A major pharmaceutical success story of the late 20th century was the introduction of statins into clinical medicine. This class of drugs (the firefighters) has contributed to reduced morbidity and mortality from atherosclerotic cardiovascular disease by lowering total cholesterol levels, particularly low-density lipoprotein (LDL) cholesterol (the arsonists), and also by raising high-density lipoprotein cholesterol levels, albeit less dramatically. Triglyceride levels may also be reduced. The success of this approach in older adults has also led to the controversial proposal to begin statin therapy even earlier in younger individuals with elevated lipid levels. Other benefits have also been attributed to statins, including the effects on inflammatory and immune responses after myocardial infarction.

Despite this success story, statins are not a panacea. Some patients experience adverse reactions such as myositis that preclude their taking optimal doses and, in some instances, prevent statin use altogether. Much less commonly, statins can lead to rhabdomyolysis, especially in combination with drugs such as gemfibrozil. More recently, the US Food and Drug Administration mandated a change in labeling that warns consumers that statins can lead to poorer control of blood glucose levels in patients with type 2 diabetes mellitus. Alternative approaches to the treatment of elevated cholesterol levels, for example, therapy with niacin or drugs that influence cholesterol metabolism such as ezetimibe, have either failed in randomized clinical trials or fallen out of favor because of the relatively weak strength of evidence.

**Arsonists and Firefighters**

The Perpetual Inflammatory Civil War for Survival

Joel S. Karliner, MD

Atherosclerosis is a chronic inflammatory condition, driven by a multitude of factors. In this issue of *Circulation*, Chatterjee et al describe an alternative experimental approach to statin therapy. Sphingosine is an unsaturated 18-carbon alcohol that forms the backbone of sphingolipids, which are essential for normal cell membrane structure and function. Sphingolipid metabolites include ceramide and sphingosine 1-phosphate (S1P), signaling molecules considered to have opposing effects, such as myositis that preclude their taking optimal doses and, in some instances, prevent statin use altogether. Much less commonly, statins can lead to rhabdomyolysis, especially in combination with drugs such as gemfibrozil. More recently, the US Food and Drug Administration mandated a change in labeling that warns consumers that statins can lead to poorer control of blood glucose levels in patients with type 2 diabetes mellitus. Alternative approaches to the treatment of elevated cholesterol levels, for example, therapy with niacin or drugs that influence cholesterol metabolism such as ezetimibe, have either failed in randomized clinical trials or fallen out of favor because of the relatively weak strength of evidence.

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The mechanisms whereby GSL synthesis inhibition influences cholesterol metabolism and atherosclerosis have been previously investigated. For example, in human foam cells and macrophages, the GSL lactoceramide resulted in cholesterol accumulation. This observation led to a molecular trap hypothesis which states that increased cholesterol sequestration can be stimulated by GSLs in late endosomes/lysosomes. Subsequently, Galar et al reported that PDMP enhanced cholesterol export from cholesterol laden macrophage foam cells via ABCA1. As noted above, Chatterjee et al also described an increase in the mRNA for this transporter in response to PDMP treatment. Other transporters similarly affected included the aforementioned CD36 and SR-B1. PDMP also enhanced cholesterol metabolism via for several decades that these glycosphingolipids (GSLs) are present in human plasma. GSLs such as lactoceramide are also found in excess in atherosclerotic plaque intima and have been implicated in aortic smooth muscle cell proliferation.

Inhibitors of GSL synthesis that exhibit a profound effect on lipid metabolism have been developed. Among these is N-3-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (D-PDMP), which blocks the synthesis of the GSL glucosylceramide. Chatterjee et al fed a high-fat, high-cholesterol diet to male mice deficient in apolipoprotein E (ApoE−/−). This diet resulted in increased aortic wall thickening and extensive aortic calcium deposits, which were prevented by a daily oral gavage of 10 mg/kg D-PDMP. Increased arterial stiffness was also prevented by D-PDMP. Similarly, progressive aortic atherosclerosis and coronary artery plaque deposition were reduced/prevented by D-PDMP treatment. In these mice, PDMP decreased glycosyltransferase activity in the aorta, reduced levels of oxidized LDL and triglycerides, and increased the expression of transporter genes involved in cholesterol efflux. The mRNA for 3-hydroxy-3-methylglutaryl-coenzyme A reductase increased, which would be expected to augment cholesterol synthesis, but total plasma cholesterol was decreased. This may in part be associated with an increase in the mRNA of molecules involved in cholesterol efflux such as scavenger receptor class B type 1 (SR-B1), CD36, and the ATP-binding cassette transporter A1 (ABCA1) reported in the article. However, the authors do not show any measurements of either the protein levels or activities of these moieties, nor do they discuss the possible mechanisms involved. They also examined atherosclerosis in New Zealand white rabbits fed a similar diet and treated or not with D-PDMP, which had the same effect as in ApoE−/− mice. Similar findings were reported by Bietrix et al in APOE*3 Leiden and LDL receptor−/− mice by using the iminosugar N-(5′-adamantane-1′-yl-methoxy)-pentyl-1-deoxyxojirimycin, which is also a glucosylceramide inhibitor. The mechanisms whereby GSL synthesis inhibition influences cholesterol metabolism and atherosclerosis have been previously investigated. For example, in human foam cells and macrophages, the GSL lactoceramide resulted in cholesterol accumulation. This observation led to a molecular trap hypothesis which states that increased cholesterol sequestration can be stimulated by GSLs in late endosomes/lysosomes. Subsequently, Galar et al reported that PDMP enhanced cholesterol export from cholesterol laden macrophage foam cells via ABCA1. As noted above, Chatterjee et al also described an increase in the mRNA for this transporter in response to PDMP treatment. Other transporters similarly affected included the aforementioned CD36 and SR-B1. PDMP also enhanced cholesterol metabolism via...
the LDL receptor pathway as evidenced by increases in LDL receptor protein mass and elevated expression of the sterol regulatory element-binding protein.8 In vascular smooth muscle cells, PDMP has also been reported to enhance interleukin-1β stimulation of nitrite, thereby providing an additional mechanism whereby this GSL may be of benefit in atherosclerotic vessels.

The first rate-limiting step in the sphingolipid biosynthetic pathway is the formation of 3-keto-dihydrosphinganine from palmitate and serine to form 3-keto-dihydrosphinganine (not depicted). The latter is reduced to dihydrosphinganine followed by acylation to yield dihydroceramide, which in turn generates ceramide via the action of desaturases. Ceramide is at the hub of several pathways, because it can be transformed into sphingomyelin, sphingosine, and sphingosine 1-phosphate, ceramide 1-phosphate, or glucosylceramide. As noted in the text, glucosylceramide (and lactylceramide) foster cellular cholesterol accumulation and reduce cholesterol export. D-PMMP inhibits these actions of glucosylceramide, retarding cholesterol accumulation and enhancing cholesterol export via transporter molecules such as SR-B1, CD36, and ABCA1. CDase indicates ceramidase; CerS, (dihydro)ceramide synthase; CK, ceramide kinase; D-PDMP, d-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol; GCase, glucosyl ceramidase; GCS, glucosyl ceramide synthase; SK, sphingosine kinase; SMase, sphingomyelinase; SMS, sphingomyelin synthase; SPPase, sphingosine phosphophosphate phosphatase; and SPT, serine palmitoyl transferase.

In a more recent report, Wang et al19 studied ApoeR61 h/h mice that express a form of mouse apolipoprotein E that closely resembles the native mouse protein at 5% of normal plasma levels. These ApoeR61 h/h mice, also known as HypoE mice,20 were bred to mice deficient in SR-B1. The HypoE allele predisposes to diet-induced hyperlipidemia20 that causes occlusive coronary atherosclerosis and myocardial infarction when the resulting ApoeR61 h/h/SRB1 −/− mice are fed a diet rich in fat and cholesterol. Wang et al19 then asked whether FTY720 placed in the drinking water could retard atherosclerotic obstruction of coronary arteries and aortic root atherosclerosis, as well. In the ApoeR61 h/h/SRB1−/− mice, mortality was high during 4 weeks of high-fat, high-cholesterol feeding in comparison with animals fed the same diet plus FTY720 (34% versus 5%, P<0.02).

Similar to the study of Poti et al,18 there was no reduction in serum lipids, nor were any effects on coronary or aortic root atherosclerosis observed. Thus, Wang et al19 noted reduced numbers of T and B cells, and an increased proportion of Tregs. A remarkable new finding was that, in addition to enhancing longevity, FTY720 surprisingly and substantially improved left ventricular function measured by serial echocardiography that could have been a consequence of immunosuppression.19 This observation suggests that S1P1 agonism could be useful in the treatment of heart failure.

In summary, the report by Chatterjee et al emphasizes the importance of biochemical arson as a key element in the pathogenesis of atherosclerosis, and the current article and other recently published data provide evidence that the manipulation of immune system responses can damp down the flames responsible for these conflagrations.

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References
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