triggered 15-epi-LXA₄ levels were increased by 81 mg of aspirin daily and inversely correlated with thromboxane.⁵ Stable analogues of 15-epi-LXA₄ have been prepared that display potent in vivo antiinflammatory properties. Angioplasty initiates LX formation that is further induced by concomitant aspirin or pioglitazone triggered LX₄₄ generation that was inhibited by selective pharmacological targeting of either COX-2 or 5-LO. Both atorvastatin and pioglitazone induced...
COX-2 expression and together had an additive impact on 15-epi-LXA₄ generation. Although these findings of immunoreactive 15-epi-LXA₄ formation were not validated by either physical means of detection or identification of the biosynthetic precursor 15R-HETE, they appear to indicate that aspirin is not a prerequisite for COX-2–derived 15-epi-LXA₄ formation. The authors speculate on potential mechanisms, including posttranslational modification of COX-2 by S-nitrosylation, a process they have recently identified as integral to atorvastatin-mediated cardioprotection from infarction. Indeed, aspirin-triggered 15-epi-LXA₄ induces nitric oxide production from both endothelial and inducible nitric oxide synthases for antiinflammation. In view of the present results, aspirin-initiated nitric oxide could provide an amplifying mechanism for continued 15-epi-LXA₄ generation by S-nitrosylation of statin-induced COX-2, even if pharmacological or temporal and spatial factors limit the availability of new COX-2 to aspirin. Complete inhibition of 15-epi-LXA₄ production by COX-2 inhibition diminishes the likelihood of important involvement of cytochrome p450 enzymes in statin-induced myocardial 15-epi-LXA₄.

Both LXA₄ and 15-epi-LXA₄ interact with LXA₄ receptors, termed ALX. This G protein–coupled receptor is widely expressed in human and rodent tissues, and the rat receptor was recently characterized. Of interest, antiinflammatory signaling via ALX is mechanistically linked to polyisoprenyl phosphates (Figure). Although HMG-CoA reductase inhibition by statins reduces mevalonate formation, continued flux through this pathway is critical for the generation of isoprenoids that are vital for diverse cellular functions (reviewed in Schonbeck and Libby). Complete inhibition of isoprenoid biosynthesis by statins is toxic, and isoprenoid levels are preserved in even severe mevalonic aciduria (<1% mevalonate kinase activity), a genetic disease that is the functional equivalent of HMG-CoA reductase inhibitor therapy for polyisoprenyl phosphate biosynthesis. In addition to sterols, polyisoprenyl phosphates have many potential biosynthetic fates, including ubiquinone, protein prenylation, and dolichol. Synthesis of the polyisoprenyl phosphate presqualene diphosphate (PSDP) is considered essential because mice that lack squalene synthase are embryonic lethal at midgestation. Of note, the generalized inflammation of hyperimmunoglobulin D (IgD) syndrome and periodic fever is associated with mevalonate kinase deficiency and low isoprenoid levels, indicating that select isoprenoids have counterregulatory roles for inflammation.

Human polymorphonuclear leukocytes (PMNs) carry a natural deficiency in mixed function oxidase activities in the cholesterol biosynthetic pathway, yet polyisoprenyl phosphate biosynthesis remains preserved. PSDP is present in unactivated PMN membranes, and receptor-mediated agonists stimulate a rapid, transient, and reciprocal turnover of PSDP to its monophosphate form, presqualene monophosphate (PSMP). The transient changes in PSDP after LTB₄ receptor activation are concurrent with the kinetics of LTB₄ for PMN activation and deactivation. Coactivation of ALX and LTB₄ receptors prevents LTB₄-initiated decrements in PSDP and inhibits responses to LTB₄, but not

Formation of endogenous antiinflammatory lipid mediators by therapeutic agents. Similar to aspirin, atorvastatin and pioglitazone can trigger the formation of myocardial 15-epi-LXA₄, a potent counterregulatory mediator that serves as an agonist of ALX. Activation of ALX prevents the conversion of PSDP to PSMP, and PSDP is a potent regulator of phospholipase D, phosphatidylinositol 3-kinase, and generation of reactive oxygen species.
PSMP, displays significant inhibition of phosphatidylinositol 3-kinase, phospholipase D, and D_2_ generation, suggesting a novel signaling role for these polyisoprenyl phosphates as endogenous regulators of cell responses. The impact of therapeutic concentrations of statins on cellular PSDP levels and remodeling events has yet to be established.

In conclusion, the findings of Birnbaum et al provide further evidence for important regulatory roles for eicosanoids in cardiovascular disease. Their results bring into focus the tightly orchestrated interplay between COX and LO actions in the generation of the potent antiinflammatory mediator 15-epi-LXA_4_ in rat myocardial tissues. Although the biosynthetic details of the conversion of arachidonate to 15-epi-LXA_4_ in the absence of aspirin remain to be elucidated, this biochemical pathway appears to be used by both atorvastatin and pioglitazone and involves both COX-2 and 5-LO. Already established for aspirin-triggered 15-epi-LXA_4_, it will be of interest to know whether these biosynthetic mechanisms for statins and thiazolidinediones are also present in human tissues. The endogenous biosynthesis of antiinflammatory and proresolving lipid mediators provides potential effector mechanisms for several of the interesting inflammatory and proresolving lipid mediators provides potential effector mechanisms for several of the interesting immunomodulatory actions of these agents—a remarkable, yet serendipitous observation by astute clinical researchers. This shared property of these very successful drugs holds promise for designing new, even more effective cardiovascular protective therapeutic strategies.

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**References**


5. Serhan CN. Lipoxins and aspirin-triggered 15-epi-lipoxins are the first endogenous regulators of cell responses. The impact of therapeutic concentrations of statins on cellular PSDP levels and remodeling events has yet to be established.


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