VOLUME 8 | ISSUE 3 | JULY - SEPTEMBER 2017

Atherosclerosis as an autoimmune disease

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Abstract

Atherosclerosis, a highly prevalent disease in the adult population, presents constantly increasing rates in the pediatric population. Data from recent studies correlate atherosclerosis with autoimmune mechanisms. The role of Th17, Treg, IL-6, PAF, reinforce this position. The role of autoimmunity is clear both in the pathophysiology of atherogenesis, as well as in the treatment effect of statins as drugs of choice. The aim of this review was to highlight the autoimmune model of atherosclerosis. The pathophysiology of atherosclerosis, as well as the mechanisms of action of statins in the treatment of atherosclerosis, including their pleiotropic effects, are described. LDL is known to play an important role in the pathophysiology of atherogenesis. The oxidized form of LDL, the oxLDL, leads to uncontrolled production of Platelet-Activating Factor. Moreover, the entrance of oxidized LDL in the subendothelial space results to the formation of "foam cells". Statins cause reduction of LDL- cholesterol in the serum, but also exhibit anti-inflammatory and immunomodulatory effects reducing the production of proinflammatory cytokines secreted by T cells and antigen-presenting cells.

Key words: atherosclerosis; "foam cells"; oxLDL; Tregs; Th17; statins; IL-16

SUBMISSION: 12/05/2017 | ACCEPTANCE: 12/10/2017

Introduction

Atherosclerosis is a very common disease, which concerns not only adults, but children as well. In the recent years there have been increasing studies, which suggest that atherosclerosis is not just caused by the accumulation of cholesterol in the coronary arteries. The purpose of this review is to present existing evidence showing that atherosclerosis is an autoimmune disease. We describe the pathophysiology of atherosclerosis and discuss the mechanisms of actions of statins on the treatment of atherosclerosis focusing on their pleiotropic effects to support the autoimmune nature of atherosclerosis.

Citation

Kotsiafti A, Eleutheriou D, Stabouli S. Atherosclerosis as an autoimmune disease. *Hell J Atheroscler* 2017; 8: 76-85

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Pathophysiological mechanisms of atherosclerosis -The role of autoimmunity

Atherosclerosis could be considered as a multifactorial chronic inflammatory disease with immunological involvement. The role of the immune system may be evident both in the pathophysiology and the progression of the disease. Cholesterol and triglycerides are insoluble in plasma and transported by VLDL and LDL lipoproteins, which are associated with apolipoprotein B100 (ApoB-100). The interaction of the positively charged Apo-B with negatively charged proteoglycans leads to the retention of Apo-B-associated lipoproteins in the arterial wall. These lipoproteins become sensitive to oxidation, enzymatic cleavage and aggregation. Thus, are rendered immunogenic, and induce an immune response [1,3]. Oxidation of LDL in the circulation results in uncontrolled production of Platelet-Activating Factor (PAF) and oxidized PAF-like molecules. Regulatory mechanisms of the body maintain and control the PAF levels within normal limits. The uncontrolled, increased levels of PAF derived from the oxidation of LDL leads to a local inflammatory reaction in the vessel, destruction of the endothelium and increased vascular permeability. The oxidized LDL is accumulated in the subendothelial space resulting in the formation of "foam cells". Platelets, "foam cells", smooth muscle cells and lipids, create complexes, which finally constitute the components of atherosclerotic plaque [3,5].

The inflamed area activates accumulation of monocytes in the atherosclerotic plaques [6]. The number of GR1 + LY6C monocytes increases due to hyperlipidemia. Macrophages take up LDL, VLDL and oxidized lipoproteins in the atherosclerotic plaque through macropinocytosis and phagocytosis [5]. The accumulation of lipids in macrophages disturbs lipid metabolism and leads to chronic inflammation. More specifically, the accumulation of ApoB lipoproteins in the sub-endothelial space stimulates the recruitment of dendritic cells and macrophages. With the progression of atherosclerotic lesion, penetration of T lymphocytes and smooth muscle cells in the intima of the vessel leads to increased retention of ApoB lipoproteins. Accumulated lipids, apoptotic cells and defective efferocytosis make plaques unstable making them vulnerable to rupture and thrombus formation [1].

Inflammatory signaling stimulates the immune response through a family of proteins called molecular pattern recognition receptors of pathogens (pathogen-associated molecular pattern recognition receptors, PRR). This process leads to the activation of the protein complex called inflammasome. Caspase-1 is activated, which is necessary for maturation and secretion of the cytokines IL-18 and IL-1b [7]. The apoB lipoproteins, which are associated with proteoglycans, undergo a series of changes, such as oxidation and hydrolysis by secretory phospholipases A2 (sPLA2) and secretory sphingomyelinase S-SMase). These modifications induce inflammatory response characterized by chemokine secretion and changes in expression of adhesion molecules by endothelial cells which in turn, leads to increased retention and accumulation of lipoproteins. Moreover, atherosclerosis is highly associated with autophagy, which has a direct correlation with stress. Thus, chronic exposure to stressor factors induces autophagy in macrophages, depriving them of nutrients and leading to the development of atherosclerotic disease. A set of pro-inflammatory and post-inflammatory mechanisms acting on macrophages of the atherosclerotic plaque, leads to the activation of downstream cascades, such as the inflammasome, scavenger receptor (SR) / Toll-like receptor (TLR) cooperative signaling, endoplasmic reticulum (ER) stress, expression of the sterol responsive network, and efflux of cholesterol *via* ABCA1 and ABCG1 transporters.

In the hyperlipidemic surround the existence of specific autoantigens including oxLDL, heat shock protein 60/65 (HSP60/65), beta2-glycoprotein or apoB100-derived peptides has been observed [4,5]. These autoantigens are partly items of normal tissue. The identification is made by macrophages or dendritic cells (DCs). During the initial stages of plaque development DCs accumulate in the intima of arteries that experience disturbed blood flow (as a proatherogenic factor), through a mechanism involving vascular cell adhesion molecule 1 (VCAM-1) and CX3C chemokine receptor 1 (CX3CR1; also termed

fractalkine receptor or G-protein coupled receptor 13 (GPR13)). The continued accumulation of dendritic cells in the lesion area maintains and enhances inflammation in the area. Trapped modified lipids and other possible antigenic structures in these regions induce maturation of DC cells and their migration to secondary lymphoid organs, where they promote the production of antigen-specific pathogens and / or regulatory T cells. These antigen-specific T cells migrate to the atherosclerotic lesion.

Atherosclerosis has been associated by the involvement of multiple types of immune cells, including the T-regulatory (Tregs) and T-helper 17 (Th17) cells, which have been proposed to play a primary role in the induction and development of local inflammation in atherosclerotic plaque. When plaque is formed, Tregs exhibit a reduced number and functionality. Different types of Tregs prevent adverse immune responses and maintain tolerance to self-antigens preventing autoimmune diseases [8].

The majority of T lymphocytes observed in atherosclerotic lesions are CD4 + T-helper cells with phenotypic characteristics of the proinflammatory type 1 T-helper (Th1) cells producing high levels of interferon-γ (INF-γ) [6]. Interferon-γ exhibits a high pro-atheromatic activity. Natural Tregs are able to supress, among others, Th1 cells immune activity and consequently Th1 inflammation-mediated atherosclerosis is shown in animal models. The Tregs may also mediate the immune response through secretion of anti-inflammatory cells including cytokine interleukin-10 (IL-10), IL-35 and transforming growth factor beta (TGF-β). Studies have demonstrated that IL-10 and TGF-β have atheroprotective properties. The Tregs cells have the ability to suppress the activity of effector pre-atherosclerotic T cells.

The effects of Tregs in many autoimmune diseases have been demonstrated by *in vivo* and *in vitro* studies [6,8,9,10]. Administration of anti-inflammatory immunomodulators per os, increasing the immune tolerance of the intestine through the recruitment of DCs and Tregs cells in the intestinal mucosa, seems a promising method of reducing atherogenic immune response, as the induced Tregs has been suggested to have the potential of migration to sites of vascular inflammation and reduce atherogenesis [8].

Prolonged stress and the presence of other stimuli lead to apoptosis of macrophage foam cells. The ineffective clearance of apoptotic cells, because of defective efferocytosis, result in the accumulation of apoptotic cells which induce secondary necrosis and formation of necrotic core. The death of smooth muscle cells and the degradation of the extracellular matrix proteins by proteases lead to the destabilization of the fibrous cap atheroma making it prone to rupture [11].

Statins

Statins are competitive inhibitors of the HMG-CoA reductase, an enzyme that regulates the production of cholesterol in the liver. Statins reduce the levels of LDL-cholesterol in the serum, thus providing protection against major risk factors of atherosclerosis. Due to their effect on lipid metabolism statins are prescribed for hypercholesterolemia in order to prevent cardiovascular disease in patients with high risk for adverse cardiovascular outcomes-myocardial infarction and stroke-as well as in patients with symptomatic atherosclerosis.

In addition to lipid lowering effect, statins also have anti-inflammatory and immunomodulatory effects, which contribute equally to atherosclerosis treatment. They can reduce the production of proinflammatory cytokines by T cells and antigen-presenting cells (APCs) [12]. Statins also reduce the expression of major histocompatibility class II proteins, induced by IFN and prevent the APC-mediated Th1 differentiation, as well as the secretion of IL-17 by Th17 cells [13]. Furthermore, mevalonate is needed for the synthesis of farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), lipid intermediates, which activate several proteins by prenylation, including members of the Ras and Rho GTPase family. Since statins prevent the synthesis of mevalonate they also affect intracellular signaling mediated by Ras and Rho GTPases [13]. Both *in vitro* and *in vivo* experiments have shown that Ras and Rho intracellular pathways promote vascular muscle cell migration and proliferation and neointimal hyperplasia. Therefore, the prevention of the Ras and

Rho GTPases activation could delay the progression of atherosclerosis [14].

Statins also prevent the formation of atherosclerotic plaques by protecting vascular endothelium from oxidative stress. They increase the activity of endothelial nitric oxide synthase (eNOS), an enzyme that forms NO from reactive nitrogen and oxygen species. eNOS in conditions that promote atherogenesis looses its ability to produce NO and produces superoxide anions instead. A number of studies have shown that statins promote NO production in the cardiovascular system, and thus may protect from atherosclerosis [15]. Statins also improve cell defence against oxidative stress by increasing the expression of a number of enzymes, which reduce free radicals (superoxide dismutase, glutathione synthase, glutathione peroxidase, glutathione reductase and glutamylcysteine synthetase) [15].

Homeostasis of the endothelium is regulated by the angiopoietin-TIE receptor system. Angiopoietin-1 is consistently secreted by regular endothelial cells, activates the tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (TIE-2) which ensures the proper functionality of the endothelium. Ang-2 is mainly synthesized in endothelial cells and stored in cytoplasmic secretory organelles called Weibel-Palade bodies (WPBs). This peptide is an antagonist of Ang-1. Binding of Ang-2 to the TIE-2 receptor promotes a pro-inflammatory and pro-angiogenic phenotype of the endothelium, resulting in the development of atherosclerotic lesions [16]. Ang-2 is released from WPBs in response to several conditions, which promote atherosclerosis (e.g. trauma, hypoxia, histamine) [17]. The NO produced by endothelial cells is a known inhibitor of Ang-2 exocytosis. Therefore statins, which as described above upregulate eNOS, have a protective role against the atherogenic activity of Ang-2 [17].

Statins exert a protective role in patients with atherosclerotic plaques since they prevent plaque rupture [18]. In animal studies it has been reported that increased serum levels of Tregs resulted in reduction of atherosclerotic plaques [19]. Tregs exert their anti-inflammatory role by secreting two major anti-inflammatory cytokines TGF-β and IL-10. A recent study showed that simvastatin treatment increased the levels of Tregs both in atherosclerotic plaques in mice and in the peripheral circulation in patients with atherosclerosis. They also increased the expression of TGF-β, IL-10 and Forkhead/winged helix transcription factor (Foxp3), a marker of Tregs which is necessary for their activity and proliferation [20]. It was also noted that simvastatin increased the levels of Tregs and their markers with an independent to lipid lowering mechanism [20]. This promotion of Tregs accumulation indicates another possible mechanism by which statins prevent the development and stabilize atherosclerotic lesions.

Although many studies have proved that statins have many immunomodulatory pleiotropic effects in addition to lipid lowering, the mechanism by which these effects are carried out are still under investigation. Blocking of HMG-CoA reductase is not enough to exert these pleiotropic effects [13]. Some additional mechanisms, which have been described, are downregulation of NADPH oxidase, inhibition of Ras and Rho prenylation and protection of NO signaling [18].

Statins are classified as lipophilic and hydrophilic depending on their water solubility. Since the primary site of statin actions is the liver their ability to enter hepatic cells is essential for their function. Hydrophilic statins enter the liver *via* carrier-mediated uptake, while lipophilic statins enter by passive diffusion a process which is not not fo liver. This means that lipophilic statins are widely distributed throughout the body [14]. Both hydrophilic and lipophilic statins have been reported to have pleiotropic effects, but the widespread distribution of lipophilic statins indicates that they are likely to exert pleiotropic effects more efficiently [14].

In clinical studies involving patients with atherosclerosis, the elevated levels of LDL cholesterol and triglycerides in their serum, makes it difficult to determine whether additional mechanism besides lipid lowering contributed to the final result. In the JUPITER study cardiovascular morbidity and C reactive protein levels, whose elevated levels are considered a predictor of cardiovascular diseases in both general population and high risk population, were reduced after long term statin treatment in patients without hy-

perlipidemia [21]. This indicates that lipid lowering is not the only mechanism by which statins prevent cardiac events, although in the same study LDL cholesterol levels were reduced to very low normal levels.

Evidence of the importance of statins' pleiotropic effects can be found in clinical studies regarding patients with other autoimmune disorders. The TARA trial showed that patients with rheumatoid arthritis, who were treated with atorvastatin, had increased C reactive protein levels and improved vascular functions [13]. In another study, patients with systemic lupus erythematosus treated with atorvastatin exhibited improved vasodilation. The study included patients with an increased risk of atherosclerosis, and patients without risk factors reporting that both groups had similar beneficial results [22]. This study therefore indicates that statins exert vasoprotective effects independent of lipid lowering.

Relationship between atherosclerosis and autoimmune diseases

Beyond the autoimmune background of the atherosclerotic disease itself, atherosclerosis is reported in with increased frequency in autoimmune diseases. Studies in pediatric populations show that children with rheumatic diseases have an increased incidence of atherosclerosis [28]. Children with systemic lupus erythematosus (SLE), dermatomyositis and juvenile idiopathic arthritis (JIA) may have endothelial dysfunction leading to atherosclerotic lesion [28]. Mechanisms of cellular and humoral immunity are implicated in the atheromatosis induction in patients with systemic lupus erythematosus and rheumatoid arthritis [30]. In these patients a five-fold higher incidence of atherosclerosis compared to the general population has been reported [31]. Immune system over-activity, oxidative stress and chronic inflammation in these patients incurred in endothelial function. The immunological mechanisms that can lead to endothelial dysfunction in SLE and RA include mainly type II (cytotoxic reactions) and type III (immune complex injury) reactions [31]. In rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), endothelial cell activation, increased vascular permeability and ultrafiltration are observed [31]. These procedures lead to functional alterations and ultimately damage to the vessel. In addition, circulating immune complexes (IC) that promote the accumulation of monocytes are observed. The monocytes are retained in the lumen, releasing proinflammatory mediators that participate in the endothelial damage [31]. Patients with SLE and RA, having an increased risk of atherosclerosis and cardiovascular risk, which has been reported to reduce their life expectancy by 10-15 years [31], may benefit from ultrasound scan of carotids and coronary arteries as increased calcification and atherosclerosis are observed in preclinical stages [32].

Inflammatory bowel disease (IBD) consists of a number of chronic inflammatory diseases. Chronic inflammation promotes development of atherosclerosis in this category of patients. Patients with IBD may have an increased thickness of the carotid artery [32]. An additional biomarker, associated with atherosclerotic frequency, high-sensitivity C-reactive protein (hs-CRP), has also been found increased in the same group of patients [32]. In patients with Crohn's disease, even in times of recession, significantly elevated levels of hs-CRP have been reported compared to the normal population [32].

In many chronic inflammatory diseases, chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis (RA), there is a direct relationship between atheromatosis and dyslipidemia levels. Besides, there is a direct link between inflammation and lipids [33]. Circulating cholesterol levels can be correlated with disease activity. During periods of high inflammatory status, a change in the lipid composition is observed favoring the formation of atherosclerotic plaques in RA rashes [33].IL-32, a pro-inflammatory cytokine, involved in the pathogenesis of RA, induces pro-inflammatory cytokine activation such as IL-1β, IL-6, TNFα and IL-8, which are involved in the development of atherosclerotic plaques [33]. TNFα is also involved in the pathogenesis of IBD and COPD [33]. The latter is known to be associated with the development of atherosclerosis and cardiovascular risk. An important fact is the expression of IL-32 in macrophages, which are present in atherosclerotic lesions. The development of specific IL-32 isoform in-

hibitors in order to inhibit the growth of atherosclerotic plaques has been highlighted as a promising treatment in patients with RA [33].

IL-6 has been demonstrated to play an important pro-atherogenic role. A recent study regarding patients with rheumatoid arthritis showed that elevated serum levels of IL-6 and TNF-a increased the expression of scavenger receptors in endothelial cells. Those receptors promote atherosclerosis by binding oxLDL and causing endothelial injury. OxLDL also induces the production of MCP-1 by endothelial cells [24]. MCP-1 is a monocyte chemoattractant protein, which increases the concentration of monocytes in the subendothelial space and causes the formation of foam cells and subsequently accelerates the formation of atherosclerotic plaques [25]. The adhesion and migration of monocytes into the subendothelium space is also facilitated by the expression of intercellular adhesion molecule-1 (ICAM-1). Cardiotrophin-1 is an IL-6 type cytokine found to stimulate the expression of both ICAM-1 and MCP-1 in human aortic endothelial cells promoting atherosclerosis [26]. Moreover, IL-6 classic-signaling was reported to promote Th17 cell differentiation and activation, while trans-signaling can suppress the activation of Tregs [23].

In clinical practice, antibodies against IL-6R are used only in treatment of rheumatoid arthritis (RA). Tocilizumab, a monoclinic antibody against both IL-6R and sIL-6R, has been successful in helping RA patients by alleviating their symptoms [26]. Since IL-6 plays a significant role in the pathogenesis of both atherosclerosis and RA, recent studies have shown that tocilizumab is also beneficial in the prevention of the formation of atherosclerotic plaques in patients with chronic inflammatory diseases. A recent study demonstrated that toxilizumab improved endothelial function and reduced aortic stiffness in patients with RA diminishing the risk of accelerated atherosclerotic plaque formation[26]. Additionally, increased IL-6 levels are found in atherosclerotic lesions [25] and elevated IL-6 levels in the serum of healthy men have been associated with higher risk of cardiovascular events [26]. It is evident that the lowering of IL-6 effects caused by IL-6R inhibition is protective against atherosclerosis. Tocilizumab treatment has also been reported to increase the levels of total cholesterol in the blood stream and improve the ratio of HDL in total cholesterol [15]. TNF-a blockade has also been shown to reduce the risk of cardiovascular events in RA patients [24]. Tocilizumab inhibits the activation of both IL-6R and sIL-6R and as a side effect the beneficial role of IL-6 classic-signaling is suppressed [23]. As a result, the patients are more susceptible to bacterial infections. The necessity to overcome these side effects has led to the development of antibodies against the gp130 protein which block the trans-signaling, while the classic-signaling *via* membrane bound IL-6R remains unaffected. The sgp130Fc protein has shown encouraging results in animal models of RA and atherosclerosis and clinical trials have started recently [24]. Despite these findings it is necessary to evaluate the effect of IL-6R antibodies in patients without RA or other inflammatory disorders to determine if the protective role of IL-6R antibodies against atherosclerosis is exerted by direct effect on the atherosclerotic lesions or due to the improvement of the health of the patients.

Latent Autoimmune Diabetes of Adulthood (LADA) is the most prevalent form of autoimmune diabetes [30]. In diabetes, advanced glycation end products (AGEs) are increased. These are pro-oxidants and induced oxidative stress leading to the formation of atherosclerotic plaques [30]. An ultrasound scan shows an increased incidence of atherosclerosis in people with LADA-type diabetes compared to classical type 1 diabetes and type 2 diabetes. Specific carotid atherosclerotic plaques are observed in 73.2% of patients with LADA, 57.1% in patients with type 1 diabetes and 56.9% in type 2 diabetes patients [30]. Patients with LADA diabetes have increased difficulty in regulating blood glucose levels and elevated levels of HbA1c [30]. High levels of HbA1c have been associated with increased incidence of atherosclerosis and coronary lesions [30]. Also, in patients with autoimmune diabetes, poor glycemic control and hypoglycaemic episodes are related to pro-inflammatory status contributing to the development of atherosclerosis [30]. Despite the increased use of statins in patients with LADA, the incidence of atherosclerosis

rotic plaque in the carotid arteries remains high [30].

Psoriasis is another autoimmune disorder associated with the development of atherosclerosis. Patients with psoriasis and psoriatic arthritis, collectively called psoriatic disease (PsD), have an increased risk of developing cardiovascular disease (CVD) [36]. Patients with psoriasis have been reported to have increased platelet mass index (PMI) and mean platelet volume (MPV) [34]. These markers were associated with greater ability to form atherosclerotic plaques In addition patients with psoriasis have higher levels of plasma endocan and homocysteine [35]. Homocysteine is well known to play a significant role in the development of atherosclerosis while endocan is an indicator of vascular endothelial damage. Finally, elevated levels of TNF-α and IL-17 levels have been reported in psoriatic patients [37].The above findings support that psoriasis could be a risk factor for cardiovascular diseases [35] In addition to psoriasis, another condition, which has been associated with the development of atheromatosis, is atopic dermatitis [37]. The pathophysiology of atopic dermatitis involves Th17, Th2, Th22 and Th1, which are also involved in pathophysiology of atherosclerotic plaque development [37]. Chronic inflammation causes recurrent vascular injury accelerating atherosclerosis suggesting that individuals with autoimmune diseases may have a higher tendency to develop endothelial dysfunction.

Conclusions

Accumulating evidence pose new horizons for the study, understanding and treatment of atherosclerotic lesion. The immune disease model opens new investigation roads of atherosclerosis by setting new evidence for further investigation in the future.

Conflict of Interest

All authors declare no conflict of interest.

Περίληψη

Αθηροσκλήρωση και αυτοανοσία

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Η αθηροσκλήρωση αποτελεί ασθένεια ιδιαίτερα διαδεδομένη στον πληθυσμό των ενηλίκων, ωστόσο παρατηρούνται συνεχώς αυξανόμενα ποσοστά και στον παιδιατρικό πληθυσμό. Η αθηροσκλήρωση είναι μια πολυπαραγοντική νόσος που συνδέεται με περιβαλλοντολογικούς παράγοντες. Νέα δεδομένα μελετών συσχετίζουν την αθηροσκλήρωση με αυτοάνοσους μηχανισμούς. Ο ρόλος των Th17, Treg, IL-6, PAF, ενισχύουν αυτή τη θέση. Ο μηχανισμός της αυτοανοσίας μπορεί να συμμετέχει, τόσο στην παθοφυσιολογία της αθηρογένεσης, όσο και στη θεραπεία και την επίδραση των στατινών ως φάρμακα εκλογής. Σκοπός αυτής της ανασκόπησης είναι να αναλύσει το αυτοάνοσο μοντέλο της αθηροσκλήρωσης. Πρόκειται να περιγραφεί η παθοφυσιολογία της αθηροσκλήρωσης, να αναλυθεί ο μηχανισμός μέσω του οποίου οι στατίνες συμβάλλουν στη θεραπεία της αθηροσκλήρωσης με ποικιλότροπες επιδράσεις – παρόμοιες με αυτές άλλων αυτοάνοσων παθήσεων ενισχύοντας έτσι την αυτοάνοση φύση της αθηροσκλήρωσης. Αναλυτικότερα, σημαντικό ρόλο στην παθοφυσιολογία της αθηρωματικής πλάκας διαδραματίζει η LDL και συγκεκριμένα η οξειδωμένη μορφή της -oxLDL-η οποία οδηγεί στην ανεξέλεγκτη παραγωγή του Παράγοντα Ενεργοποίησης των Αιμοπεταλίων. Αποτέλεσμα της όλης διαδικασίας είναι η είσοδος της LDL στον υπενδοθηλιακό χώρο και ο σχηματισμών των «αφρωδών κυττάρων». Τα τελευταία αποτελούν βασικό χαρακτηριστικό της αθηρωματικής πλάκας. Στη συνέχεια γίνεται περιγραφή της διαδικασίας ενεργοποίησης και διέγερσης των αυτοαντισωμάτων. Τέλος, η ανασκόπηση καταλήγει στη δράση και την αποτελεσματικότητα των στατινών για την αντιμετώπιση της αθηρωματικής αλλοίωσης. Η δράση τους ωστόσο δεν περιορίζεται στη μείωση των επιπέδων της LDL-χοληστερόλης στον ορό, καθώς οι στατίνες παρουσιάζουν αντιφλεγμονώδεις και ανοσοτροποποιητικές δράσεις, μειώνοντας την παραγωγή προφλεγμονωδών κυτταροκινών από Τ κύτταρα καθώς και των κυττάρων που έχουν αντιγονική δράση.

Λέξεις ευρετηρίου: αθηρωσκλήρωση, «αφρώδη κύτταρα», oxLDL, Tregs, Th17, στατίνες, IL-16

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