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More than Inflammation: Interleukin-1β Polymorphisms and the Lipid Metabolism

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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.

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Abbreviations: ApoE, Apolipoprotein E; CHOL, cholesterol; LDL, low-density lipoprotein; LPL, lipoprotein lipase, TG, triglycerides.

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-1β bioactivity in these persons, because IL-1β is known as the main driver of IL-6 synthesis (15). IL-1β 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-1β 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 patients with systemic inflammation, particularly in patients with sepsis (19). Due to the inhibition of LPL activity, the breakdown of lipids results in higher levels of TG and very low-density lipoprotein in the circulation. Delgado-Lisa *et al.* (11) should be congratulated because they link the earlier *in vitro* and animal studies to the human *in vivo* physiology by showing that a genetic variant of *IL-1B* that is associated with an increased bioactivity also results in higher TG and CHOL after a physiological meal.

What are the implications of these findings for human physiology? On the one hand, the most obvious consequence, as suggested by the authors themselves, is that the resulting persistent heightened state of inflammation in the individuals bearing the -1473 CC *IL-1B* variant may contribute both directly (inflammation in the arterial wall) and indirectly (high CHOL) to the atherogenic process. In addition, the repeated postprandial increase in IL-1 bioactivity in these individuals can have important effects on glucose metabolism, with toxic effects on the pancreatic β-cells (20, 21) as well as increased insulin resistance at the level of the adipose tissue (16). Beyond metabolic diseases, the increased proinflammatory profile in individuals bearing the -1473C allele can also have consequences on autoinflammatory diseases such as gout, a condition in which IL-1β is known to play a crucial role in the pathogenesis (22) and in which the synergism between uric acid crystals and free fatty acids has been shown to be necessary to induce IL-1β production and inflammation (23).

On the other hand, one should not forget that the cytokine-induced cholesterol release has been most likely evolved as a protective mechanism during infections. Proinflammatory cytokines both activate host defense mechanisms 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.

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