Research from both the bench and the clinic has provided increasing evidence for cross-talk between cholesterol metabolism and the immune system, providing a greater understanding of host response to infection and of the inflammatory components of cardiovascular disease, such as atherosclerosis. A recent example is research by Reboldi et al. showing that 25-hydroxycholesterol tightly regulates interleukin-1β, a potent cytokine.

The metabolite 25-hydroxycholesterol is an oxysterol and is derived from cholesterol (Fig. 1A). Although it influences cholesterol homeostasis by means of the suppression of sterol regulatory element–binding proteins (SREBPs), its main effect appears to be on immune regulation. The most potent enzyme that transforms cholesterol into 25-hydroxycholesterol is cholesterol 25-hydroxylase (CH25H), which is prominently produced in monocytes, macrophages, and dendritic cells — the major cell types of the innate immune system synthesizing interleukin-1β. (CH25H is not expressed in the liver, the organ most active in synthesizing fatty acids and cholesterol.) Mice lacking Ch25h have normal cholesterol homeostasis (and also synthesize small amounts of 25-hydroxycholesterol) but have marked changes in their inflammatory response.

The expression of CH25H is very strongly induced by lipopolysaccharide, by type I interferons — important antiviral cytokines, one of which (interferon-β) is used to treat the inflammatory disease multiple sclerosis — and by viral infection, leading to increased concentrations of 25-hydroxycholesterol. Reboldi et al. found that 25-hydroxycholesterol mediates the inhibition of interleukin-1β induced by type I interferon. More specifically, 25-hydroxycholesterol inhibits pro–interleukin-1β gene transcription as well as the inflammasome-mediated activation of interleukin-1β (Fig. 1B) by inhibiting the activation of SREBP. They found that the macrophages of Ch25h-knockout mice produce more interleukin-1β when exposed to lipopolysaccharide and that this can be corrected by adding 25-hydroxycholesterol to the culture medium. The Ch25h-knockout mice were more susceptible than wild-type mice to lipopolysaccharide-induced lethality because of increased cytokine production.

A rare hereditary disease linking cholesterol metabolism and inflammation is mevalonate kinase deficiency. Mevalonate kinase is an early enzyme in the cholesterol pathway (Fig. 1A), and mutations in the mevalonate kinase gene cause a substantial reduction in enzyme activity. Patients with mevalonate kinase deficiency have lifelong recurring episodes of generalized inflammation with fever, mediated by cytokines such as interleukin-1β. Many patients with mevalonate kinase deficiency have increased serum concentrations of IgA and IgD, and such increased concentrations are also seen in mice deficient in mevalonate kinase. The current hypothesis is that defective protein isoprenylation (resulting in the diminished activation of guanosine triphosphatases [GTPases]) represents the link between a deficiency of mevalonate kinase and inflammation (Fig. 1A). But a deficiency in 25-hydroxycholesterol is also a hypothetical link, the more so because 25-hydroxycholesterol also affects B cells. Ch25h-knockout mice also have increased serum levels of IgA. In addition, it is well known that viral infection (and vaccination) can provoke an inflammatory attack in persons with mevalonate kinase deficiency. Although a prompt inflammatory response is important in combating pathogens, an overly robust inflammatory response can damage the host and cause complications. Containing inflammation as soon as the infection is under control is therefore important. The inhibition of interleukin-1β by 25-hydroxycholesterol may represent a containment mechanism. Several studies have shown other inhibitory roles of 25-hydroxycholesterol in cell models of viral in-
Infection, such as the inhibition of viral entry into the cell, and in the inhibition of viral replication.\textsuperscript{4} On the other hand, Gold et al.,\textsuperscript{5} using a systems biology approach, found that 25-hydroxycholesterol amplifies inflammation. They found that \textit{Ch25h}-knockout mice are more likely than wild-type mice to survive influenza, owing to less inflammatory damage. Additional studies are required to resolve the conundrum.

Statins, which are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (Fig. 1A), have been suggested to confer a survival benefit in influenza, although hard evidence is still lacking. Diverse antiinflammatory effects, as well as some proinflammatory effects,\textsuperscript{2} have been attributed to statins. So far, however, the effects of either statins or hypercholesterolemia on macrophage production of 25-hydroxycholesterol are unclear.

Although questions remain unanswered, the study by Reboldi et al. offers insight into the role of 25-hydroxycholesterol in immunity and, more specifically, into the host response against viral infection. With the current multiple viral threats to populations around the world, new insights into the host response to viral infection — which may provide fodder for new clinical approaches to treatment — are more than welcome.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Figure 1. Derivation of 25-Hydroxycholesterol and the Inhibition of Interleukin-1β by 25-Hydroxycholesterol. Panel A shows a simplified representation of the cholesterol pathway, with three activating enzymes indicated in green. Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. The genetic defect in mevalonate kinase deficiency is located in mevalonate kinase. Panel B shows that the production of 25-hydroxycholesterol is induced by type I interferons, released during viral infection, and also by lipopolysaccharide. The metabolite 25-hydroxycholesterol reduces the production of interleukin-1β by the inhibition of pro–interleukin-1β transcription and by the inhibition of activation of pro–interleukin-1β by inflammasomes. \textit{Ch25h} denotes cholesterol 25-hydroxylase, and \textit{Il1b} the gene encoding interleukin-1β.

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