Interleukin-6 and Tumor Necrosis Factor-alpha, Which May Boost Homocysteine by Decreasing Hepatic S-Adenosylmethionine, May Mediate the Cardiovascular Risk Associated with Moderately Elevated Homocysteine

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Abstract

Controlled trials of vitamin supplementation have clarified that, whereas moderately elevated homocysteine (Hcy) is a risk factor for cardiovascular events, it is not a mediating risk factor in this regard, but rather is serving as a marker for other metabolic factors that are genuinely pernicious to vascular health. There is limited evidence that interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) can suppress methionine adenosyltransferase activity in hepatocytes – an effect which would be expected to raise plasma homocysteine by lessening cystathionine beta-synthase activity. Moreover, there is ample reason to suspect that both IL-6 and TNF-alpha play a role in mediating the cardiovascular risk associated with metabolic syndrome and chronic inflammation – in part by promoting hepatic synthesis of the acute phase reactant serum amyloid A, which is emerging as a potent determinant of vascular risk. Hence, it is hypothesized that Hcy's utility as a vascular risk factor reflects the fact that it can serve as a marker for elevated plasma levels of IL-6 and TNF-alpha. Further clinical, cell culture, and epidemiological studies are required to test this hypothesis.

Homocysteine – a Marker but not Mediator of Vascular Risk

Although considerable prospective epidemiology has linked moderate elevations of plasma homocysteine (Hcy) to increased risk for cardiovascular events, the failure of homocysteine-lowering vitamin supplementation to decrease risk for such events in controlled clinical trials (aside from a possible small reduction in stroke risk that might or might not reflect Hcy lowering) strongly suggests that can Hcy is serve as a marker for some metabolic state which is the true mediator of excess cardiovascular risk.[1-5] It is proposed here that systemic elevations of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), associated with metabolic syndrome and chronic inflammatory disorders, can increase plasma Hcy via their impact on the liver, and that these cytokines are genuine mediating risk factors for atherogenic disease.

Cystathionine Beta-Synthase Activity Determines Homocysteine Levels

The predominant catabolic fate of methionine is conversion to homocysteine, following which the enzyme cystathionine beta-synthase (CS) irreversibly condenses homocysteine with serine to generate cystathionine.[6] In steady state, the net rate at which homocysteine is generated from

methionine and then converted to cystathionine (the homocysteine flux) is evidently determined by the habitual dietary intake of methionine. However, at any given rate of methionine intake, the equilibrium *concentration* of homocysteine will necessarily vary inversely with the activity of CS. Not surprisingly, the exceptionally high homocysteine levels associated with homocystinuria often reflect homozygosity for mutations that severely impair the expression or activity of CS.[6, 7]

S-adenosylmethionine (SAM) is a strong allosteric activator of CS, and also boosts its level by protecting it from proteolysis;[6, 8, 9] this makes good sense homeostatically, since when SAM levels are unduly low, it is desirable to conserve Hcy as a precursor for SAM synthesis. The elevations of plasma Hcy observed when folate and/or B12 status is poor reflect the fact that hepatic SAM levels (and hence CS activity) are relatively low owing to inefficiency of the folate/B12-dependent remethylation pathway that regenerates methionine from Hcy. More generally, hepatic SAM content can be expected to correlate inversely with plasma Hcy. Circumstances which put increased demand on hepatic methylating capacity (and hence lower hepatic SAM) – such as administration of high-dose niacin - are associated with increased plasma Hcy.[10, 11] The Hcy "gender gap" – men tend to have higher levels – likely reflects the fact that the methyl requirement for hepatic creatine synthesis is greater in men.[12, 13]

IL-6 and TNF-alpha Mediate Vascular Risk, in Part via Serum Amyloid A

Elevated IL-6, primarily of adipose origin, is a key feature of metabolic syndrome.[14] Plasma IL-6 correlates directly with risk for coronary disease in prospective studies, and Mendelian randomization analysis suggests that IL-6 bioactivity is indeed a mediating factor in this regard.[15-19] This could reflect its stimulatory impact on hepatic production of certain acute phase reactants[20] – hepatocyte-specific knockout of the IL-6 receptor suppresses atherogenesis and vascular remodeling in mice[21, 22] - and possibly direct effects on the vasculature.[23, 24] Although a role for plasma TNF-alpha in the mediation of cardiovascular risk associated with metabolic syndrome is less clear, the favorable impact of anti-TNF therapy on arterial stiffness, carotid intima-media thickness, and risk for cardiovascular events in patients with rheumatoid arthritis (who are at greatly increased cardiovascular risk) strongly suggests that TNF-alpha, like IL-6, participates in the adverse impact of chronic systemic inflammation on vascular health.[25-29]

It is notable that IL-6 and TNF-alpha interact synergistically in hepatic induction of serum amyloid A.[30, 31] Whereas Mendelian randomization studies have tended to discount the acute phase reactants C-reactive protein and fibrinogen as mediators of cardiovascular risk,[32-37] there is considerable and growing evidence that serum amyloid A (SAA) may in fact be a mediator of this risk. SAA plasma levels correlate positively with risk for cardiovascular events, SAA acts directly on endothelial cells, vascular smooth muscle and monocytes to exert pro-inflammatory effects, injections of SAA promote atherogenesis in rodents, and polymorphisms of the SAA

gene have been linked clinically to carotid intima-media thickness and ankle-to-brachial index.[38-48] Moreover, a number of studies show that statin therapy tends to lower elevated SAA[49-53] – possibly explaining why statin therapy targeting elevated C-reactive protein in normolipemic patients has been associated with favorable outcomes.[54] Hence, in light of evidence that IL-6 and TNF-alpha cooperate to boost SAA expression, it is reasonable to suspect that SAA is a key mediator of the adverse impact of IL-6 and TNF-alpha on vascular health.

IL-6/TNF-alpha May Boost Homocysteine by Lowering Hepatocyte SAM Levels

The chief source of SAM in mature hepatocytes is methionine adenosyltransferase I/III (MAT I/III); the enzyme MAT II also participates in SAM generation, primarily in fetal hepatocytes and in regenerating liver. Frago and colleagues have demonstrated that IL-6 and TNF-alpha each act on rat primary hepatocytes and on H35 rat hepatoma cells to suppress transcription of the gene coding for MAT I/III, and to decrease total hepatocyte MAT activity (a reduction of 34-47%).[55] This phenomenon may play a key role in hepatic regeneration (in which hepatic IL-6 and TNF-alpha are markedly elevated), as SAM has been found to act as an antagonist of the activity of hepatocyte growth factor.[56]

If IL-6 and TNF-alpha likewise suppress MAT activity in human hepatocytes, then – assuming that other factors remain equal - the associated reduction in hepatic SAM would be expected to reduce CS activity, and hence elevate hepatic and systemic levels of Hcy. A literature search does indeed reveal several clinical studies in which Hcy levels have been shown to correlate directly with plasma IL-6 and/or TNF-alpha in patients with diabetes or metabolic syndrome[57-61] – albeit such findings have not been universal.[62, 63]

In aggregate, these considerations suggest that a moderate elevation of Hcy may serve as a marker for increased plasma levels of IL-6 and/or TNF-alpha, and, in light of the fact that the latter are likely to play mediating roles in atherogenic disease, this may account for the clear association between Hcy elevation and cardiovascular risk. And the fact that IL-6 levels tend to rise with age may help to explain why Hcy likewise increases during aging.[64] Further studies evaluating the impact of IL-6/TNF-alpha on hepatocyte Hcy metabolism (preferably employing human hepatocytes), assessing clinical correlations of plasma levels of IL-6, TNF-alpha, and attempting to determine whether correction for IL-6/TNF-alpha markedly attenuates the association between Hcy and cardiovascular outcomes in epidemiological studies, would be warranted to test this hypothesis.

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