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Review

Role of HDL, ApoA-I, and related peptides in protection against atherosclerosis

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ABSTRACT

The purpose of this review is to summarize recent reports on the role of HDL (High Density Lipoprotein) and apolipoprotein A-I (apoA-I) mimetics in protection against atherosclerosis. HDL and HDL mimetic peptides continue to demonstrate beneficial effects in preclinical studies. HDL-cholesterol is only a minor part of the HDL particle and the reason HDL levels are expressed as HDL-cholesterol is the simplicity of measurement of the cholesterol associated with HDL particle. In addition, the composition of HDL, its function and protective capacity is not reflected by its cholesterol content. Several major studies have shown that simply increasing the amount of circulating HDL-cholesterol does not reduce the risk of coronary heart disease (CHD) events, CHD deaths, or total mortality. HDL-cholesterol does not define the lipids and the proteins associated with HDL and the HDL-proteome can be just a mediator or a marker of CHD. The efficacy of apolipoprotein A-I (apoA-I) in preliminary human studies and in improving atherosclerosis in animal models makes it an attractive therapeutic candidate. However, it has 243 amino acid residues, necessitating it to be given intravenously and making it difficult and expensive to synthesize. ApoA-I is a selective target for myeloperoxidase-catalyzed oxidation, which results in impairment of the ability of HDL to promote cholesterol efflux. HDL could be a therapeutic target by modifying its protein and lipid cargo to improve its anti-inflammatory properties. Treatment with apolipoprotein mimetic peptides is among the methods that can modify the lipid and protein cargo of HDL. In summary one reason for the failure of the new compounds that increased HDL-cholesterol levels but did not reduce coronary events could be interference in the function of cholesterol ester transfer protein (CETP). An additional reason could be that the composition and the function of HDL was not the focus of the studies. Mere increase of HDL-cholesterol might not always be sufficient and there is a need to increase the level of HDL molecules that actually protect against atherosclerosis.

KEYWORDS: HDL, apoA-I mimetic peptide, inflammation, cancer, CHD, lysophosphatidic acid, intestine, 4F, 6F

INTRODUCTION

HDL function vs. HDL-cholesterol

For the past four decades low levels of serum HDL-cholesterol has pointed to elevated risk for patients and a large body of evidence suggests

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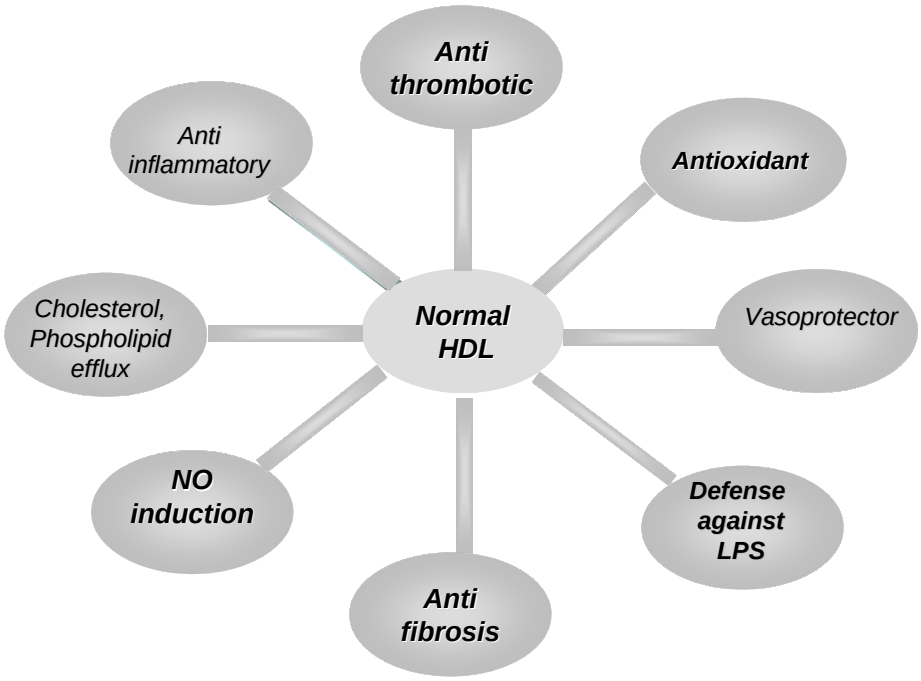

Figure 1. Protective role of HDL in various settings.

that HDL may play a variety of anti-atherogenic roles (Figure 1) [1]. For decades efforts were made to raise HDL-cholesterol with the hope to reduce cardiovascular risk. At this time however, based on the failure of large randomized trials, levels of circulating HDL-cholesterol are not thought to be a therapeutic target. According to the established guidelines, in patients at risk, low-density lipoprotein (LDL)-cholesterol and non-HDL-cholesterol are recommended to be the primary and secondary targets of therapy. In addition information on the individual total-cholesterol and HDL-cholesterol components is significant and needed. Both are currently examined as two separate, but related, risk factors in risk assessment/treatment recommendations [2, 3, 4]. Additionally, at present the joint consideration of non-HDL-cholesterol and of HDL-cholesterol is recommended and followed widely. Interestingly the question has been raised that if low levels of HDL-cholesterol predict elevated risk of adverse cardiovascular outcomes, then would high or very high plasma concentrations of HDL-cholesterol mean predicting reduced risk? In fact, high levels of HDL-cholesterol, namely >60 mg/dL was recommended by ATP II (Adult treatment panel II) guidelines to be added, as a negative risk factor. The logic has been that otherwise the presence of any traditional cardiovascular disease risk factors might be counteracted. In 1957 the association between high HDL-C (High Density Lipoprotein-Cholesterol) and longevity was initially suggested [5]. However, later it was discovered that genetic variations in cholesterol ester transfer protein (CETP) can be the cause of high HDL-cholesterol. Subsequently more extensive epidemiological and clinical studies did not unanimously confirm association between high HDL levels due to CETP polymorphism and longevity [6, 7, 8, 9]. Further disappointment of course followed in light of the findings from the large clinical trials on CETP inhibitors that showed very high increases in HDL-cholesterol levels with no reduction in events or mortality [10]. This is not surprising since the rise in HDL-cholesterol in response to pharmacological inhibition of CETP is not due to increased cholesterol uptake from the target tissues. Instead it is due to the blockade of the CETP-mediated exchange of cholesterol ester (CE) for triglycerides between HDL and LDL/ IDL (Intermediate Density Lipoprotein) particles in the plasma. Given the critical role of CETP in

transforming oxidation-prone, atherogenic and pro-inflammatory IDL and CE-poor LDL to CE-rich LDL which can be readily removed by the liver via LDL receptor, blockade of CETP can actually promote atherosclerosis by facilitating accumulation of atherogenic lipoproteins. Thus the rise in HDL-C and the fall in LDL-C (Low Density Lipoprotein-Cholesterol) with these agents represent a potentially harmful phenomenon which accounts for the failure of the randomized clinical trials of CETP inhibitors.

Measuring HDL-cholesterol levels, provides only information about the size of the HDL pool, but does not predict HDL composition or function and protective capacity against lipid oxidation. The main component of HDL, apolipoprotein A-I (apoA-I) [11] is largely responsible for reverse cholesterol transport through the macrophage ATP-binding cassette transporter ABCA-1. It has been shown to have beneficial effects in preliminary human studies and in improving atherosclerosis in animal models [12, 13]. However the high cost of synthesizing it renders its long term therapeutic use impractical [14].

ApoA-I however, can be damaged by oxidative mechanisms which render this apolipoprotein less capable of promoting cholesterol efflux. HDL also contains a number of other proteins that are affected by the oxidative environment of the acute response. Modification of the protein components of HDL can convert it from an anti-inflammatory to a pro-inflammatory particle. One way to reverse this is using mimetic peptides with extremely high affinity for binding oxidized lipids to renew and reactivate HDL [15]. The failure of the recent clinical trials resulting in high HDL-cholesterol that did not reduce cardiovascular events has raised the question: is HDL-cholesterol a risk factor or is it a biomarker of risk? The inconsistencies observed in the relationship between HDL-cholesterol level and CVD (Cardio Vascular Disease) risk in large epidemiologic studies has generated the proposal that rather than being directly causative in this process, HDL-cholesterol may be more of a biomarker of risk. It is well known that HDL-cholesterol levels inversely correlate with cigarette smoking, insulin resistance, serum triglycerides, small dense LDL particles, waist circumference, and obesity. These conditions lead to complications that even with careful adjustment for the above covariates it is difficult to adequately assess the risk or association with HDL-C levels. Although administering HDL has been shown to reduce the plaque burden in the cholesterol-fed rabbits [16] and improve flow mediated artery dilation in individuals with low serum HDL-cholesterol levels [17], more robust and direct evidence indicating effect on lesion and particularly on outcome is needed in humans. Unfortunately since HDL-cholesterol is so closely intertwined with other factors that influence CVD risk, it is unlikely that epidemiologic studies will ever be able to adequately resolve this issue. Therefore in light of the recent concerns, it has been recommended that extensive research into the clinical significance and biology of low HDL-cholesterol should continue. Continued work on the development of new drugs that can raise the circulating levels and improve the composition and function of HDL particles is also emphasized (Figure 2) [10].

HDL mimetics

One of the areas that has attracted interest is mimetics of HDL or apoA-I mimetic peptides. Small peptides that mimic some of the properties of apoA-I have been shown in preclinical models to improve HDL function and reduce atherosclerosis without altering HDL-cholesterol levels. HDL mimetics containing a peptide or protein have been constructed with as many as 243 and as few as 4 amino acid residues. They all bind lipids found in HDL. Some HDL mimetics have been constructed without a peptide or protein component but they contain lipid. Many have a remarkable ability to bind oxidized lipids while others promote cholesterol efflux and many have anti-inflammatory properties (Figure 3).

Segrest, Anantharamaiah and colleagues designed an 18-amino acid peptide that mimicked the class A amphipathic helixes contained in apoA-I [6, 18, 19] and was called 2F because of the two phenylalanine residues on the hydrophobic face. A series of peptides were tested for their ability to inhibit LDL oxidation and LDL-induced production of monocyte chemoattractant-1 (MCP-1) in response to LDL-derived oxidized lipids *in vitro* [20, 21], and peptides 4F and 5F were selected for testing in

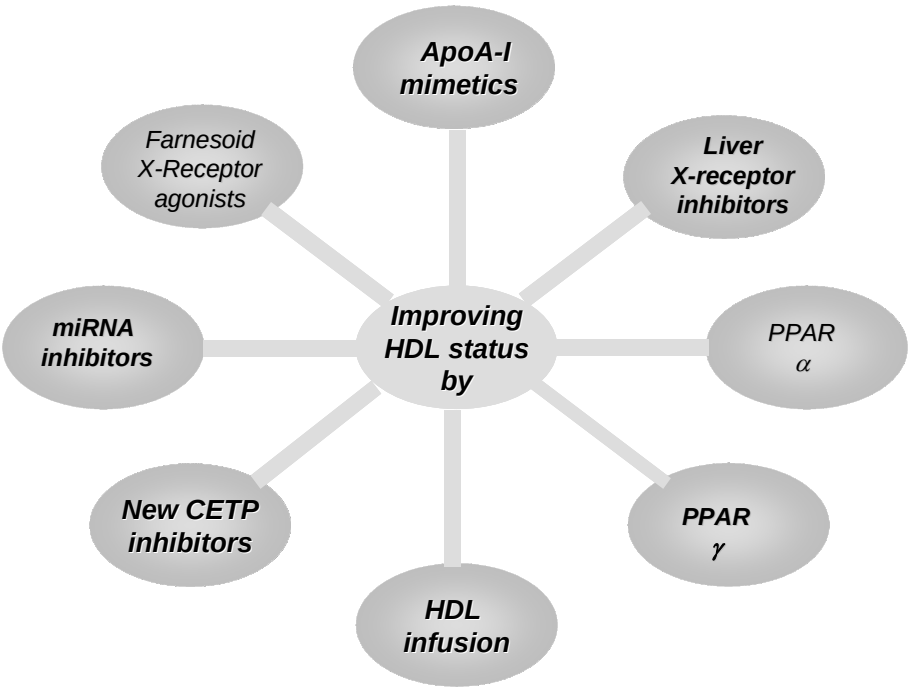

Figure 2. Efforts toward improving HDL levels, composition and function.

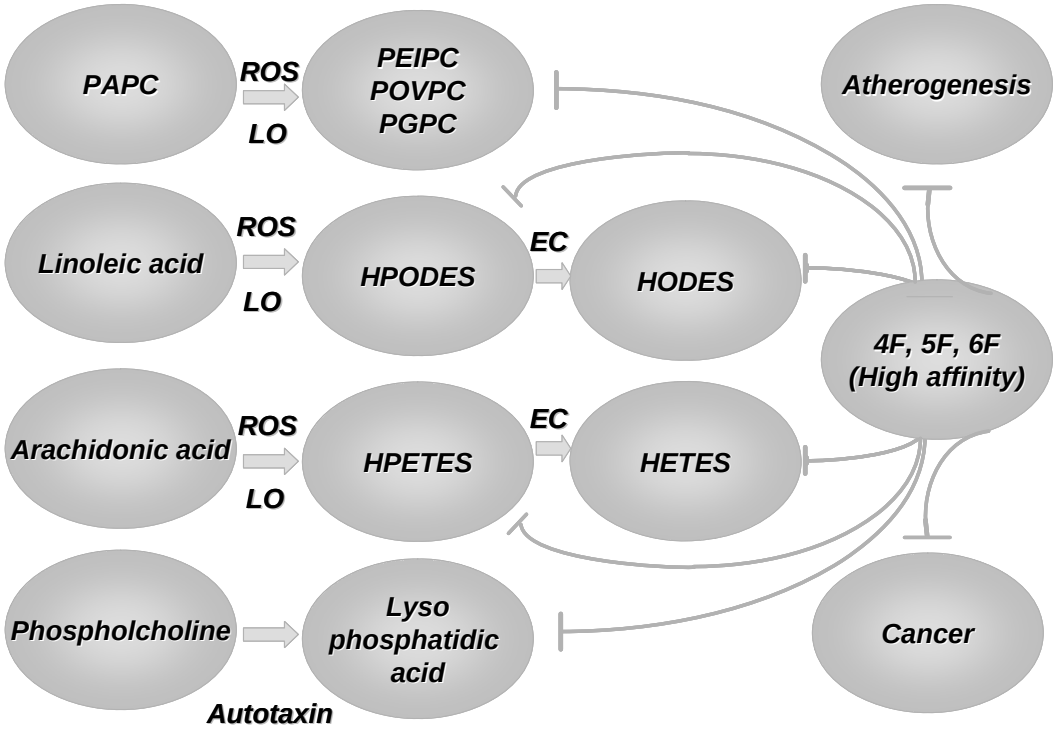

Figure 3. Lipid oxidation and protection by apoA-I mimetic peptides. ROS, reactive oxygen species; LO, lipoxygenase; EC, endothelial cells; HPODE, hydroperoxyoctadecadienoic acid; HPETE, hydroperoxyeicosatetraenoic acid; HODE, hydroxyoctadecadienoic acid; HETE, hydroxyeicosatetraenoic acid.

animal models. The peptide 5F when injected into mice with diet-induced atherosclerosis resulted in improvement in the anti-inflammatory properties of HDL [21] and significant reduction in atherosclerosis [22].

Administration of the 4F peptide improved a number of pathological processes in animal models including Type I diabetes [23, 24], Type II diabetes [25, 26], influenza A pneumonia [27], obesity [25, 26], hyperlipidemia and sickle cell-induced vascular dysfunction [28], scleroderma [29], hepatic fibrosis [30], arthritis [31], vascular dementia [32], Alzheimer's disease [33], chronic kidney disease and hyperlipidemia-induced renal inflammation [34, 35]. In a mouse model [36] 4F peptide inhibited accelerated vein graft atherosclerosis and in old apoE-null mice was found to synergize with statins and cause regression of atherosclerotic lesions [37]. D-4F significantly improved the anti-inflammatory properties of HDL in humans with CHD following a single oral dose [38]. The 4F peptides and apoA-I bind non-oxidized lipids with similar affinities. Oxidation of PAPC (palmitoyl arachidonoyl phosphatidylcholine) produced a series of oxidation products which potently induce MCP-1 by stimulating human aortic endothelial cells [39]. The binding affinity of L-4F for these oxidized phospholipids was several million-fold greater than it was for apoA-I [40]. It was hypothesized that apoA-I mimetic peptides which bind pro-inflammatory oxidized lipids with such high affinity will be found to be anti-inflammatory and that has proven to be the case.

It was reported [41] that the 3F-2 peptide which has bioactivity and binding characteristics very similar to 4F had a plasma $T_{1/2}$ of approximately 30 minutes. In other studies on HDL remodeling *in vitro* and in cholesterol efflux, tandem 4F-based peptides were superior to a single 4F peptide [42]. The tandem peptides reduced serum amyloid A (SAA) in apoE-null mice. In other studies [43] a tandem peptide was found to be particularly potent in stimulating ABCA1-mediated cellular efflux when it contained five alanine residues in the second helix. While peptides based on the helical segment of apoA-I_{Milano} that contains cysteine variants were strong inhibitors of lipid peroxidation, cysteine-free peptides were found to be weak inhibitors of lipid peroxidation [44]. Interestingly in studies in WHHL (Watanabe heritable hyperlipemic) rabbits plasma cholesterol levels were reduced and arterial endothelial function was improved by a dual-domain peptide with a class A amphipathic helix linked to the receptor-binding domain of apoE (Ac-hE-18A-$NH_2$0) [45]. In addition plasma lipid hydroperoxide levels were reduced, paraoxonase-1 activity was increased, and superoxide anion levels were reduced.

ApolipoproteinJ is an HDL associated protein that has anti-inflammatory properties [45]. A 10-amino acid residue from apoJ containing a G* helix reduced atherosclerosis in apoE-null mice and rendered HDL anti-inflammatory in mice on Western diet and in monkeys [46].

Other mimetic peptides

Several smaller peptides such as those with amino acid sequences KRES and FREL that are not capable of forming a helix were also found to be able to improve HDL anti-inflammatory properties in monkeys and mice and reduce atherosclerosis in apoE-null mice [47]. Infusion of a class A amphipathic peptide containing 22 amino acid residues complexed with egg sphingomyelin and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine and without terminal blocking groups led to regression of aortic valve stenosis in rabbits maintained on a cholesterol-enriched diet supplemented with vitamin D_2 [48, 49]. When two 18A peptides were joined by a proline residue forming the peptide 37pA it was possible to elucidate atherosclerotic plaque composition in a mouse model of atherosclerosis by constructing nanoparticles from the 37pA and delivering MRI contrast agent into arteries. Although particles made from the 37pA demonstrated better lipid-binding properties *in vitro*, particles made with 18A or 37pA gave similar desirable contrasts for the detection of atherosclerotic macrophages [50].

Using HDL lipids to make mimetics

As an alternative approach to making HDL or apoA-I mimetic compounds, the lipid constituents of HDL were utilized [50]. Infusion of large unilamellar vesicles into patients with coronary atherosclerosis may have improved nitroglycerin-mediated dilation but it did not significantly improve brachial artery flow-mediated dilation.

There was a reduction in peripheral blood monocyte CD11b, neutrophil adhesion to fibrinogen matrix and an improvement of HDL inflammatory properties when recombinant HDL was infused into 13 male patients with type 2 diabetes mellitus [52]. Interestingly the plasma from the subjects demonstrated increased ability to receive cholesterol from THP-1 macrophages following the infusion of the recombinant HDL [53]. Infusion of recombinant HDL in another study involving 13 diabetic subjects with type 2 diabetes mellitus increased plasma insulin, stimulated AMP-activated protein kinase in skeletal muscle and reduced plasma glucose levels [53].

Making oral mimetics more stable

Niclosamide is a compound that has been in clinical use for the treatment of parasitic infections for more than 3 decades and has very low toxicity for humans. At acid pH, L-4F results in a very tight association with 4F that protects the peptide from trypsin digestion. This helps absorption of oral L-4F while maintaining its biological activity [54]. Niclosamide was also able to bind a class G* amphipathic that binds oxidized lipids, improves HDL function, reduces oxidized lipid induced MCP-1 production in artery wall cells and inhibits arterial lesions in the mouse models [54].

For the purpose of diagnosis and treatment of acute coronary events the use of HDL mimetics via intravenous administration is useful and practical. Since large unilamellar vesicles [50] and reconstituted HDL particles [4, 18, 48, 50, 51] appear to require intravenous infusion, these preparations are likely beneficial in a diagnostic test or in acute situations [51, 52]. For chronic conditions and complications the use of finer compounds that can be administered orally [29, 30, 48-51, 54, 35, 3, 38], or via subcutaneous injection appears to be more optimal and attractive. For example as stated above, the peptide 4F containing 18-aa residue was well tolerated and synergized with statins [37] in mice. The 4F peptide was recently shown to reverse a variety of pathological conditions in the $LDLR^{-/-}$ mice that was exposed to diesel ultrafine particles [56].

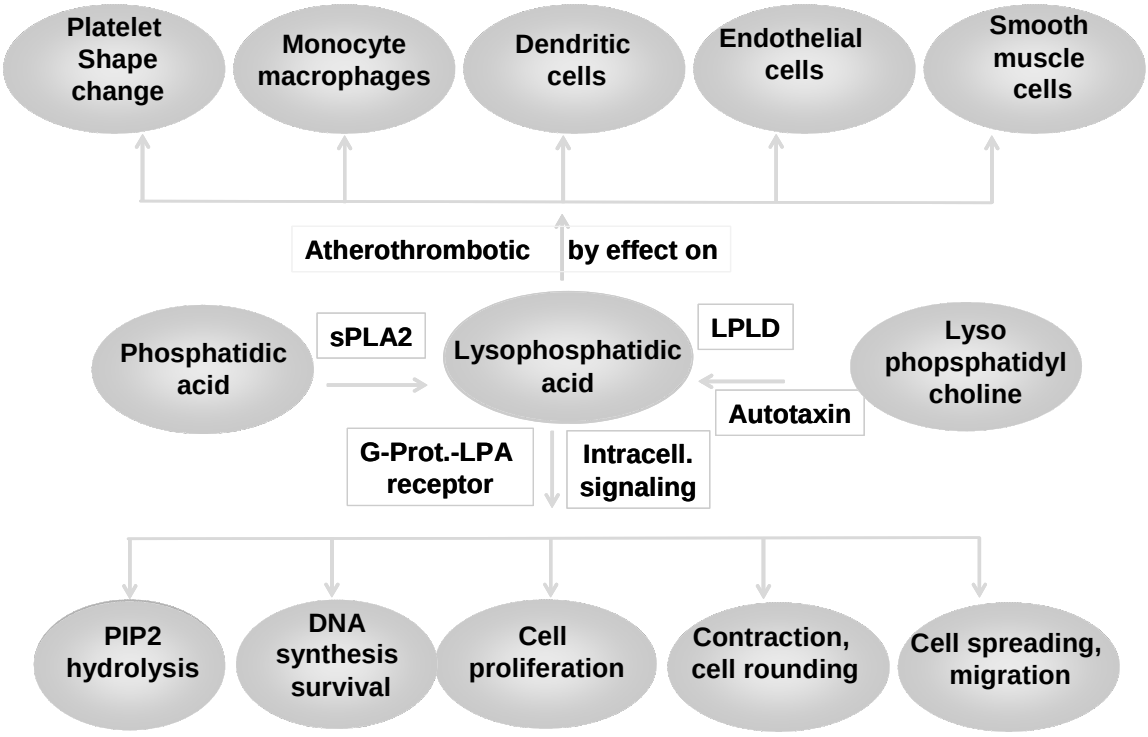

Figure 4. The role of apoA-I mimetic peptides preventing atherothrombotic and carcinogenic effects of lysophosphatidic acid.

Additionally 4F was shown to rescue pulmonary hypertension in rats and in $LDLR^{-/-}$ mice on Western diet through induction of microRNA193 [57].

Studies in patients with CHD have suggested that 4F may possess additional benefit in patients taking statins [38]. It, therefore, has been suggested that in treating chronic complications, the use of these peptides could be appropriate and beneficial. Studies on lipoproteins from patients with heart failure [58] or with renal failure [59-63] support this suggestion. HDL and LDL from the heart failure patients contained orders of magnitude higher levels of oxidized lipids, and treatment of the HDL and LDL from heart failure patient or HDL from renal failure patients with nanogram levels of 4F *in vitro* removed the oxidized lipids from HDL and improved the HDL anti-inflammatory capacity [58-63].

Three new developments have generated special excitement in the area of peptide mimetics: First, intestine appears to play a major role in the metabolism and effect of apoAI peptide mimetics [64, 65], second, in preclinical studies these peptides have anti-cancer potential and third, expression of these peptides in edible plants to minimize the cost of their production seems to be promising.

Antitumor activity of peptides

In mouse models of ovarian cancer and colon cancer 4F was shown to significantly reduce the number, size and volume of tumors [66, 67]. This is at least partially due to the extremely high affinity of the peptide (Kd = 1.0E-10) for the potent tumor promoter lysophosphatidic acid (Figure 4) [66, 67].

Expression of mimetic peptide in edible plants

To reduce the cost of production of the peptide, 6F was expressed in tomatoes [68], and the resulting transgenic tomato introduced as lyophilized powder into the high-fat high-cholesterol diet of LDL-receptor-deficient mice reduced systemic inflammation and the lesion burden [68, 69].

CONCLUSION

Information on plasma HDL-cholesterol levels does not necessarily help predicting the risk of CHD. HDL protective capacity appears to be a better index [70]. Robust assays for determination of HDL functionality are urgently needed. Prevention of oxidative and inflammatory pressure should help prevent damage to HDL and its conversion to a proinflammatory agent. As discussed above, a variety of peptides and combination of lipids, and proteins have been made to mimic apoA-1 and HDL. These compounds can help HDL to maintain or regain its protective function [70]. Over one hundred studies and investigations have employed them in various animal models of metabolic and inflammatory disorders with promising outcomes. Early human trials indicate that they can potentially play diagnostic and therapeutic roles.

KEY POINTS

- Apolipoprotein A-I mimetic peptides show beneficial effects in a large number of animal models of CAD (Coronary Artery Disease), in cancer and dozens of other diseases.
- The GI tract appears to be of particular importance in the anti-inflammatory effect of the peptides since oral administration does not highly raise the blood levels and yet reduces the systemic inflammatory pressure.
- Since the mimetic peptide use needs to be long term and the cost of chemical synthesis is high, there is a need to be able to generate them in an economical manner.

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CONFLICT OF INTEREST STATEMENT

No relations to disclose.

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