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Interleukin-1beta may act on hepatocytes to boost plasma homocysteine – The increased cardiovascular risk associated with elevated homocysteine may be mediated by this cytokine

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ABSTRACT

The results of multi-center trials of B vitamin supplementation reveal that, whereas moderately elevated homocysteine predicts increased risk for coronary disease, it does not play a mediating role in this regard. This essay proposes that interleukin-1beta can act on hepatocytes to suppress expression of the hepatocyte-specific forms of methionine adenosyltransferase; this in turn can be expected to decrease hepatic activity of cystathionine-β-synthase, leading to an increase in plasma homocysteine. It is further proposed that interleukin-1beta (IL-1β) is a true mediating risk factor for cardiovascular disease, and that elevated homocysteine predicts coronary disease because it can serve as a marker for increased IL-1β activity. Potent statin therapy may decrease IL-1β production by suppressing inflammasome activation – thereby accounting for the marked protection from cardiovascular events observed in the classic JUPITER study, in which the enrolled subjects had low-normal Low Density Lipoprotein cholesterol but elevated C-reactive protein.

Introduction

IL-1β and IL-6 likely play mediating roles in cardiovascular disease

Whereas a moderate elevation of plasma homocysteine has clearly been established as a risk factor for coronary events in prospective epidemiology, the failure of homocysteine-lowering B vitamin supplementation to reduce risk for such events in large multicenter controlled trials demonstrates that homocysteine is not a mediating risk factor in this regard [1–3]. (Folate supplementation may however modestly lower stroke risk when baseline folate status is mediocre.) [3–6]. Analogously, whereas C-reactive protein (CRP) likewise can predict coronary risk, Mendelian randomization analyses suggest that it is unlikely to be a true mediating risk factor [7,8]. This situation has led cardiologists to consider the possibility that the cytokines primarily responsible for hepatic induction of acute phase proteins such as CRP – interleukin-1beta (IL-1β) and interleukin-6 (IL-6) – are the true mediating risk factors associated with elevated CRP [9].

Mendelian randomization studies are consistent with the thesis that IL-6 does indeed play a mediating role in cardiovascular (CV) disease [10,11]. With respect to IL-1β, this cytokine promotes pro-inflammatory behavior in vascular endothelium, and stimulates vascular smooth muscle proliferation [12–17]. *In vivo*, exogenous IL-1β promotes coronary intimal lesions, whereas ApoE-deficient mice in which IL-1β is also knocked out, or in which monoclonal antibodies are administered to target this cytokine, are less prone to atherogenesis [18–21]. An inhibitor of IL-1β convertase suppresses neointimal hyperplasma in pigs given a coronary stent [22]. IL-1β promotes conversion of macrophages to foam cells, and its secretion from macrophages is triggered by oxidized LDL particles [23]. The hypothesis that IL-1β is a driver of CV disease is thus consistent with much pre-clinical data, and is now being tested in the CANTOS multi-center trial; this is evaluating the impact of canakinumab, a monoclonal antibody targeting IL-1β, on risk for recurrent coronary events in patients with stable angina and elevated CRP [24].

Abbreviations: CAD, Coronary Artery Disease; CBS, cystathionine beta-synthase; CRP, C-reactive protein; CV, cardiovascular; IL-1β, interleukin-1beta; IL-6, interleukin-6; LDL, Low Density Lipoprotein; SAM, S-adenosylmethionine.

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Can statin therapy decrease IL-1β production?

Can the thesis that IL-1β/IL-6 mediates coronary disease be harmonized with evidence that potent statin therapy reduces CV risk in those with low/normal LDL but elevated CRP? In the multicenter JUPITER trial, patients with no history of heart disease, low to normal LDL, and CRP >2 mg/L were randomized to receive 20 mg rosuvastatin daily or placebo. Those allocated to active therapy achieved a highly significant 54% reduction in myocardial infarction and a 20% reduction in all-cause mortality [25]. Could decreased production of IL-1β have mediated much of this benefit? Inflammasomes centered on the protein NLRP3 are required for the production of active IL-1β – they activate caspase-1, which in turn cleaves pro-IL-1β to generate the active cytokine [26]. When patients who had experienced a myocardial infarction or unstable angina were randomized to receive either 5 mg or 20 mg rosuvastatin daily for 4 weeks, peripheral blood monocyte levels of NLRP3 and of IL-1β in those receiving the 20 mg dose declined significantly relative to baseline and to final levels in the 5 mg group [27]. Another recent study randomized patients with Coronary Artery Disease (CAD) to receive either 2.5 mg daily of rosuvastatin or 10 mg daily of atorvastatin for 8 months; mRNA and protein levels of NRLP3 in peripheral blood mononuclear cells, as well as plasma IL-1β, declined from baseline in the atorvastatin group but not in those receiving rosuvastatin (likely reflecting the low dose of the latter employed) [28]. In rats with diet-induced diabetes, rosuvastatin treatment favorably influenced diabetic cardiomyopathy, an effect associated with reduced levels of NRLP3, caspase-1, and IL-1β in ventricular tissue [29]. Although some *in vitro* studies demonstrate that statins can boost NRLP3 expression, this seems likely to reflect the impact of high, supra-clinical concentrations [30,31]. Hence, the marked protection conferred by rosuvastatin in the JUPITER study might reflect, at least in part, down-regulation of inflammasome activity and decreased production of mature IL-1β.

Since oxidants generated by NADPH oxidase have been shown to promote inflammasome activity in several studies, and since potent statin therapy can down-regulate NADPH oxidase activity by decreasing isoprenylation of Rac, it is conceivably that a moderate suppression of NADPH oxidase activity plays a role in the inhibitory impact of statin therapy on inflammasome activity [32–39]. Furthermore, if 20 mg daily rosuvastatin has a sufficiently potent impact on Rac1/NADPH oxidase activity to down-regulate inflammasomes, it can be expected to decrease cardiovascular risk in other ways as well [40–42].

IL-1β may act on hepatocytes to raise plasma homocysteine levels

There is reason to suspect that IL1β can act on hepatocytes to increase circulating levels of homocysteine. Methionine adenosyltransferases I and III (MAT I/III) – tetramers and dimers of the same subunit – are chiefly responsible for S-adenosylmethionine (SAM) synthesis in hepatocytes [43]. Activation of sphingomyelinase in hepatocytes – or exposure of hepatocytes to short-chain cell-permeable forms of its product ceramide – down regulates MAT I/III at both the protein and mRNA level [44,45]. A key feature of IL-1β signaling is activation of neutral sphingomyelinase [46–48]. Hence, when IL-1β acts on the liver, it is reasonable to expect that it will suppress MAT I/III activity, leading to a reduction in hepatic levels of SAM. Cystathionine beta-synthase (CBS) activity in the liver is responsible for homocysteine disposal, and SAM functions as an allosteric activator for this enzyme, notably boosting its Vmax but not changing its Km [49]. Hence, the reduction of SAM levels induced by IL-1β activity will be associated with a reduction in CBS activity. Since, in steady state, the total daily flux through CBS is nearly equivalent to the rate of methionine ingestion (minus the small amount of methionine diverted to polyamine synthesis), the only way to maintain this flux when CBS has a reduced Vmax will be an increase in homocysteine level that better saturates its binding to CBS. Consistent with this analysis, genetically determined reductions in MAT I/III are associated with increased plasma homocysteine [50–52]. Hence, barring any unknown countervailing effects, hepatic IL-1β signaling can be expected to increase plasma homocysteine levels.

Since IL-1β is difficult to measure in plasma, there have been few studies attempting to correlate plasma levels of IL-1β with those of homocysteine. One such study, evaluating 612 healthy men, found a positive correlation between these parameters: $r = 0.249$, $P < 0.001$ [53]. Homocysteine also correlated with TNF-alpha and IL-6, albeit less tightly. In a much smaller study (70 subjects) including Alzheimer's patients, a significant correlation between homocysteine and IL-1β could not be established [54]. Smokers are known to have increased homocysteine levels, and the IL-1β content of the serum, bronchiolar lavage fluid, and gingival crevicular fluid of smokers is reported to be elevated [55–59]. Analogously, rheumatoid arthritis is associated with elevated homocysteine, and this disorder is characterized by increased levels of IL-1β in serum and synovial fluid [60–64]. And homocysteine is elevated in various other systemic inflammatory disorders, such as SLE [65,66].

If potent statin therapy does indeed decrease IL-1β production, and IL-β acts on the liver to increase homocysteine levels, it would be reasonable to expect that statin therapy that is sufficiently potent could decrease homocysteine. Indeed, 2 clinical trials and a rat study document this effect with rosuvastatin [67–69] – albeit other studies do not, possibly owing to suboptimal dose [70,71].

The most definitive way to assess IL-1β's impact on homocysteine levels would be to observe the impact of canakinumab therapy on homocysteine; unfortunately, a large study evaluating the impact of this drug on diabetics found notable reductions in CRP, IL-6, and fibrinogen – but failed to measure homocysteine [72]. Hopefully, the CANTOS trial will remedy this deficiency. If this study establishes that canakinumab can decrease CV events, while also lowering homocysteine, then it will be reasonable to conclude that elevated homocysteine has been functioning as a marker for the true mediating risk factor, IL-1β.

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