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Practical strategies for modulating foam cell formation and behavior

Uitz E *et al*. Modulating foam cell formation and behavior

Elisabeth Uitz, Babak Bahadori, Mark F McCarty, Mohammed H Moghadasian

**Elisabeth Uitz, Babak Bahadori,** Department of Internal Medicine 2, University Hospital of St. Poelten, Karl Landsteiner Private University of Health and Life Sciences, Probst-Fuehrer-Str. 4, Austria

**Mark F McCarty,** Catalytic Longevity, Carlsbad, CA 92009, United States

**Mohammed H Moghadasian,** Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, R2H 2A6 Manitoba, Canada

**Author contributions:** Uitz E designed and wrote the manuscript and performed the majority of data analysing; Bahadori B and McCarty MF provided analytical tools and were also involved in data analysing and editing the manuscript; Moghadasian M co-ordinated and provided the data collection of all the human material in addition to providing mental support for this work.

**Correspondence to: Elisabeth Uitz, MD,** Department of Internal Medicine 2, University Hospital of St. Poelten, Karl Landsteiner Private University of Health and Life Sciences, 3100 St. Poelten, Probst-Fuehrer-Str. 4, Austria. [elisabeth.uitz@aon.at](mailto:elisabeth.uitz@aon.at)

**Telephone:** +43-2742-900472221 **Fax:** +43-2742-900419006

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**Abstract**

Although high density lipoprotein (HDL)-mediated reverse cholesterol transport is crucial to the prevention and reversal of atheroma, a recent meta-analysis makes evident, that current pharmaceutical strategies for modulating HDL cholesterol levels lower cardiovascular risk only to the extent that they concurrently decrease low density lipoprotein (LDL) cholesterol. This corresponds well with findings of a recent Mendelian randomization analysis, in which genetic polymorphisms associated with HDL cholesterol but no other known cardiovascular risk factors failed to predict risk for myocardial infarction. Although it is still seems appropriate to search for therapies that could improve the efficiency with which HDL particles induce reverse cholesterol transport, targeting HDL cholesterol levels *per se* with current measures appears to be futile. It may therefore be more promising to promote reverse cholesterol transport with agents that directly target foam cells. Macrophage expression of the cholesterol transport proteins ABCA1, ABCG1, and SR-BI is transcriptionally up-regulated by activated liver X receptors (LXR), whereas nuclear factor (NF)-kappaB antagonizes their expression. Taurine, which inhibits atherogenesis in rodent studies, has just been discovered to act as a weak agonist for LXRalpha. Conversely, it may be possible to oppose NF-kappaB activation in macrophages with a range of measures. Induction of heme oxygenase-1, which can be attained with phase 2 inducer phytochemicals such as lipoic acid and green tea catechins, promotes reverse cholesterol transport in macrophages and inhibits atherogenesis in rodents, likely due to, in large part, NF-kappaB antagonism. Inhibition of macrophage NADPH oxidase activity with the spirulina-derived bilirubin-mimetic phycocyanobilin may also oppose NF-kappaB activation, and salicylic acid similarly should be useful for this purpose. The AMPK activator berberine promotes macrophage reverse cholesterol transport in cell culture; metformin probably shares this property. Many of these measures could also be expected to promote plaque stability by suppressing foam cell production of inflammatory cytokines and matrix metalloproteinases, and to reduce intimal monocyte infiltration by anti-inflammatory effects on vascular endothelium. Direct targeting of foam cells with agents such as phase 2 inducers, spirulina, salicylate, taurine, and berberine or metformin, may hence have considerable potential for preventing and reversing atheroma, and for preventing the plaque rupture that triggers vascular thrombosis.

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**Key words:** Atherosclerosis; Cholesterol; Inflammation; Phytochemical; Nutraceutical; Atherogenesis; Plaque; Cytokine; Antioxidant

**Core tip:** Reverse cholesterol transport from foam cells is of key importance to prevention and control of atherosclerosis. This essay reviews the molecular biology of foam cell regulation, and proposes that certain agents may be capable of acting directly on foam cells to amplify reverse cholesterol transport while also promoting plaque stability by limiting foam cell production of inflammatory cytokines and matrix metalloproteinases. Phase 2 inducers such as lipoic acid and green tea catechins, spirulina, salicylate, taurine, and AMPK activators such as metformin or berberine, appear to have potential in this regard – while acting in additional ways to benefit vascular health.

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**PHARMACEUTICAL HIGH DENSITY LIPOPROTEIN MODULATION HAS PROVED DISAPPOINTING**

Although reverse cholesterol transport from foam cells mediated by HDL particles clearly plays a key role in the prevention and control of atherosclerosis (Figure 1) and its complications[1-3], a recent meta-analysis strongly suggests that current pharmaceutical measures for increasing HDL cholesterol (*e.g.*, niacin, fibrates, CETP inhibitors) do not enhance health outcomes in at-risk subjects – or rather, only do so to the extent that, like niacin, they favorably influence other determinants of atherogenesis such as LDL and apoB-bearing lipoproteins[4]. The failure of niacin in the AIM-HIGH trial – despite evidence of benefit in other studies[5, 6] – might then be explained by the fact that patients in the control group received a higher dose of statin such that reductions of LDL cholesterol were equivalent in each group[7]. Analogously, a Mendelian randomization analysis has determined that genotypes associated with elevated HDL cholesterol (but no other known determinants of cardiovascular risk), are not associated with a decline in risk for myocardial infarction[8]. (A similar analysis focusing on genetic determinants of LDL cholesterol provides striking confirmation of LDL’s pathogenicity[9].) The well-established epidemiological association of low HDL cholesterol with increased cardiovascular risk might therefore reflect the fact that low HDL cholesterol levels can serve as a marker for metabolic states – such as the metabolic syndrome – that are truly pathogenic; a similar analysis applies to moderately elevated homocysteine. There still may be scope for developing new drugs or procedures that improve the capacity of HDL particles to achieve reverse transport[10-13] – but available pharmaceutical agents capable of elevating HDL cholesterol do not seem to have that property. As the authors of the recent meta-analysis note: “Raising high density lipoprotein cholesterol without considering effects on high density lipoprotein function seem to have little promise for the prevention of cardiovascular events[4].”

It bears mentioning that the low HDL cholesterol levels seen in subjects carrying the Milano variant of apoA-1 are not associated with aggravated cardiovascular risk[14]; perhaps this reflects the efficiency with which Milano HDL delivers cholesterol to the liver for catabolism. Conversely, the elevation of HDL cholesterol associated with niacin therapy may reflect the fact that clinical concentrations of niacin ~~impede~~ lower the liver’s ability to catabolize holo-HDL particles[15]; while this increases the circulating apoA-1 pool, the amount of cholesterol per HDL particle also rises. Whether the increase in HDL associated with moderate alcohol consumption – likely attributable to enhanced hepatic synthesis of apoA-1[16] – is partially responsible for the decrease in cardiovascular risk observed in by prudent drinkers, is not yet clear; activation of AMPK by ethanol-derived acetate may contribute to alcohol’s vascular benefits[17].

**TARGETING FOAM CELLS DIRECTLY TO MODULATE FOAM CELL FORMATION AND BEHAVIOUR**

Despite the seeming inutility of current efforts to modulate HDL, it may still be feasible to promote reverse cholesterol transport with agents that act directly on foam cells to enhance their capacity to export cholesterol. Moreover, some of these agents could be expected to decrease foam cell uptake of modified LDL particles, and to work in other ways to promote plaque stabilization.

Egress of cholesterol from macrophages and foam cells is mediated by several membrane transport proteins, namely ABCA1, ABCG1, and SR-BI; ABCA1 preferentially interacts with lipid-poor apoA-1, ABCG1 can transfer cholesterol to all HDL particles, and SR-BI interacts with a wide range of lipoproteins[18]. The transcription of ABCA1 and ABCG1 is promoted by the LXR receptor, a transcription factor whose physiological activation is mediated by certain hydroxylated metabolites of cholesterol produced within macrophages which can function as ligands for LXR[19, 20]. (Increased intracellular cholesterol in macrophages also promotes increased expression of SR-BI, although this effect does not seem to be mediated *via* LXR[21].) In this way, increased cholesterol uptake by macrophages provokes a compensatory increase in cholesterol export induced by cholesterol metabolites. This LXR-mediated promotion of reverse cholesterol transport *via* HDL can be antagonized by a number of pro-inflammatory cytokines and agonists which have the common effect of activating NF-kappaB; concurrent suppression of NF-kappaB activity largely eliminates this inhibition of reverse cholesterol transport[22-27]. NF-kappa B activity somehow opposes the transcription of ABCA1, ABCG1, and SRB-1; how this occurs is still unclear. The balance between LXR and NF-kappaB activities is hence a key determinant of foam cell formation. NF-kappaB activation also is mediator of inflammatory cytokine production by foam cells, and can promote plaque destabilization by inducing production of matrix metalloproteinases[25, 28] – whereas LXR suppresses production of MMP-9[29].

***Heme oxygenase-1, phase 2 inducers, bilirubin, and spirulina***

A number of studies reveal that induction of heme oxygenase-1 (HO-1) in foam cells promotes reverse cholesterol transport, induces increased expression of ABCA1, ABCG1, and SR-BI, and acts in other ways to suppress foam cell production of pro-inflammatory cytokines and plaque-destabilizing metalloproteinases[30-37]. Hence, HO-1 induction can aid prevention of plaque formation, promote plaque regression, and render plaque more stable. Suppression of NF-kappaB activation appears likely to underlie many of these protective effects, since HO-1 activity has been shown to impede NF-kappaB activation in a number of ~~or~~ circumstances[38-47]. (There appears to be no evidence that HO-1 could influence LXR function.) Macrophage HO-1 induction can also oppose AP-1 activation, an effect which could be expected to reduce uptake of modified LDL by diminishing expression of the SR-A receptor[32, 33]. The respective roles of HO-1 products carbon monoxide and biliverdin/bilirubin in favorable modulation of foam cell function have not yet been clarified. As HO-1 can be induced by phase 2-inductive phytochemicals *via* the Nrf2 transcription factor[48], such agents evidently have potential for promoting reverse cholesterol transport and aiding prevention, regression, and stabilization of plaque. Lipoic acid, a broad range of flavanoids (including notably green tea catechins), isothiocyanates from crucifera, and organosulfur compounds from garlic and onions, can serve as phase 2 inducers[49-57] – albeit what intakes of these might have a functionally significant impact on HO-1 in foam cells is unknown. Lipoic acid is of particular interest in this regard, inasmuch as well-defined dose schedules (600-1800 mg daily) exert protective effects in diabetic neuropathy, which seem likely to reflect phase 2 induction[58]. Not surprisingly, lipoic acid exerts anti-atherosclerotic activity in rodents[59-62].

The antioxidant effects of HO-1 are mediated largely by bilirubin, which functions physiologically to inhibit certain isoforms of NADPH oxidase[63-66]. The inverse correlation of serum bilirubin levels with cardiovascular risk observed in many epidemiological studies[67-69] may well reflect the antioxidant impact of free bilirubin on the vascular wall – endothelium, foam cells, and smooth muscle cells. A number of agonists which stimulate NF-kappaB activity in macrophages concurrently activate NADPH oxidase, which boosts NF-kappaB activation *via* oxidant mechanisms[70-79]. It is therefore reasonable to suspect that HO-1 induction promotes reverse cholesterol transport, in part, by suppressing the up-regulatory impact of NADPH oxidase on NF-kappaB activity. Consistent with this possibility, the ability of advanced glycation endproducts to suppress expression of ABCA1 and ABCG1 expression in macrophages is blocked by inhibitors of NADPH oxidase[80, 81]. Macrophage NADPH oxidase activity could also be expected to promote foam cell formation by promoting oxidative modification of LDL.

Recent studies indicate that bilirubin’s antioxidant effect can be mimicked by phycocyanobilin (PhyCB), a prominent light-absorbing chromophore in cyanobacteria such as spirulina; PhyCB is a metabolite and close structural analog of biliverdin, the precursor of bilirubin[82, 83]. Not surprisingly, the only study to date which has evaluated oral administration of spirulina or its PhyCB-bearing protein phycocyanin in a rodent model of atherogenesis (cholesterol-fed hamsters) observed a profound anti-atherosclerotic effect[84]. An anti-inflammatory impact on vascular endothelial cells, coupled with a suppressive impact on intimal foam cell formation, seems likely to account for this observation. The ability of bilirubin and of PhyCB to maintain reverse cholesterol transport in macrophages stimulated with various pro-inflammatory agonists that otherwise would inhibit it, should be assessed.

***Salicylate suppresses NF-kappaB activity***

Activation of NF-kappaB can often be suppressed more directly with salicylate, a direct inhibitor of IKK-beta, in clinical doses that do not entail important inhibition of cyclooxygenase, and hence are relatively safe[85-88]. In foam cells *in vitro*, aspirin (which shares salicylate’s capacity to inhibit IKK-beta) was found to suppress the transcriptional activity of NF-kappaB and – likely as a result – boost expression of ABCA1 and SRB-1 while suppressing that of matrix metalloproteinase-9 (a mediator of plaque instability)[25]. In doses of 3-4.5 g daily, salicylate (preferably as salsalate) has been shown to modestly aid glycemic control in diabetics, likely *via* its inhibition of IKK-beta[89-91]; it might be feasible to employ salicylate in comparable doses to promote reverse cholesterol transport and stabilize plaque in patients with atheroma.

***Taurine as an LXR agonist***

Pharmaceutical LXR agonists can promote reverse cholesterol transport in macrophages, and some of these are being evaluated as potential new drugs for control of atherosclerosis[92-94]. Unfortunately, most such agents also boost hepatic lipogenesis *via* LXR activity, an effect viewed as undesirable[94]. A particularly intriguing recent discovery is that the essential cofactor taurine can act as a weak agonist for LXRalpha; moreover, taurine can enhance the expression of ABCA1and ABCG1, and promote reverse cholesterol transport, in cultured macrophages[95]. Curiously, owing to a countervailing effect, taurine fails to promote hepatic lipogenesis, and is very well tolerated[95]. A number of studies have demonstrated that dietary taurine can impede atherogenesis in rodent models of this disorder[96-103]; this effect is stronger than could be predicted from the modest hypolipidemic effects of taurine in rodents, and it would be of interest to know whether a favorable impact on the function of intimal macrophages plays a role in taurine’s anti-atherosclerotic activity. If so, taurine – which appears to have minimal impact on serum lipids in humans – might have clinical utility for preventing and controlling atherosclerosis[104, 105]. Of related interest is the possibility that taurine’s antioxidant activity may be helpful for preventing LDL modification mediated by hypochlorous acid, a myeloperoxidase product[106]. Moreover, rodent and limited clinical studies suggest that taurine supplementation has the potential to favorably influence platelet stability, blood pressure, and the failing heart[107]. The continuing neglect of this inexpensive and well tolerated nutrient by clinical researchers is mystifying.

***AMPK activators***

The anti-diabetic nutraceutical berberine, whose clinical efficacy resembles that of metformin in being contingent on activation of AMPK, has exerted anti-atherogenic effects in some but not all rodent models of this disorder[108-110]. The AMPK activator AICAR has been shown to promote reverse cholesterol transport in cultured macrophages by boosting expression of ABCG1[111]. Studies examining the impact of berberine on cultured macrophages report that it can exert a range of effects likely to antagonize foam cell formation and stabilize plaque – inhibiting activation of NADPH oxidase and NF-kappaB, inhibiting MMP-9 expression, and antagonizing cholesterol accumulation by inducing expression of ABCA1 or SRB-1, or suppressing expression of the LOX-1 LDL receptor for oxidized LDL[112-114]. On the other hand, one study found that berberine exposure increased macrophage uptake of modified LDL by increasing expression of the SRA-1 receptor[115]. The impact of metformin on foam cell function appears to have received little or no study. *In vivo*, berberine could also be expected to reduce foam cell formation by decreasing circulating LDL; it boosts hepatocyte expression of the LDL receptor by a mechanism that is complementary to that of statins[116].

**CONCLUSION**

It should not go unnoted that many of the agents discussed here – notably phase 2 inducers[117-122], PhyCB[123-125], salsalate[126-128], and berberine or metformin[129-134] – have the potential to impede foam cell formation by exerting anti-inflammatory effects on endothelial cells that would be expected to impede monocyte migration across the endothelial barrier into arterial intima. Each of these agents can work in various ways to inhibit endothelial NF-kappaB activity, which promotes the adhesion of monocytes to the endothelial surface and their subsequent transmigration (Figure 2)[135-137].

In summation – whereas current pharmaceutical strategies for increasing HDL cholesterol appear to have little clinical utility (aside from those which concurrently lower LDL levels), other clinically feasible measures which directly influence intimal macrophages have the potential to promote reverse cholesterol transport, and hence achieve the primary purpose intended for HDL elevation. These measures include administration of phase 2-inducing nutraceuticals (such as lipoic acid, green tea catechins, and cruciferous isothiocyanates), spirulina or PhyCB, salsalate, taurine, and berberine. These effects are mediated primarily by inhibition of NF-kappaB activation or by LXRalpha agonism. Moreover, most of these agents might be expected to impact foam cell function in other complementary ways that would be clinically useful – suppressing macrophage uptake of modified LDL, and inhibiting macrophage production of inflammatory cytokines and matrix metalloproteinases that could destabilize plaque. And most of them, *via* direct anti-inflammatory effects on vascular endothelium, should also impede foam cell formation by suppressing transendothelial migration of monocytes. These agents evidently merit further evaluation, both in animal models and ultimately clinical trials, as measures for preventing, reversing, and stabilizing arterial plaque. And the fact that most of these agents are nutraceuticals suggests that they might be especially feasible for use in primary prevention.

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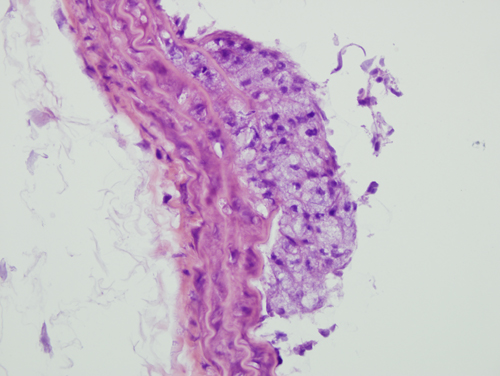
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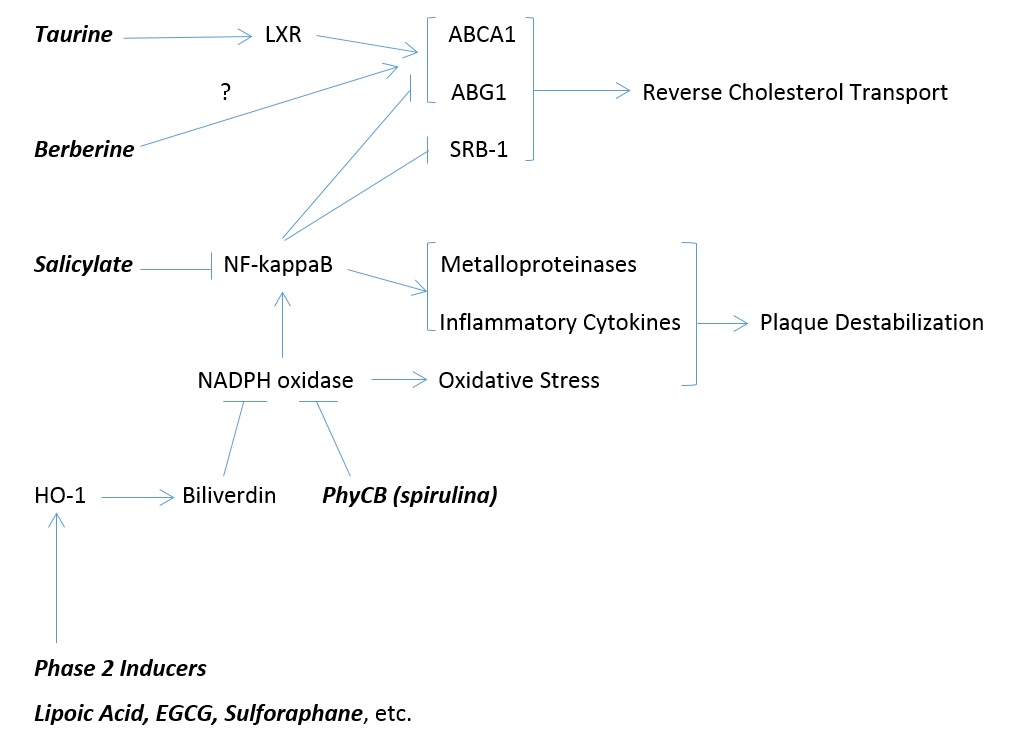
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**Figure 1 An atherosclerotic plaque at its early stage of development in the thoracic aorta of an** **apolipoprotein E-KO mouse is illustrated.** The plaque is primarily composed of apparent foam cells. HE staining × 400.



**Figure 2** **Nutraceutical/drug regulation of foam cell cholesterol transport and plaque stability.** LXR: Liver X receptors.