Atherosclerotic Assault

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Summary

Atherosclerosis is a cardiovascular inflammatory disease that occurs in major arteries and leads to heart attacks, stroke, and peripheral artery disease. This disease has a high mortality rate in Europe, the United States, and much of Asia. Researchers have developed a strain of genetically modified mice deficient in ApoE as a model for antherosclerosis. In this review, we aim to discuss the current advances at the molecular level and therapeutic approaches in the treatment of atherosclerosis. Two different secretory phospholipase A2's (sPLA$_2$), Groups V and X, hydrolyze low density lipoproteins(LDL) promoting spontaneous aggregation and generation of lyso-PC that evokes proatherogenic cellular events, respectively. The modified LDLs are internalized by the monocyte-derived macrophages via two scavenger receptor family members SR-A and CD36. Active macrophages induce the uptake of native LDL resulting in macrophage cholesterol accumulation, referred to as foam cell formation. Pathways that promote foam cell formation include lipoprotein lipase expressed in macrophages, chemokines such as MCP-1 expressed in monocytes, and fractalkine expressed on activated endothelial cells. Researchers have discovered that fractalkine, which undergoes ectodomain shedding by metalloproteinases, engages G-protein coupled receptors and upregulates integrins. Moreover, a single amino acid polymorphism of fractalkine receptors reduces coronary artery disease *in vivo*. There is currently no cure for atherosclerosis, but several studies have shown ways to treat the disease by reducing foam cell formation. These methods include immunization of immunoglobulin and LDL, anti MCP-1 gene therapy, and the use of the anti-oxidative effects of pomegranate juice.

Introduction

Atherosclerosis is a pathological process that occurs in major arteries. It is the underlying cause of heart attacks, stroke, and peripheral artery disease. Despite advances in prevention and treatment, atherosclerosis remains the leading cause of mortality in the United States. Although well-established risk factors such as elevated serum cholesterol, high blood pressure, diabetes, smoking, gender, and obesity have been identified, these factors do not fully account for an individual's risk of cardiovascular disease (CVD). Genetic factors in addition to those linked to the above risk factors also play an important role. Identifying these factors is likely to lead to a better understanding of pathogenesis and to improved treatment and prevention strategies.

The symptoms of atherosclerosis are highly

variable. Patients with mild atherosclerosis may have a myocardial infraction, or sudden cardiac death, which may be the first sign of coronary heart disease. However, many patients with an anatomically advanced disease stage may have no symptoms and experience no functional impairment.

Atherosclerosis is inflammation of vessel walls arising from interaction of monocytes with vascular, endothelial, and smooth muscle cells (SMC's) (Combadiere et al., 2003). At the molecular level, interactions among these cell types involve low-density lipoproteins (LDL's), adhesion molecules, and chemoattractants (Lucas et al., 2003). One of the first events in atherogenesis is endothelial activation in an inflammation site leading to close interactions with the circulating monocytes. Monocytes adhere to the inflamed endothelium which then migrate and accumulate in the intima (Lesnik et al., 2003). The monocyte trafficking is directed by chemokines (Fig. 1) (Lesnik et al., 2003). Further interactions between recruited inflammatory cells, the extracellular matrix (ECM), the resident vascular cells ultimately lead to the formation of atherosclerotic lesions—accumulation of plaque, (Lucas et al., 2003).

Many years of study have been conducted to reveal the biological basis of atherosclerosis at the celluar and molecular level. The mechanism or pathway behind the uptake of LDL by monocytes is unknown. Some of the most common studies for atherosclerosis are the interaction of monocytes with endothelial cells and SMC's along with molecules like LDL, adhesion molecules, and chemoattractants.

Some of the recent findings of atherosclerosis at the molecular level include the role of macrophages and chemokines. The purpose of this article is to review the studies that uncovered the key pathways of atherosclerosis that make connections between atherosclerosis and the molecular interactions at the cellular level. The main topics that will be covered in this article include the differentiation of monocytes into macrophages, the modification and uptake of LDL by monocytes, the role of chemokines in recruitment of monocytes and vascular SMC's, and the possible disease therapies (Fig. 1).

Modification of LDL

Modified LDL's are recognized by receptors on macrophages (Fig. 2). Formerly, modified LDL was thought to be only oxidized or acetylated LDL. Although this hypothesis is still widely accepted, recent studies show evidence for the uptake of LDL modified through different pathways. One such pathway includes the enzyme Phosopholipase A$_2$ (PLA$_2$). PLA$_2$ is a family of enzymes that hydrolyzes a fatty acid ester bond of glycerophophololipids, producing fatty acids and lysophospholipds. Secretory PLA$_2$ (sPLA$_2$) are low in molecular weight and require a catalytic amount of Ca^{2+} for activity. Currently, nine sPLA$_2$'s have been identified in humans (IB, IIA, IID, IIE, IIF, III, V, X, and XII) (Hanasaki et al., 2002).

Hydrolysis of LDL by sPLA$_2$-V

Group V sPLA$_2$ hydrolyzes phosphatidylcholine (PC), which makes up most of the LDL (Wooten-Kee et al., 2004). Hydrolysis of LDL by sPLA$_2$-V was shown to promote spontaneous particle aggregation (Wooten-
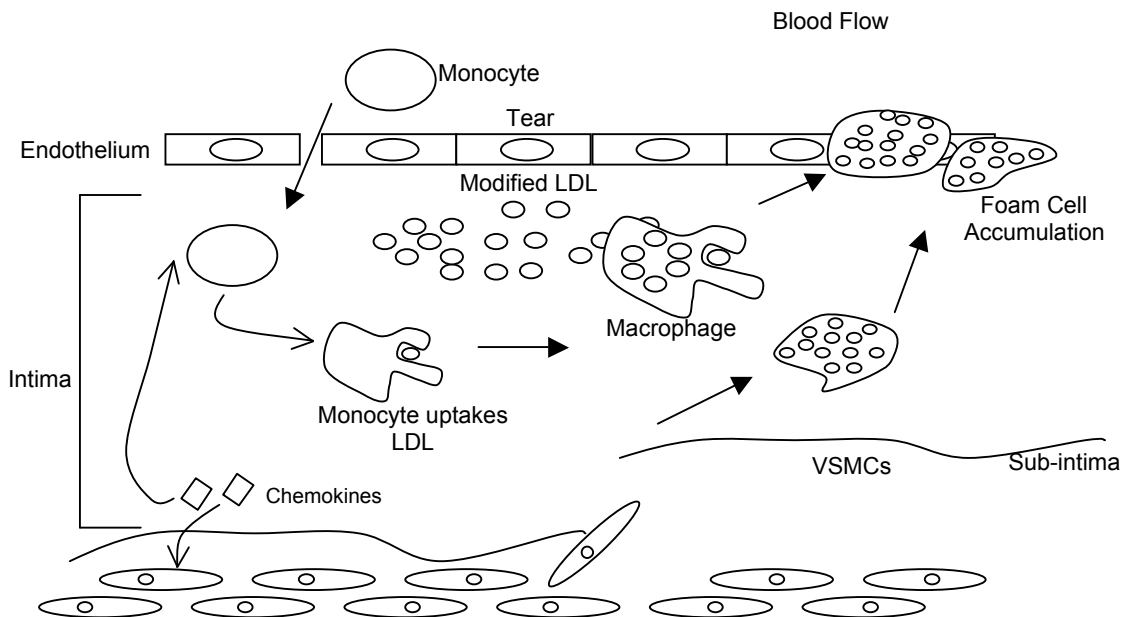
Figure 1. Pathology of Atherosclerosis.
A tear in the endothelium attracts the monocytes, which enter the arterial wall. Monocytes uptake low density lipoproteins (LDL), and differentiate into macrophages. Macrophages release cytokines that direct migration of monocytes from the blood to the sites of inflammation. Macrophages uptake more LDL and become foam cells.

Kee et al., 2004). LDL treated with secretory sphingomylinase (s-SMase) also induces aggregation. This aggregation is associated with atherogenic lipid accumulation in the arterial wall.

Both sPLA$_2$-V and s-SMase have been found in atherosclerotic lesions (Wooten-Kee, 2004). The ECM also plays an important role in aiding in the retention of hydrolyzed LDL through co-localization with sPLA$_2$-V (Wooten-Kee et al., 2004). These results lead to the conclusion that sPLA$_2$-V and s-SMase work together with the ECM to enhance LDL retention as well as aggregation (Wooten-Kee et al., 2004).

Hydrolysis of LDL by sPLA$_2$-X
LDL treated with sPLA$_2$-X was found to degrade PC at about the same rate as oxidized LDL. However, the amount of lyso-PC was increased by about 70% compared to ox-LDL (Hanasaki et al., 2002). Lyso-PC is believed to aid in the induction of various chemokines and cell adhesion molecules (Hanasaki et al., 2002). Also, the sPLA$_2$-X-treated LDL released more unsaturated fatty acids, while ox-LDL released more conjugated dienes due to oxidative stress (Hanasaki et al., 2002). Uptake of sPLA$_2$-X-treated LDL into macrophages was also increased, as well as a visible increase in the size of lipid droplets compared to macrophages incubated with ox-LDL (Hanasaki et al., 2002). These results suggest that a sPLA$_2$ inhibitor could be used to decrease atherogenesis.

Uptake of Modified LDL

Uncontrolled cholesterol accumulation in macrophages occurs through the internalization of modified LDL (Fig. 1). The modified LDL must first be recognized by a receptor. This section is dedicated to two prominent receptors, CD36 and SR-A.
CD36 and SR-A
CD36 is known to be a receptor for modified LDL. In the absence of CD36, the uptake of ox-LDL decreased by about 88% (Febbraio et al., 2004). Similarly, when bone marrow containing CD36 was transplanted into CD36
This study was able to differentiate between
knockout mice (CD36$^{-/-}$ mice), there was a 2-fold increase in plaque development (Febbraio et al., 2004). macrophage CD36 and CD36 expressed elsewhere (such as endothelium and muscle cells), indicating that specifically targeting macrophage CD36 would lead to a decrease in atherogenesis (Febbraio et al., 2004). Although CD36 was found to bind and uptake ox-LDL, extensively modified ox-LDL degrades preferentially through SR-A indicating that CD36 is preferred only for mildly oxidized LDL (Kunjathoor et al., 2002). CD36 was found to have a very small affect on ac-LDL. In contrast, SR-A was found to bind and uptake both ox-LDL and ac-LDL. Furthermore, in the absence of CD36 and SR-A, degradation of ac-LDL was only decreased by about 50%, indicating that a different pathway is used (Kunjathoor et al., 2002).

Foam cell formation

The migration of monocytes to the arterial wall and its differentiation into macrophages is intended to remove lipoprotein particles. The continuous migration of monocytes and the uptake of modified LDLs by monocytes and macrophages leads to the development of atherosclerotic lesions. The earliest stages of these lesions are referred to as fatty streaks (Glass et al.,
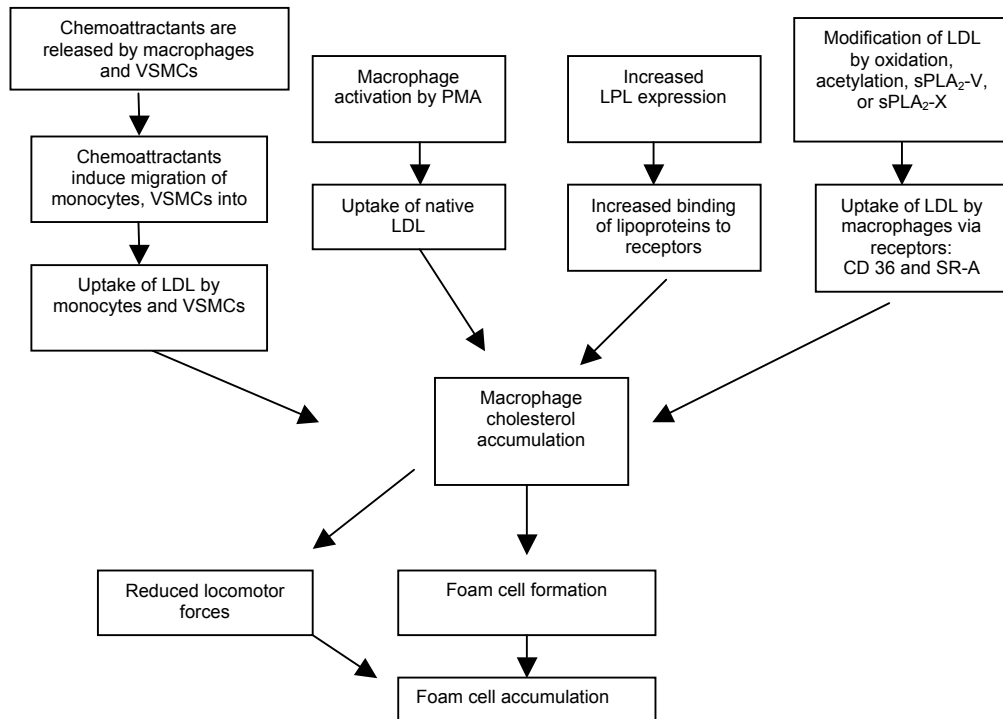
Chemoattractants are released by macrophages and VSMCs

Macrophage activation by PMA

Increased LPL expression

Modification of LDL by oxidation, acetylation, sPLA$_2$-V, or sPLA$_2$-X

Chemoattractants induce migration of monocytes, VSMCs into

Uptake of native LDL

Increased binding of lipoproteins to receptors

Uptake of LDL by macrophages via receptors: CD 36 and SR-A

Uptake of LDL by monocytes and VSMCs

Macrophage cholesterol accumulation

Reduced locomotor forces

Foam cell formation

Foam cell accumulation

Figure 2. Specific Pathways of Foam Cell Formation.
Chemokines attract more monocytes and VSMCs which bind and uptake modified LDL through SR-A and CD36 receptors. PMA activates macrophages to take up native LDL. Increased LPL expression increases binding of LDL. Incresed binding and uptake lead to macrophage formation and furthermore foam cell formation. Foam cell accumulation occurs through decreased locomotor forces.

2001). Recent evidence suggests locomotor forces are affected by the cholesterol accumulation in macrophages (Zerbinatti et al., 2003). The presence of lipoprotein lipase (LPL) promotes foam cell formation (Fig. 2) (Babaev et al., 2003). Research is continuously being done to gain an understanding of the mechanisms underlying foam cell formation.

Macrophage and Locomotion
Monocytes enter the intima and begin to uptake LDL. Once loaded with cholesterol, the monocyte-derived macrophages are enlarged (Fig. 1). This excess cholesterol is delivered to the liver for excretion in bile acids by macrophages. The macrophages that turn into foam cells lose the ability to migrate after excessive ingestion of modified forms of lipoproteins. These foam cells accumulate in the arterial wall because their mobility is reduced. (Fig. 1) The average and peak forces generated by the cells and distribution of actin are all associated with the locomotor force generation of macrophages. The peak force is used as a measurement of the locomotor abilities of the cells (Zerbinatti and Gore, 2003). When cells were incubated with oxidized low density lipoprotein (Ox-LDL), the ability of macrophages to generate average and peak forces was reduced by 50%. Cells loaded with aggregated LDL (Agg-LDL) at the same medium concentration as Ox-LDL (100 µg protein/ml) had no significant effect on the forces generated by macrophages. Cells loaded with Agg-LDL at concentrations of 300 µg protein/ml reduced the magnitude peak force of the macrophages by slightly less than 50% but had no significant effect on the average force. Ox-LDL also reduced the levels of actin

in the cells, whereas Agg-LDL increased the levels of actin. The disruption of actin levels affects the cells' ability to generate normal locomotor forces. These results indicate that the cholesterol accumulation is one of the major factors in the loss of motility in foam cells. Also, the uptake of Ox-LDL is more effective than Agg-LDL in disrupting the locomotor forces generated by macrophages (Zerbinatti and Gore, 2003).

Uptake of LDLs
Studies have shown that modified LDL is a major source of cholesterol accumulation in monocyte-derived macrophages. In previous studies, native LDL was not shown to cause foam cell formation, because the cellular receptor that binds native LDL is poorly expressed on differentiated macrophages. The discovery of fluid phase endocytosis— an uptake pathway that can be activated in macrophages—suggests that LDL uptake and macrophage cholesterol accumulation do not depend on LDL binding to receptors (Kruth et al., 2002). The activation of monocyte-derived macrophages with a phorbol ester (PMA) stimulated native LDL uptake, resulting in massive macrophage cholesterol accumulation (Fig. 2). These results show that modification of LDL is not required for foam cell formation to take place and that foam cell formation occurs with native LDL when macrophages are activated with PMA (Kruth et al., 2002).

Lipoprotein Lipase
LPL is an enzyme that breaks down fat molecules. This enzyme is synthesized by the macrophages and by macrophage-derived foam cells in atherosclerotic

lesions. LPL can function as a ligand that promotes binding of lipoproteins to the LDL receptor (LDLR)-related protein (Babaev et al., 2000). LDLR$^{-/-}$ mice have enhanced susceptibility to diet-induced atherosclerosis. These mice are used as models to study the impact of macrophage LPL expression at different stages of atherosclerosis. The mean aortic lesion area was reduced by 33% in LDLR$^{-/-}$ mice deficient in LPL. The extent of atherosclerosis was also significantly reduced in LDLR$^{-/-}$LPL$^{-/-}$ and LDLR$^{-/-}$LPL$^{+/-}$ (heterozygous LPL) mice. These results show that the macrophage LPL expression promotes atherogenesis during the stage of fatty streak formation (Fig. 2).

Chemokines

Chemokines are a large family of chemoattractants that direct migration of monocytes from the blood to sites of inflammation (Fig. 1). Chemokines such as monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), and fractalkine (FKN) have been identified in human atherosclerotic lesions.

Ectodomain shedding
Ectodomain shedding, the proteolytic cleavage of cell surface proteins, is an important mechanism by which cells regulate the proteins expressed on their surface. Several types of membrane proteins undergo ectodomain shedding, including chemokines, tumor necrosis factor (TNF), growth factors, and adhesion molecules (Garton et al., 2001). One study (Garton et al., 2001) showed that TACE (TNF-α-converting enzyme)—one of the most well characterized metalloproteinases known to date—cleaved and shedded FKN, generating soluble FKN. Additionally, the expression of TACE was upregulated under a variety of inflammatory conditions *in vivo*, suggesting that TACE becomes activated during inflammatory responses (Satoh et al., 2000). Thus, TACE-mediated cleavage and ectodomain shedding of FKN is thought to regulate FKN function *in vivo*. Previous studies have shown that FKN can exist either as a membrane-anchored cell surface protein or as a soluble chemokine. The soluble form of FKN is known to be a potent chemoattractant for monocytes and T cells (Bazan et al., 1997).

FKN receptor polymorphism
Later studies by Moatti and colleagues (2001) identified two common single-nucleotide polymorphisms in the open reading frame of FKN receptor (CX3CR1), causing conservative amino acid changes (V249I and T280M). The study demonstrated that the I249 allele of the CX3CR1 gene is associated with a reduced risk of acute coronary events. Decreased expression of CX3CR1 could have resulted in less efficient interaction between monocytes and injured endothelium in subjects exposed to coronary risk factors. Hence, it is hypothesized that the use of agents blocking the FKN to CX3CR1 interaction might help prevent the onset and progression of atherosclerotic lesions.

CX3CR1/FKN pathway

Combadiere and colleagues (2003) identified a direct and major role for the CX3CR1/FKN pathway in the development of macrophage-rich atherosclerotic lesions. Along with the presence of FKN in murine atherosclerotic plaques, the study showed that FKN-

binding and chemotactic activities were altered in CX3CR1$^{-/-}$ monocytes compared to controls. Also, homozygous CX3CR1$^{-/-}$apoE$^{-/-}$ mice showed a substantial decrease in macrophage infiltration within the arterial wall compared to apoE$^{-/-}$ mice alone. The role of CX3CR1 was further emphasized by a marked reduction in atherosclerotic lesion size at two different atherosclerosis-prone sites (aortic sinus and thoracic aorta) in CX3CR1$^{-/-}$ mice. The aforementioned results were observed despite similar plasma cholesterol levels and leukocyte blood counts between the two groups. Additionally, only one muted CX3CR1 allele was sufficient to induce the full atherosclerosis phenotype, thus implying the crucial role for CX3CR1 in macrophage accumulation in inflammatory sites of apoE$^{-/-}$ mice. Treatments that interrupt FKN binding to CX3CR1 are considered a possible treatment of CVD (Lesnik et al., 2003).

IFN and TNF
In 2003, Lesnik and colleagues demonstrated prominent FKN expression in macrophage-rich areas of the lesions, consistent with the analysis of human atherosclerotic lesions. They suggested that macrophages are unlikely to be the primary source of FKN in atherosclerotic sites. Previous *in vitro* studies have reported that human SMCs express FKN after treatment with (IFN-γ) interferon-gamma (Ludwig et al., 2002). This was confirmed when the combination of IFN-γ and TNF-α, two cytokines that are known to be present in atherosclerotic plaques, dramatically upregulated FKN expression in murine SMCs but not in macrophages (Lesnik et al., 2003).

Lesnik and colleagues (2003) observed that FKN staining was not uniform. Moreover, SMCs located directly beneath lesional macrophages expressed high levels of FKN. These data suggested that soluble FKN present on the surface of activated SMCs and/or endothelial cells plays a direct role in recruiting monocytes/macrophages into developing inflammation. This study provided a mechanistic basis for the observations that patients with FKN receptor polymorphism have a decreased incidence of coronary artery disease (Moatti et al., 2001).

Other Chemokines
MCP-1 and IL-8 play important functional roles in atherogenesis. The individual deletions of MCP-1 (Gu et al., 1998; Gosling et al., 1999), CCR2 (Boring et al., 1998), the IL-8 receptor (Boisvert et al., 1998), or CX3CR1 each resulted in at least a 50% decrease in atherosclerotic lesion area, suggesting that each of these chemokines cannot be acting completely independently. Lesnik and colleagues (2003) proposed that each cannot be providing completely redundant functions. They proposed a concerted mechanism of FKN, MCP-1, and IL-8 to recruit circulating monocytes into the sub-endothelial space. In this model, FKN and MCP-1 can be envisioned acting sequentially such that full-length FKN, along with adhesion molecules, serves to capture flowing monocytes, which then migrate along an MCP-1 gradient into the sub-endothelial space. Evidence for the notion that chemokines can perform both chemoattractant and adhesive functions in atherogenesis comes from the work of Huo and colleagues (2001), which showed that IL-8 captures flowing monocytes in the mouse carotid artery (Fig. 2). The relative contributions of full-length and soluble FKN to atherogenesis can be better explained with the

creation of mice in which FKN is mutated to a non-cleavable form.

VSMCs chemotaxis
Lucas and colleagues (2003) demonstrated that primary human SMCs express the CX3CR1 receptor and undergo specific CX3CR1-mediated chemotaxis to FKN *in vitro*. They suggested that FKN, rather than acting as a proinflammatory cytokine in human atherosclerosis, may play an important role in vascular remodeling through the recruitment of SMCs into the atherosclerotic plaque. The ability of FKN to synthesize substantial amounts of extracellular matrix favors the development of stable atherosclerotic lesions rather than macrophage-rich vulnerable plaques (Lucas et al., 2003). It remains unknown if atherosclerotic plaques with high levels of FKN progress to stable plaques with high numbers of SMCs and fibrous caps.

Treatments

Immunoglobulins Treatment
Intravenous immunoglobulins (ivIg) are a solution of globulins containing antibodies taken from larger pools of plasma from human blood. In addition to its use as substitution therapy for primary and secondary antibody defenses, ivIg is used increasingly in patients with autoimmune and systemic inflammatory diseases, such as atherosclerosis (Nicoletti et al., 1998). Although the mechanism of ivIg is unknown, it may involve the Fc- and V domains of its structure. ivIg could regulate the production of autoantibodies against oxLDL, modulate T cell functions in plaques, and affect phagocytosis and cytokine production by macrophages (Nicoletti et al., 1998). Studies showed that reduction of fatty streaks was best observed when ivIg was injected into apoE$^{-/-}$ mice when they were first put on a high-cholesterol diet. The prevention of atherosclerosis was observed when ivIg was injected after two months on a high-cholesterol rather than the beginning of treatment. T cells of ivIg treated mice exhibited a lower basal proliferation, but with the addition of a growth factor, T cells could be induced to proliferate. This suggests that ivIg inhibits T cell activation (Nicoletti et al., 1998). The amount of antibodies to oxLDL was shown to be reduced by ivIg.

LDL immunization
OxLDL in atherosclerotic lesions can stimulate the recruitment of immune cells (Zhou et al., 2000). Ten percent of T cells that are cloned from humans respond to oxLDL. As a result, humoral and cellular immune response to oxLDL affects the fate of atherosclerosis. In previous studies, LDL immunization has been shown to induce protection against atherosclerosis. Zhou et al. (2000) assessed the role of cellular and humoral immune response involved in this protection. They showed that immunization with homologous plaque homogenate as well as homologous malondialdehyde-LDL inhibits plaque growth. The study also showed that antibody responses to oxLDL and plaque antigens are T-cell dependent.

Adenovirus-Mediated Gene Therapy
Macrophage scavenger receptors (MSRs) types AI/II are membrane glycoproteins that are involved in the deposition of lipids in the arterial wall during atherogenesis (Laukkanen et al., 1999). Modulating the activity of this receptor could have a major effect on atherogenesis. To modulate the activity of MSR, an adenovirus was formed that expressed a secreted version of human MSR under the control of the macrophage gene CD68 promoter (Laukkanen et al., 1999). By using this mechanism, Laukkanen and colleagues (1999) studied the effects of "decoy" scavenger receptor on the metabolism of modified LDL in macrophages. This study showed that the secreted form of MSR inhibits the accumulation of lipids as well as foam-cell formation in macrophage tumor cells (RAW 264). It was confirmed that the binding of modified LDL to the secreted version of MSR inhibits the binding of modified-LDL to native MSR.

Anti-MCP-1 Gene Therapy
MCP-1 is a chemokine important for macrophage recruitment in the arterial wall and its activation. Recent studies have demonstrated that MCP-1 expression is increased in atherosclerotic lesions. Blocking the expression of MCP-1 or its receptor CCR2 decreases atheroma formation in hypercholesterolemic mice (Ni et al., 2000). It is still unknown if blockage of the MCP-1 could be a useful site for gene therapy. To assess the use of gene therapy through the blockage of MCP-1 activity, Ni and colleagues (2000) created a MCP-1 mutant called 7ND in which the N-terminal was deleted. This mutant has been shown to bind the receptor for MCP-1 (CCR2) and block MCP-1-mediated monocyte chemotaxis (Ni et al., 2000). ApoE$^{-/-}$ mice were shown to have less atherosclerotic lesions when transfected with the 7ND than with the control. The infiltration of macrophages into the arterial wall was also reduced in 7ND transfected mice. For the first time, it was revealed that blockage of MCP-1 and its receptor CCR2 by transfection of a mutant gene reduces plaque formation.

Pomegranate Supplementation
The pomegranate tree has been used extensively in folk medicine of many cultures. Pomegranate juice (PJ) contains 85% water, 10% total sugars, and 1.5% pectin, ascorbic acid and polyphenolic flavonoids. Pomegranate juice, very rich in flavonoids, was recently shown to be antiatherogenic, and this effect is probably related to its potent antioxidative activity. Kaplan and colleagues (2001), studied the effect of PJ given to mice with an advanced stage of atherosclerosis. They showed a significant increase in serum paraoxonase activity in mice that were given PJ for two month compared to placebo and control mice. Serum paraoxonase is a high density lipoprotein (HDL)-associated esterase, and it was shown to protect from oxidation lipids in lipoproteins and in lesions by its hydrolytic and peroxidative like properties (Kaplan et al., 2001). Administration of PJ for two months also decreased the macrophage lipid peroxidation. The uptake of oxLDL and atherosclerotic lesion size was reduced upon treatment with PJ. To date, there have been no reports indicating whether antioxidant polyphenols and flavonoids contained in PJ can reverse oxidation sensitive-genes and increase the expression of endothelial NO synthase (eNOS). eNOS synthesizes nitric oxide (NO), which relaxes the walls of the coronary arteries and arterioles as well as controls vascular oxidative stress and the expression of redox-regulated genes. Evidence exists that eNOS activity is reduced at sites of perturbed shear stress (Nigris et al., 2005). Nigris and colleagues (2005) showed that eNOS activity was increased and the expression of ELK-1 was significantly decreased when examining the preventive and therapeutic measures of PJ in high and low atherosclerotic prone areas. However, p-JUN

expression was only decreased by therapeutic effects significantly in high-prone areas. Thus, beneficial effects were elicited by PJ during chronic intervention (Nigris et al., 2005).

Conclusion

This paper focused on several different cell and molecular advances in the study of atherosclerosis within the last five years. LDL can be modified in various ways, and in all of which they are still able to be bound and uptaken primarily through CD36 and SR-A macrophage receptors. Macrophages activated by PMA can also uptake native LDL. LPL promotes the binding of LDL to the receptors, thus promoting atherogenesis. The uptake of modified LDL reduces the mobility of foam cells, promoting aggregation. Chemokines have been shown to promote the progression of atherosclerosis by attracting more monocytes as well as SMCs to the lesion site. Cleavage of fractalkine and polymorphism in CX3CR1 play a major role. Although no cure has been found, creating a non-fucntional macrophage receptor and blocking the activity of chemoattractants (such as MCP-1) may have therapeutic effects. Also, the antioxidant effects of PJ lead to less oxidation of LDL, therefore reducing foam cell formation. Although much is known about the pathways involved in atherosclerosis, there are still many unanswered questions. In order to better understand the pathway, it will be necessary to find other sources of activation of monocytes initiating uptake of native LDL, the receptor responsible for degradation of $sPLA_2$-modified LDL, and the pathway of degradation of ac-LDL. These answers will lead to a greater understanding of atherogenesis which would direct relevant research for a cure.

Acknowledgements

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