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PERSPECTIVE

The Pathogenic Role of Foam Cells in Atherogenesis: Do They Represent Novel Therapeutic Targets?

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Abstract: ***Background*****:** Foam cells, mainly derived from monocytes-macrophages, contain lipid droplets essentially composed of cholesterol in their cytoplasm. They infiltrate the intima of arteries, contributing to the formation of atherosclerotic plaques.

Pathogenesis**:** Foam cells damage the arterial cell wall *via* the release of proinflammatory cytokines, free radicals, and matrix metalloproteinases, enhancing the plaque size up to its rupture.

Therapy**:** A correct dietary regimen seems to be the most appropriate therapeutic approach to minimize obesity, which is associated with the formation of foam cells. At the same time, different types of antioxidants have been evaluated to arrest the formation of foam cells, even if the results are still contradictory. In any case, a combination of antioxidants seems to be more efficient in the prevention of atherosclerosis.

Keywords: Atherosclerosis, cholesterol, low-density lipoproteins, foam cells, obesity, atheromatic plaques, antioxidants.

1. INTRODUCTION

There is evidence that cardiovascular diseases (CVD), neurodegenerative disease, and malignancy are strictly associated with the obesity epidemic, which, in turn, depends mainly on western-type diet consumption [1, 2]. With particular reference to CVD, dietary fats accumulate into monocytes-macrophages either intra-abdominally or in the context of terminal arteries wall (*e.g.*, coronary arteries), thus, generating foam cells [3]. In this respect, foam cells contribute to atherosclerotic plaque formation, coronary obstruction, and myocardial ischemia [4].

According to a classical definition, foam cells originate from a dysregulated lipid accumulation into mammalian macrophages with lipid droplet formation into the cytoplasm. The pathogenic role of foam cells has been ascertained in several metabolic diseases, such as atherosclerosis-related hyperlipidemia, diabetes mellitus / insulin resistance, and obesity [5-8]. Inflammatory systemic diseases, such as systemic erythematosus lupus [9], rheumatoid arthritis [10], sarcoidosis [11], and inflammatory bowel disease [12], may also increase cardiovascular risk and cardiovascular-related morbidity and mortality.

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However, it is worthwhile mentioning that foam cells have been detected in other pathologies, such as tuberculosis, multiple sclerosis, and cancer [13-15]. Lipid droplets are mainly composed of a phospholipid monolayer, containing several proteins and surrounding a core of cholesteryl esters and triglycerides [16]. They accumulate within the cellular endoplasmic reticulum (ER) bilayer and grow *via* synthesis of neutral lipids or fusion of small vesicles and, ultimately, can be broken down either by lipolysis or lipophagy [17].

Of note, lipid droplets exert a plethora of actions, modulating the immune function and antimicrobial activity of macrophages, promoting the production of eicosanoids while inhibiting antigen presentation by dendritic cells in cancer [18-20].

With particular reference to foam cell biogenesis, data are controversial. According to Guerrini and Gennaro, foam cells in atherosclerotic lesions originate from cholesterol-rich macrophages, while those present within tuberculous granulomas are relatively abundant in triglycerides [21].

In this perspective, the foam cell-mediated pathogenesis of the inflammatory process, with particular reference to atherosclerosis, will be illustrated. Finally, therapeutic strategies aimed to prevent or reduce foam cell formation will be discussed.

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2. DIFFERENT STEPS OF THE ATHEROGENIC PROCESS

The fatty streak formation represents a precocious sign of atherosclerosis and depends on the accumulation of low-density lipoproteins (LDL) beneath the arterial intima thickness [22, 23]. In particular, the glycocalyx of the innermost layer of artery walls regulates LDL transport into the intima, which can cross the endothelium *via* transcytosis through vesicles [24, 25]. Once activated, endothelial cells express on their surface some adhesion molecules, such as the intracellular adhesion molecule -1 and vascular adhesion molecule (VCAM)-1, P-selectin, and E-selectin for the binding of incoming leukocytes to occur [26]. Among leukocytes, monocyte-derived macrophages entrap oxidized (ox)-LDL to form foam cells [27, 28]. On the other hand, monocytes not involved in forming foam cells secrete some cytokines, growth factors, procoagulant factors, and free radicals, promoting LDL oxidation.

Atherosclerotic plaque is essentially a consequence of the accumulation of cholesterol, macrophages, cell debris, and connective tissue within the inner layer of the vessel wall [29]. After that, the migration of smooth muscle cells (SCMs) towards the intima leads to forming a fibrous cap rich in collagen, SMCs, macrophages, and T cells [30, 31]. Either macrophages or SMCs release matrix metalloproteinases (MMP)-1,2,8 and 13 that can digest the fibrous cap [32]. The balance of inflammatory activities in the arterial wall may affect the destiny of arterial plaques, as they could evolve in stable or unstable and, therefore, more susceptible to rupture formations [33, 34].

3. FOAM-CELL INDUCED INFLAMMATION

Compelling evidence has revealed that lipid droplets accumulate in foam cells and promote the synthesis of eicosanoids, which, in turn, are involved in systemic inflammation and cancer [35, 36]. For the synthesis of eicosanoids to occur, lipid droplets activate an array of enzymes, *e.g.*, phospholipase A2, Mitogen-Activated Protein Kinases (MAPK), prostaglandin E-synthase, and leukotriene C4-synthase [37]. Following activation of the enzymatic machinery, mobilization of arachidonic acid culminates in the production of prostaglandins (PGs) and leukotrienes. In pleural macrophages from mice infected with *Mycobacterium (M.) tuberculosis* Bacillus Calmette-Guérin (BCG), lipid droplets enriched in cyclo-oxygenase (COX)-2 have been detected [38]. Inhibiting *in vitro* formation of lipid droplets in BCG-infected murine peritoneal macrophages markedly reduced the production of PGE2. As it displays anti-inflammatory proprieties, this condition facilitates pathogen persistence [39, 40]. Alox5 -/- mice deficient in lipoxin 4, when infected with *M. tuberculosis*, exhibited about 100 times lower bacteria burden in the lungs in comparison to *ptges*-/- mice, deficient in PGE2 [41]. Conclusively, the generation of eicosanoids seems to be implicated in the regulation of tuberculosis clinical course.

The inflammatory profile of foam cells is sustained by *in vitro* studies. In murine macrophages, oxLDL bounded to the CD36/Toll-like receptor (TLR)-4, -6 complex, thus enhancing the synthesis and release of proinflammatory cytokines [42, 43]. In another report, evidence has been provided that long-chain saturated fatty acids mediated lipid-induced inflammation in bone-marrow-derived macrophages from *tlr4*-/- C57BL/6 mice, reprogramming macrophage metabolism [44].

A series of papers demonstrated that NRL Family Pyrin Domain Containing 3 inflammasome activation with release of interleukin (IL)-1 beta was attained by: 1) Cholesterol crystals from human and murine macrophages [45]; 2) Saturated fatty acid-induced stress of ER in human and murine macrophages [46]; 3) Lipid-induced lysosome and mitochondrial alteration in murine macrophages [47, 48]; 4) Autophagy induction and atherosclerotic progression, respectively [49].

Quite interestingly, human monocyte-derived macrophages, *in vitro* incubated with circulating lipoproteins or lipoprotein-derived from human atheroma, underwent intracellular lipid infiltration, inflammasome activation, and IL-1 beta secretion [50].

As recently reviewed by Guerrini and Gennaro [21], murine foamy and non-foamy macrophages, isolated from atherosclerotic lesions, changed their profile over time. In the early phase of plaque formation, macrophages did not exhibit an inflammatory profile in the attempt to get rid of intimal lipoproteins. Instead, in the progression of atherosclerosis, macrophages augmented their content of lipid droplets and aggravated lesions, becoming more inflammatory.

Alternatively, one cannot exclude that different subsets of foam cells may exist and induce chronic inflammation *via* mechanisms other than proinflammatory cytokine production [51].

Besides cytokines, evidence has been provided that foam cells may release MMPs and extracellular vesicles, which can determine tissue damage [52]. In rabbit and human atherosclerosis, foam cells *via* secretion of MMP-14 in the presence of lower amounts of the MMP-3 inhibitor, TIMP-3, contributed to plaque rupture [53]. These data are confirmed by the evidence that pravastatin, an MMP-3 inhibitor administered to patients with carotid artery stenosis, reduced the MMP content while elevating the levels of TIMP-1 and the amount of collagen in the context of carotid plaques [54].

Extracellular vesicles, enriched in proteins, lipids, and RNA, when released by murine foam cells, can foster vascular smooth muscle cell adhesion (VSMC) and migration *in vitro*, thus, accelerating the atherosclerosis process [55]. Furthermore, according to Nguyen and associates [56], transferring miR-146a from vesicles may involve target genes implicated in cell migration and adhesion.

Another function exerted by foam cells is to cause necrosis in both atherosclerosis and tuberculosis, thus, leading to chronic inflammation and tissue damage [57, 58].

In atherosclerosis, excessive accumulation of cholesterol leads to apoptosis of foam cells, which are not entirely eliminated by efferocytosis, ultimately giving rise to secondary necrosis and inflammation [59, 60]. In this last regard, Guerrini and Gennaro [25] have proposed that defective efferocytosis of foam cells by macrophages may

depend on different mechanisms: 1) Foam cells express "do not me" signals, such as the CD47 marker [61]; 2) Proteolytic removal from the macrophage surface of the apoptotic receptor, CD36 and the efferocytosis receptor, c-Mer tyrosine kinase, during atherogenesis [62, 63]; 3) Defective efferocytosis exerted by foam cells, because of the competition between lipid uptake and apoptotic cell uptake [64]; 4) Defective macrophage autophagy and reduced efferocytosis of foam cells [65].

In the course of tuberculosis, foam cells favor disease progression through the production of caseum and, thus, granuloma formation leads to lung destruction [66]. Furthermore, foam cells contribute to chronic inflammation in tuberculosis, releasing their proinflammatory content during necrosis [60].

The inflammatory role of foam cells in the progression of atherosclerosis is depicted in Fig. (**1**).

4. OBESITY-RELATED FOAM CELLS AND ATHEROSCLEROSIS

Foam cells infiltrate the adipose tissue in murine models of obesity and human obesity [67]. Macrophages of the adipose tissue are the significant sources of tissue foam cells, which account for low-grade inflammation and insulin resistance [68, 69]. In high-fat diet (HFD) C57BL/6 obese mice, adipose foam cells co-cultured with fat explants reduced insulin responsiveness, thus, playing a noxious role [8]. On the contrary, in ob/ob mice, inhibiting lipoprotein lipase of macrophages reduced foam cell formation with impairment of glucose tolerance, thus, suggesting a beneficial role of foam cells [70].

Besides adipose tissue foam cells, those accumulating in the arterial intima represent a precocious manifestation of atherosclerosis [71, 72]. Poznyak and associates [73] reviewed that circulating LDL and modified LDL are internalized bay macrophages, pericytes, and VSMCs, which, in turn, become foam cells once they enter vessel walls.

Hypercholesterolemia remarkably increases the risk of developing atherosclerosis. This phenomenon is mainly attributable to high circulating LDL cholesterol and apolipoprotein (apo) B 100 [74]. Infiltration of the complex LDL cholesterol/apoB 100 into the artery wall activates the transformation of monocytes into macrophages.

Even though macrophages and SMCs can take up native LDL, modified LDLs are the significant lipids in foam cells. OxLDLs are the principal modified LDL with small dense LDL, electronegative LDL, and desialylated LDL undergoing oxidation. Lipids internalization into macrophages at the intima thickness level occurs in the presence of scavenger receptors (SRs), with SR-AI and SR-AII exhibitting high affinity for acetylated LDL and oxLDLs [75]. Of note, desialylated LDL are more atherogenic given their higher cellular uptake and slower degradation rate.

In human aortic intima, modified LDL particles have been associated with collagenase-resistant arterial debris, collagen, elastin, and proteoglycans, thus, favoring cholesterol accumulation in cultured cells. Furthermore, LDL-containing circulating immune complexes led to cholesterol accumulation in cultured cells better than modified LDL alone, inducing proinflammatory cytokines and apoptosis in macrophages [76].

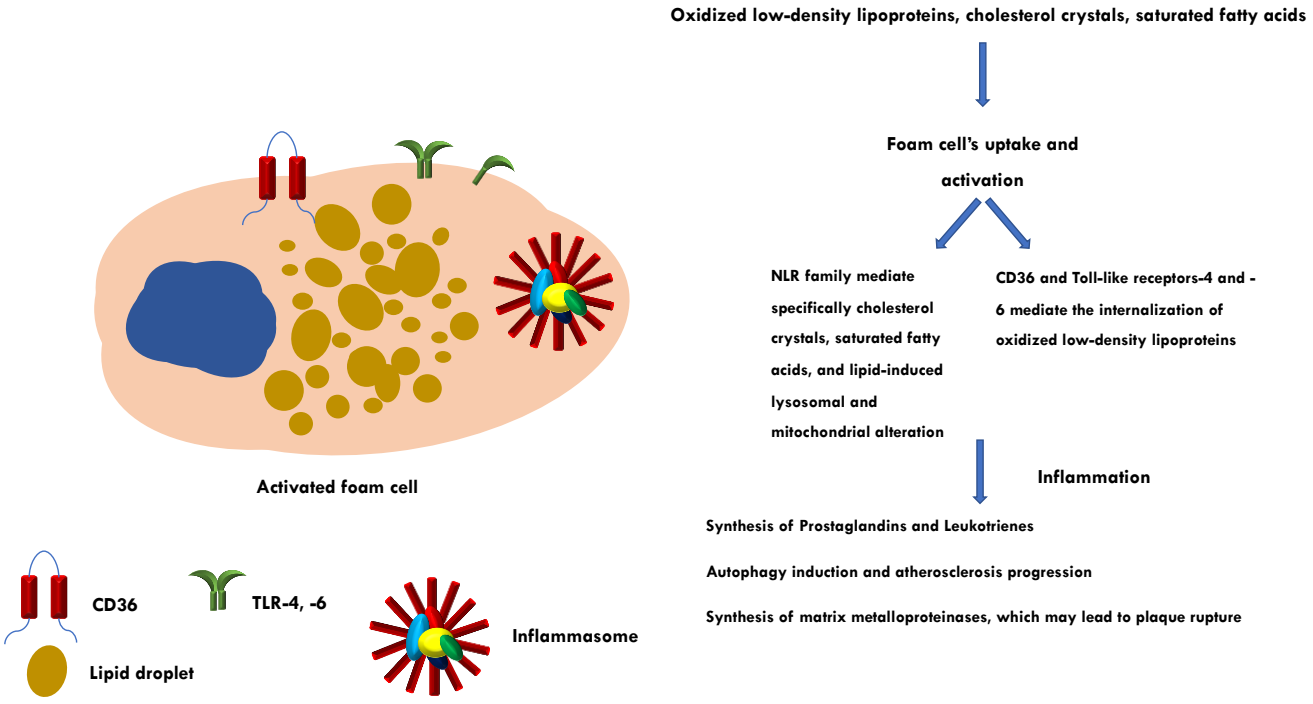

Fig. (1). A simplified description of foam cell's role in lipid scavenger activities, inflammatory activation, and consecutive modification of endothelial morphology in the context of atherosclerosis. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Several receptors mediate lipid accumulation in macrophages. For instance, CD36 is a specific binding site for oxLDL particles, facilitating their uptake [77, 78]. Following binding between CD36 and oxLDLs, the phosphorylation of Src kinases occurs, which, in turn, activates JUN-kinase 1 and 2 and Vav, a guanine nucleotide exchange factor ultimately leading to oxLDLs uptake [77].

All the above processes of lipid accumulation in macrophages are upregulated by Wnt5a activation *via* the Fz5 pathway [74] and Peroxisome Proliferator-Activated Receptor (PPAR)-gamma activation by p38 MAPK signal [79].

Three Toll-like receptors (TLRS), namely TLR2, TLR4, and TLR9, participate in foam cell formation. TLR2 acts *via* CD36, co-expressing with Wnt5a, while TLR4 utilizes the phosphoinositide 3-kinase (PI3K)/mTORC2 pathway [80].

Quite interestingly, there is evidence that macrophages *via* TLR4/myeloid differentiation primary response 88/PI3K/spleen tyrosine kinase/Protein Kinase B pathway allow the lysosomal synapse to degrade LDL and accumulate lipids [81].

Finally, TLR9 may participate in foam cell formation *via* Interferon Regulatory Factor 7 and nuclear factor kappa-light-chain enhancer of activated B cells (NF-kappa B) activation and p38 MAPK pathway [82].

It is noteworthy that modified LDL particles tend to undergo self-association of lipoprotein particles, thus preventing them from binding to specific LDL receptors [83, 84]. Therefore, an aliquot of modified LDL is engulfed by phagocytosis, bypassing the intervention of the LDL receptor.

Cellular uptake of modified LDL leads to cholesterol esterification [85]. LDL accumulated into the intracellular lysosomes and are hydrolyzed into free cholesterol (Fc) and fatty acids. Fc, in turn, undergoes re-esterification by acyl-cholesterol transferase 1, which leads to an excessive accumulation of cholesterol esters within cytoplasmic lipid droplets.

The last stage of cholesterol metabolism in macrophages is cholesterol efflux. ATP-binding cassette transporter 1 (ABCA1), ATP-binding cassette subfamily G member-1 and SR Class B Type 1 account for the active transport of cholesterol and phospholipids out of macrophages, followed by Apo A1 and high-density lipoprotein removal, thus, preventing foam cell formation [86].

The link between obesity and atherosclerosis is schematized in Fig. (**2**).

5. THERAPEUTIC ATTEMPTS TO PREVENT FOAM CELL FORMATION

OxLDLs promote the formation of foam cells, and, therefore, inhibition of the apoptotic pathway has been taken into consideration for preventing tissue damage [87]. OxLDL molecules trigger the caspase cascade oxidation through the mitochondrial apoptotic pathway and proteasomal alteration and accumulation of cytosolic calcium [88-90]. In this direction, in LDL-/- murine macrophages, the inhibition of the proapoptotic protein Bax decreased apoptosis associated with accelerated atherosclerosis [91]. Furthermore, abrogation of the apoptosis inhi-

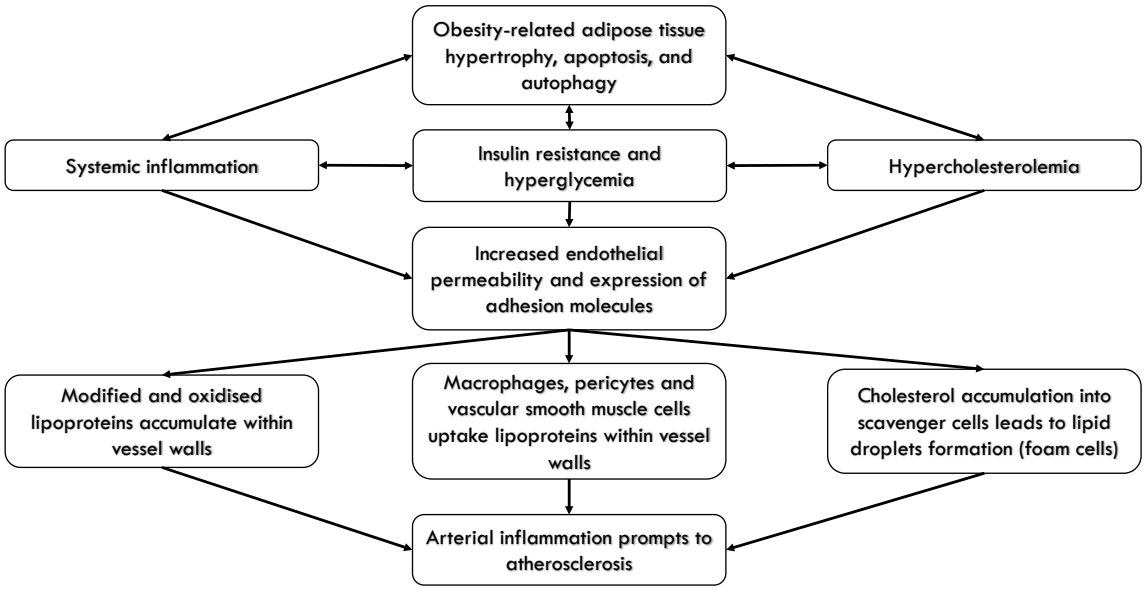

Fig. (2). A simplified diagram illustrating the leading mechanisms of atherogenesis in obesity-related endothelial dysfunction. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

bitor expressed by macrophages, AIM, resulted in higher apoptosis of macrophages with reduction of the size of atherosclerotic lesions [92]. On the other hand, in female *apoE*-/- mice, enhanced apoptosis due to Bcl-2 deficiency caused more marked plaque necrosis [93].

Besides targeting apoptosis, adequate clearance of post-apoptotic foam cells should be performed to avoid secondary necrosis and further local inflammation [94]. Consequentially, promoting efferocytosis of apoptotic macrophages has been experimented with using Liver X Receptors (LXR), glucocorticoids, and PPAR-gamma activation [95-98].

Another strategy is represented by reducing lipid uptake by macrophages, blocking the triggering receptor expressed on myeloid cells (TREM-1), which led to downregulation of CD36 and monocyte accumulation within atherosclerotic lesions [99]. Such a pharmacological intervention markedly reduced the size of atherosclerotic lesions by up to 60%.

5.1. Statins

Statins are used as inhibitors of cholesterol synthesis, but they have been shown to increase plaque stability in patients with established cardiovascular diseases [100, 101].

Besides the properties mentioned above, statins can inhibit foam cell formation, exert anti-inflammatory activities, and reduce cholesterol modifications within macrophages [102, 103]. Furthermore, statins could reduce circulating C-Reactive Protein, a predictor of cardiovascular diseases [104], while decreasing macrophage accumulation, downregulating adhesion molecules and integrins, and upregulating the chemokine CCR7, respectively, and facilitate macrophage emigration [105-107]. Of note, statins promote macrophage efferocytosis, inhibiting Rh0 GTPases, which, instead, abrogates macrophage uptake of apoptotic cells [108, 109].

5.2. Matrix Metalloproteinases

MMPs are released by profibrotic foam cells in the context of the atherosclerotic plaque, favoring monocyte and macrophage recruitment and leading to plaque instability, which may culminate in its rupture [110]. For instance, in human carotid plaques, MMP8 elevated levels have been detected, which may cause plaque rupture [111]. In MMP8 deficient *apoE*-/- mice, leukocyte/ monocyte recruitment, intralesional macrophages, and blood pressure were also reduced in relation to a diminished clearance of angiotensin I and its conversion to angiotensin II [112]. The role of the other two MMPs, namely MMP-9 and MMP-12, in terms of plaque protection or instability, is contradictory using animal models [113]. Such a discrepancy may depend on the location of atherosclerotic lesions and mouse gender, and further studies are needed to clarify the role of various MMPs in plaque evolution.

Interestingly, administering an MMP-8 specific inhibitor to patients who underwent carotid endarterectomy could prevent new or recurring cardiovascular events [111].

5.3. Heme Oxygenase-1

Heme Oxygenase 1 (HO-1) induction in foam cells favors reverse cholesterol transport, prevents plaque formation, and maintains consolidated plaque stability [114-116].

(S)-enantiomer of YS-51, a synthetic isoquinoline alkaloid, is an inducer of HO-1, acting *via* suppressing NF-kappa B and the consequent inflammatory pathway [117]. In this respect, further evidence has demonstrated that HO-1 induction suppresses NF-kB activity, inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in macrophages, and these effects are mediated by bilirubin [118]. In relevance to the above results, advanced glycation end products suppress ABCA1 and ABCG1 expression in macrophages *via* inhibitors of NADPH oxidase [119, 120].

Also, phase 2 inducers act as potent inducers of HO-1, and among them, lipoic acid has been shown to exert beneficial effects on diabetic neuropathy at 600-800 mg dose daily [121]. Furthermore, alpha-lipoic acid prevents rodent atherosclerosis, targeting the Ras/MERK/ ERK signaling pathway [122].

5.4. Spirulina

Spirulina is a cyanobacterium, also known as blue-green algae [123]. It is composed of many antioxidant agents and, among them, phycocyanobilin is endowed with the capacity to reduce oxidative stress in adipocytes. This effect seems to depend on the ability of phycocyanobilin to inhibit NADPH oxidase, thus, preventing systemic inflammation and insulin resistance [124]. On these grounds, phycobiliprotein C-phycocyanin from *Spirulina platensis* has been reported to play anti-atherogenic activity in cholesterol-fed hamsters [125].

5.5. Salicylate

Salicylate represents another suppressor of NF-kB, inhibiting the inhibitor of NF-kB kinase- beta (IKK-beta) [126]. Similar effects have been obtained with aspirin *in vitro*, even including abrogation of MMP-9 [127]. In the same direction, *in vivo* salsalate has also been shown to improve glucose control in people with diabetes *via* inhibition of IKK-beta at 3-4-5 g daily [128, 129].

5.6. Taurine

Taurine is a sulfur-containing non-essential amino acid, largely present in marine foods [130]. Taurine is an LXR agonist, which can reverse cholesterol transport in macrophages, preventing atherogenesis in rodent models [131, 132]. In humans, for its scarce effect on serum lipids, taurine may be employed to prevent atherosclerosis [133].

5.7. Berberine

Berberine is an isoquinoline alkaloid present in the root, rhizome, and stem bark of medicinal plants. Under the form

of hydrochloride and sulfate, it exhibits various biological activities, including reducing glycemia, regulating lipid metabolism, and cardio-protective effects [134].

As an AMPK activator, berberine has been demonstrated to display anti-atherogenic effects in animal models, as well as on macrophages *in vitro* [135-137].

As discussed in this perspective, oxidative stress represents a hallmark of the atherogenic process, mainly sustained by reactive oxygen species (ROS) and oxLDL generation. Therefore, the use of antioxidants should be advantageous for preventing and treating atherosclerosis [138].

5.8. Natural Antioxidants

Alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, and lycopene are lipid-soluble compounds contained in fruit and vegetables [139, 140]. They exhibit several protective activities able to prevent atherosclerosis-related outcomes in different manners: 1) scavenging of ROS and prevention of LDL peroxidation [139]; 2) inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase with reduction of plasma cholesterol levels [139]; 3) increase in macrophage LDL receptor activity with a decrease in circulating LDL and endothelial alteration [141, 142].

Besides carotenes, vitamin A (retinol) intake could be recommended to prevent cardiovascular disease [143]. B vitamins also possess scavenging properties, mainly in folic acid, improving endothelial function and decreasing superoxide production in human arteries [144, 145]. Quite interestingly, these activities may depend on tetrahydro-biopterin-mediated nitric oxide (NO) synthase coupling.

Vitamin C, contained in fruit and vegetables, plays various functions connected to antioxidant activity: 1) increase in NO bioavailability, inhibition of COX, and reduction of cell-to-cell adhesion [146, 147]; 2) decrease in the chain carrying alpha-tocopheroxyl radical to prevent LDL oxidation [148]; 3) prevention of leukocyte aggregation and adhesion to endothelium along with scavenging of radicals and non-radicals, such as nitrosating agents and hydrochloride acid [139].

Vitamin E is another lipid-soluble antioxidant in fruit, vegetables, egg yolk, butter, and cooking oil. Its beneficial effects against atherosclerosis are mainly based on the inhibition of CD36 and SRBI expression in VSMCs with the prevention of foam cell formation, stabilization of plaques, prevention of cholesterol-mediated endothelial dysfunction, regulation of immune response, and inhibition of thrombin formation and leukotriene synthesis [149-151]. Despite several studies on the effects of antioxidants as potential therapeutic agents against atherosclerosis, results are still controversial, and human studies are limited. In this respect, according to Malekmohammad and associates [138], there are several reasons for the failure of antioxidants to prevent human atherosclerosis. First, they should be used long-term for inducing beneficial effects, and treatment should start before disease onset. In addition, vitamin E loses its effects because of the effects of advanced oxidation. The pathogenesis of atherogenesis is multifactorial, and other unknown pathways involved in plaque formation may not be responsive to antioxidant effects. Lastly, combination instead of single therapy with antioxidants appears more effective, significantly when modifying mitochondrial oxidation.

Polyphenols are natural products usually contained in fruit, vegetables, and beverages, *i*ncluding wine, coffee, and tea. Polyphenols are also significant components of the Mediterranean diet, shown to prevent cardiovascular events due to its anti-inflammatory and antioxidant activities [152-154].

In general terms, polyphenols suppress and scavenge ROS formation while enhancing the expression of exogenous nitric oxide synthase (eNOS) and generation of NO [155, 156]. They reduce activation of redox-sensitive genes, thus, preventing expression of vascular endothelial growth factor and MMP-2 in SMCs [157, 158]. Increased production of vasodilatory factors, such as NO, endothelium-derived hyperpolarizing factor, and prostacyclin, may improve angiogenesis, reduce platelet aggregation and ameliorate arterial pressure profile. Thus, playing a protective role in atherogenesis development [158]. Polyphenols may also induce T-regulatory cells and enhance the expression of the related suppressive cytokine interleukin (IL)-10 with a consequent reduction of the synthesis of proinflammatory cytokines (IL-1 beta, IL-6, IL-17, and Tumor Necrosis Factor-alpha) in the context of the atheromatic plaque [159, 160].

Resveratrol (RES), a stilbene polyphenol mainly contained in red grapes, exerts many antioxidant activities, including inhibition of NF-kappa B and Activator Protein -1, ultimately leading to attenuation of the proinflammatory cascade of cytokines [161]. Furthermore, polydatin (PD) is a polyphenolic metabolite from *Polygonum cuspidatum*, hydrolyzed in the intestine to RES [162]. As recently reported, PD displays cardioprotective mechanisms, primarily acting on proprotein convertase subtilisin/kexin type-9 and LDR pathway at the transcriptional or functional protein level [163].

PD is an excellent therapeutic alternative in patients with hypercholesterolemia who are unresponsive or intolerant to statins.

Also, curcumin, another polyphenol derived from *Curcuma longa L*, has been demonstrated to possess anti-atherogenic effects, as it inhibits proinflammatory cytokine production from monocytes, monocytes adhesion, and transendothelial migration, lastly preventing cholesterol accumulation [164].

Mechanisms aimed to prevent foam cells' formation are listed in Table **1**.

Table 1. Major mechanisms and potential therapeutic targets for preventing foam cells formation.

Potential Targets for Therapeutic Measures to Prevent (or Minimize) Foam Cells Formation
Inhibition of the apoptotic pathway
Promotion of efferocytosis of apoptotic macrophages
Reduction of lipid uptake by macrophages
Abrogation of matrix metalloproteinases release by foam cells
Inhibition of the NF-kappa B pathway
Reduction of the oxidative stress
Induction of T regulatory cells to inhibit the inflammatory pathway

CONCLUSION

Non-communicable diseases, obesity, diabetes mellitus, CVD, and cancer are fostered by a western-type diet [165]. Western diet-related diseases are featured by the presence of foam cells, which, in turn, contribute to the inflammatory background of these pathologies. Therefore, a correct dietary regimen may represent the best measure to prevent foam cells formation and atherosclerosis-related outcomes. Notably, the Mediterranean diet has been demonstrated to prevent cardiovascular events [166, 167].

A plethora of antioxidants has been described in this perspective to target various steps of the atherosclerotic process. On the one hand, enzymatic, non-enzymatic, and synthetic compounds have been screened. On the other hand, an array of medical plants has been assayed, showing suppression of foam cells formation and VSCM and monocyte migration by acting at the endothelium, coagulation, and pro-inflammatory levels. Readers are referred to a recent review by Malekmohammad and associates for further details [138].

Despite controversial results on the effects of antioxidants as anti-atherogenic agents, administration of multiple compounds would be more effective in preventing and treating atherosclerosis.

LIST OF ABBREVIATIONS

(ABCA1)	=	ATP-Binging Cassette transporter 1
Apo	=	Apolipoprotein
BCG	=	Bacillus Calmette-Guérin
COX	=	Cyclo-Oxygenase
eNOS	=	Endogenous Nitric Oxide
ER	=	Endoplasmic Reticulum
Fc	=	Free-Cholestero
HFD	=	High Fat Diet
HO-1	=	Heme Oxygenase 1
IKK-beta	=	Inhibitor of the NF-kappa B kinase-beta
IL	=	Interleukin
LDL	=	Low Density Lipoproteins
LXR	=	Liver X Receptors
MAPK	=	Mitogen Activated Protein Kinase
MMPs	=	Matrix Metalloproteinases
NADPH	=	Nicotinamide Adenine dinucleotide phosphatase
NF-k B	=	Nuclear Factor Kappa-Light-chain-enhancer of activated B cells
NO	=	Nitric Oxide
oxLDL	=	Oxidized Low-Density lipoprotein
PD	=	Polydatin
PGs	=	Prostaglandins
PI3K	=	Phospoinositide 3-Kinase
PPAR	=	Peroxisome proliferator-activated receptor
RES	=	Resveratrol
ROS	=	Reactive Oxygen Species
SMCs	=	Smooth Muscle Cells
VSMCs	=	Vascular Smooth Muscle Cells

AUTHORS' CONTRIBUTIONS

EJ conceived the perspective, searched databases and selected articles, and wrote the manuscript. GL wrote the manuscript, searched databases, and selected articles. VAG, GDP, EG, and VT read the text, gave feedback and criticisms, and approved the final version of the manuscript.

CONFLICT OF INTEREST

Jirillo Emilio and Triggiani Vincenzo are the Editorial Board Members of the Journal Endocrine, Metabolic & Immune Disorders-Drug Targets.

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