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Increasing evidence supports the concept that IL-1 plays a role in the atherosclerotic process. The development of atherosclerotic lesions in the arterial walls of apolipoprotein E (ApoE) or low-density lipoprotein (LDL) receptor-deficient mice is markedly reduced in mice deficient in the IL-1 receptor or in the IL-1α or IL-1β themselves. The lesions are increased, however, in mice deficient in the naturally occurring IL-1 receptor antagonist (1). Moreover, treatment of ApoE-deficient mice eating a high-fat diet with anti-IL-1β antibodies prevents the arterial wall lesions (2). In ApoE knockout mice, a bacterial challenge worsens the disease but this is prevented in mice also deficient in the IL-1 receptor (3). Similarly, in mice deficient in the LDL receptor, the production of IL-1α and IL-1β by macrophages is enhanced (4). The culprit in the formation of atherosclerotic lesions is IL-1 produced by the myeloid cells rather than the endothelium or mesenchymal cells (5).

Recent insights have suggested an important role of IL-1 in atherosclerosis by inducing formation of the foam cell, which enters the arterial wall and orchestrates the inflammatory plaque. Indeed, foam cells are full of IL-1β as well as IL-1α. In fact, within a few hours after eating a fatty meal, there is increased IL-1β in the circulating monocytes (6), independent of the high or low glycemic composition of the meal (7). These in vivo clinical studies are consistent with in vitro data of several reports demonstrating an increase in gene expression and secretion of IL-1β from fresh blood monocytes exposed to oxidized LDL in vitro. Other lipids also induce IL-1β, such as cholesterol (CHOL) (8), chylomicrons (9), or triglycerides (TG) (10). One can conclude that postprandial hyperlipidemia can be a signal for the circulating monocyte to increase IL-1β production, and that IL-1β-laden monocytes entering a plaque as foam cells contribute to the atherosclerotic process. It is also not unexpected that caspase-1 contributes to the atherosclerotic process via NLRP3 (NLR family, pyridine containing domain 3) (8).

In the paper by Delgado-Lista et al. (11), individuals bearing the -1473 CC IL-1B polymorphism likely have a pronounced atherosclerotic process because this single nucleotide polymorphism is associated with increased fasting lipids in the elderly population. In younger persons with this polymorphism, when using a meal challenge, higher circulating postprandial CHOL and TG concentrations were observed. Because of the well-known relationship between IL-1β activity and the circulating IL-6 concentrations, correlations were made with IL-6. However, readers of the paper by Delgado-Lista et al. (11) should be aware that the elevated levels of IL-6 are more than just a marker of IL-1β activity. Individuals treated with monoclonal antibodies that block the IL-6 receptor (tocilizumab) have increased LDL levels (12). Thus, the study by Delgado-Lista contributes to the concept that IL-1β-driven IL-6 modulate the regulation of serum lipids by the liver.

Nevertheless, the authors concluded that elderly homozygotes for the rare allele have increased levels of fasting TG. Due to the combination of increased TG and IL-6 levels, we also hypothesize that these patients overrespond to the proinflammatory stimulus that occurs after a fatty meal. These data have considerable implications for the risk of cardiovascular events.
These authors are rather familiar with effects of this IL-1B polymorphism. They reported previously that individuals homozygous for the minor allele had a higher risk for elevated blood pressure ($P < 0.05$), as well as a nonstatistically significant trend for a greater degree of abdominal obesity and metabolic syndrome ($P = 0.07$) (13). There are several important clinical consequences of the findings presented by Delgado-Lista et al. (11). The increased release of proinflammatory cytokines after a fatty meal in individuals bearing the -1473 CC variant in IL-1B gene results in a chronic state of heightened inflammation, which has been directly related to chronic pathologies such as atherosclerosis, coronary artery disease, or metabolic syndrome (14). More specifically, the increase in postprandial IL-6 concentration in individuals bearing genetic variants of the IL-1B gene promoter bears witness to an increased IL-1B bioactivity in these persons, because IL-1B is known as the main driver of IL-6 synthesis (15). IL-1B is one of the major proinflammatory cytokines involved in atherosclerosis, metabolic syndrome, and insulin resistance (16, 17).

The study by Delgado-Lisa et al. (11) takes us, however, one step further. In addition to identifying the postprandial increase in proinflammatory cytokines in individuals bearing the -1473 CC variant, the authors also investigate the consequences of this process on TG and CHOL. Proinflammatory cytokines such as TNF and IL-1B have been known from the mid-1980s to have major effects on lipid metabolism. TNFα, initially also known as cachectin, suppresses the level of adipocyte lipoprotein lipase (LPL) (18). In addition, IL-1 was reported by the Cerami laboratory (18) to reduce LPL. LPL suppression by proinflammatory cytokines has been one of the most consistent findings in metabolic disorders in which IL-1 plays a role. Second, these findings provide strong evidence for the rationale of using anti-IL-1 compounds and induce the release of lipoproteins that bind and neutralize lipopolysaccharide and other toxic bacterial products (24). High levels of CHOL and lipoproteins protect against infections both in experimental studies (25) and in epidemiological studies in humans, especially those of old age (19). An unexplored consequence of the findings of Delgado-Lista et al. (11) is therefore the potential positive link between the -1473 CC IL-1B polymorphism and protection from complications of infectious diseases.

In conclusion, the study of Delgado-Lisa et al. (11) provides an important piece of evidence, accumulated in a clinical setting in humans to support the important role of IL-1 for the lipid metabolism. The consequences of these findings are broad. First, they help to improve understanding of the pathophysiology of metabolic and inflammatory disorders in which IL-1 plays a role. Second, these findings provide strong evidence for the rationale of using anti-IL-1 biological therapy in metabolic disorders and open the door for adjustment of this therapy according to the genetic status of an individual.

Acknowledgments

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