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IMMUNE RESPONSE IN ATHEROSCLEROSIS

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ABSTRACT

Atherosclerosis is a chronic inflammatory disease caused by a thickening or hardening of the arteries because of the buildup of cholesterol plaques in the inner lining of an artery. The disease is the leading cause of vascular disease worldwide and the most common underlying pathology of coronary artery disease, peripheral artery disease and cerebrovascular disease. Recent studies showed that Atherosclerosis is largely driven by immune factors, such as an innate immune response through myeloid cells as monocytes and macrophages. For the construction of this systematic review 13 articles were selected from the platforms MEDLINE and SciELO, using the descriptors: atherosclerosis, cardiovascular disease and immunity, and the Boolean operator "and". This review of literature summarizes and describes the immune factors related to atherosclerosis, the innate and adaptive immune mechanisms that accelerate the disease and the hypothesis that atherosclerosis includes an autoimmune response. We also concluded that even though there was a great development in recent years, further studies are still needed to properly understand the development of the disease so more efficient techniques for prognosis, diagnosis and treatment can be developed.

KEY WORDS: Atherosclerosis, Cardiovascular diseases, Immunity, Cholesterol plaques, Chronic disease.

INTRODUCTION

Atherosclerosis is a chronic disease, it has a slow lifelong progression that may start in childhood and get worse faster as you age, has changes in the immune system (immunosenescence), and disinvolve certain habits and diseases that accelerate the process of plaque building, such as smoking, sedentary lifestyle, elevated levels of cholesterol and triglycerides in the blood, dyslipidemia, high blood pressure and diabetes. *(American 2020)*. Significant age and sex differences exist in the incidence and constitution of these atherosclerotic plaques. Prior to menopause, women are relatively protected from cardiovascular disease with smaller necrotic core volumes and generally more stable plaques, which suggests a protective role for estrogen. *(Beck-Joseph; Lehoux 2021)*.

In atherosclerosis disease cellular activity and cholesterol accumulation lead to vascular remodeling and the formation of plaques (made up of cholesterol, fatty substances, cellular waste products, calcium and fibrin) in the walls of large or medium sized arteries and, as it grows, the wall of the blood vessel thickens, reducing blood flow or even blocking it and, consequently, lessens the amount of oxygen and nutrients reaching the body, causing critical tissue hypoxia. *(American 2020)*. This way, medical complications arise through the restriction of blood flow due to lumen encroachment by the plaque. *(Beck-Joseph; Lehoux 2021)*. The pathophysiological processes and remodeling of the atherosclerotic lesions can also eventually culminate in the rupture or erosion of the plaque and subsequent occlusive atherothrombosis, which results in clinical events. *(Porsch et al. 2021)*

Where the plaque of atherosclerosis develops and the type of artery affected varies in each person, it can affect the heart, brain, pelvis, legs, arms or kidneys, leading to different conditions and complications. Some examples are: angina (chest pain caused by reduction of the blood flow to the heart muscle), coronary heart disease (plaque in arteries in or leading to the heart), carotid artery disease (plaque in neck arteries that supplies blood to the brain), peripheral artery disease (plaque in arteries of the extremities) and chronic kidney disease. *(American 2020)*. The most common complications, like myocardial infarction and stroke, are caused by spontaneous thrombotic vessel occlusion and atherosclerosis, as the major underlying cause of cardiovascular disease, represent the most common cause of death, at least in the developed world, and also an important cause of morbidity worldwide. *(Frostegård, 2013)*..

Previously, arteriosclerosis was summarized as a pathology caused by the passive accumulation of cholesterol in the artery walls. However, new evidence demonstrates atherosclerosis as a chronic inflammatory disease with the involvement of auto immunological mechanisms in its induction and progression. This autoimmune response is clinically best documented by antibodies against LDL and other atherosclerosis antigens found in patients and, in many studies, high-affinity antibodies secreted by IgG-producing plasma cells were positively correlated with atherosclerosis. *(Wolf; Ley 2019)*.

The atherogenic process starts with

the accumulation of several plasma lipoproteins in the subendothelial space at sites of flow perturbation and endothelial dysfunction. This will attract cells of the innate and adaptive immune system to the arteriosclerotic plaque, local endothelial cells recruit monocytes and leukocytes to the intima (innermost layer) of the artery. In the intima, these monocytes differentiate into pro-inflammatory macrophages, causing local inflammation. Although, macrophages are unable to completely phagocytose all the LDL, thus differentiate in foam cells by taking up too much modified LDL. Cholesterol loading causes a myeloid cell response with proinflammatory cytokine secretion, in situ macrophage proliferation, and further recruitment of myeloid cells. This way creates an inflammatory environment on the arterial wall by binding to Toll-like receptors, a group of widely expressed pattern recognition receptors that cause proinflammatory signaling. Witch will bring an infiltration of cells of antigen-presenting cells (APCs), such as dendritic cells, macrophages, natural killer (NKT) cells and neutrophils and of the adaptive immune system, B and T cells. Notably, the plaque's growing content of the myeloid cells and lymphocytes correlates with the clinical complications already spoken and may predispose for future thromboembolic events. Then, with some cells death, there will be a presentation to the adaptive immune system, which will secrete IGG autoantibodies against LDL within the artery, oxidized LDL and apoprotein B. Therefore, the atherogenic process encompasses the adaptive and innate immune system, in addition to the autoimmune response.

Also an important consequence of the cholesterol loading mentioned before hand is the formation of intracellular cholesterol microcrystals, that will activate the inflammasome. Inflammasome is a molecular machinery that comprises molecules of the cytosolic nucleotide binding domain and leucine-rich repeat gene family that cleaves pro-interleukin-1β into its active form (IL-1β). This IL-1β serves as an inflammatory cytokine that enhances the expression of many proinflammatory cytokines. Notably, attenuating cholesterol storage and enhancing cholesterol efflux pathways may favor the resolution of plaque inflammation and even promote plaque regression. (*Wolf; Ley 2019*).

Current clinical guidelines and therapies for atherosclerosis are focused/limited on preventing the development of disease; like having a healthy lifestyle (good eating habits and moderate physical exercise), preventing and treating other diseases that accelerates the process of the plaque formation and using drugs that lower LDL cholesterol; and on treating, medically and surgically, the complications previously mentioned that pops up with the disease. Most antiatherosclerotic drugs use target hyperlipidemia and several other drugs have also been investigated in clinical trials as anti-inflammatory agents, but recently there are also studies that have shown that recombinant IL-19 reduces atherosclerosis development, but more studies are needed. *(Engelen et al. 2022)*. Single-cell technologies, such as single-cell mass cytometry, single-cell RNA sequencing and cellular indexing of transcriptomes and epitopes by sequencing, are ideal for mapping the cellular and molecular

composition of human atherosclerotic plaques and this way aid in the discovery of new precise immunotherapies. *(Fernandez; Giannarelli 2021)*

The present study seeks to explain and clarify the autoimmune process of arteriosclerosis, described in previous studies, including the functions of immune and inflammatory modulators in the formation and development of this pathology. We believe that further studies, that seek to investigate the role of immune system cells, are needed and will help to better understand the atherosclerosis disease, consequently helping to combat the disease itself and its complications.

MATERIALS AND METHODS

This work focuses on compiling the main explanations of the pathophysiological process of atherosclerosis, guided by the strong performance of the immune system for the formation of plaques. The construction was carried out through a systematic review of articles directed to the topic in question; with research of data from the last year taken from the main platforms (MEDLINE (National Library of Medicine), on PubMed, and SciELO (Scientific Electronic Library Online)), using the descriptors: atherosclerosis, cardiovascular disease and immunity, and the Boolean operator "and". To objectify and select the studies with more scientific evidence, the following filters were used on MEDLINE: free full text, Books and documents, systematic reviews, publication date: 1 year. And the following filters were used on Scielo: article and review article, publication year: 2020 (that was the only closest year with publications about the theme). Table 1 shows the data above.

Platform	Research	Results	After filters
MEDLINE	atherosclerosis AND immunity	9100	10
	atherosclerosis AND cardiovascular disease	128102	77
	atherosclerosis AND immunity AND cardiovascular disease	6739	7
Scielo	atherosclerosis AND immunity	7	1
	atherosclerosis AND cardiovascular disease	399	22
	atherosclerosis AND immunity AND cardiovascular disease	2	1

Table 1: Medline and Scielo Articles and the Boolean operator

RESULTS AND DISCUSSION

After the filters were applied there were 118 articles left that were classified and selected by reading all of their titles and then their abstracts. In the end 13 articles were selected, by their statistical relevance, being qualified and used for this study.

Atherosclerosis is the pathology caused by the deposition of fatty plaques in the vessel and this process occurs

through cholesterol. LDL tends to go and accumulate to the subendothelial tissue, which is the tunica intima of the vessel, usually it doesn't stay there, returning to the endothelium. This increased LDL will go through an oxidation process and change its conformation, forming ox-LDL (oxidized low-density lipoprotein) that is retained in the subendothelial tissue of medium and large arteries (*Wolf; Ley 2019*) and with that it will release chemotactic factors into the bloodstream, consequently attracting monocytes.

Elevated levels of apolipoprotein B containing lipoproteins such as low-density lipoprotein and very low-density lipoprotein are a prerequisite for atherosclerotic plaque development, independent of additional risk factors ant the pathological diffuse intimal thickening, that is the result of atherosclerosis development, is characterized by their high proteoglycan content which facilitates the retention of apolipoproteins. Through the continuous lipid retention, monocyte recruitment and foam-cell formation, the diffuse intimal thickening may progress toward sites of chronic inflammation with enhanced production of inflammatory mediators and macrophage colony-stimulating factor. Also, additional molecular processes that occur favor disease progression, such as accumulation of reactive oxygen species, increased nitric oxide production, enhanced endothelial permeability and increased monocyte recruitment from the circulation. *(Beck-Joseph; Lehoux 2021)*.

Atherosclerosis is a multiphase process characterized by the activation of endothelial cells with the expression of adhesion molecules, migration of blood monocytes/macrophages, and the transmigration of dendritic cells, T cells and some B cells into the intima, as well as the transfer of modified forms of LDL (low density lipoprotein) to matrix components. (*Ilhan; Kalkanli 2015*) . Inflammation in atherosclerosis can be induced and potentiated by HSPs (heat shock proteins) induced in the plaque by stress, oxLDL and other factors, which can become immunogenic and trigger immune responses. On other hand, infections and infectious agents present in the lesions, even though they could potentially be a cause of atherosclerosis, are not fully supported by the available scientific evidence, so they could also be just innocent bystanders. *(Frostegård, 2013)*.

The cause of the inflammation is not clarified, although there are possibilities that are not mutually exclusive. Ox-LDL, opposed to LDL, activates T lymphocytes *(Frostegård, 2013)*, which will penetrate inside the subendothelial tissue, release cytokines, trigger an inflammatory process (*Wolf; Ley 2019*) and stimulate monocytes/macrophages, in addition to other types of plaque cells. Part of this activating effect is likely mediated by inflammatory phospholipids, which will cause inflammation. On the other hand, antibodies against natural phosphorylcholine and other phospholipids may be protective, neutralizing the inflammatory effects. *(Frostegård, 2013)*. In addition, cells of the innate immune system, such as neutrophils and eosinophils, will be recruited and will die (as they are specific cells against bacterial and parasitic infections respectively) and thus signal to antigen-presenting cells (APC's), such as

macrophages , B lymphocytes and the plaque cells themselves. (*Wolf; Ley 2019*).

Recently, a new group of intracellular pattern recognition receptors was described, receiving the name of NOD-type receptors (NLRs). They are involved with the recognition of pathogen-associated molecular patterns (PAMPs) and stress signals produced by cells during infection or cell injury. NLRs also participate during the formation of a multimolecular complex called an inflammasome. *(Bolsa 2011)*. This inflammasome has the role of grouping and activating inflammatory caspases, such as caspase-1, culminating in the maturation of pro-Interleukin-1 beta and pro-IL-18, which, after interference by the inflammasome, become their active forms, called IL-1 beta and IL-18. These two cytokines play a key role in the inflammatory response present in atherosclerotic lesions, since IL-1b promotes endothelial activation with consequent cell recruitment and IL-18 induces the amplification of the TH1 response, which leads to an increase of the inflammatory process and may culminate with the rupture of atherosclerotic lesions. *(Bolsa 2011)*.

Monocytes will penetrate the endothelium, through diapedesis, into the subendothelial tissue, and they will differentiate into macrophages at the subcutaneous tissue and will phagocytize the oxidized LDL. After the macrophage phagocytizes the LDL it will be converted into a foam cell, which is filled mainly with ox-LDL and this process is increasingly stimulated and more inflammatory factors are released. *(Frostegård, 2013)*.
The macrophage will exceed its ability to phagocytose ox-LDL, become inefficient and defective and consequently form lipid crystals, causing accumulation of live and dead macrophages and lipid crystals in the region of inflammation. (*Wolf; Ley 2019*).

It is known that the atherogenic process involves both the cells of the innate immune system (through myeloid cells, such as monocytes and macrophages) along with the adaptive one, and that these cells generate several cytokines that may have pro- and anti-inflammatory functions. (*Ilhan; Kalkanli 2015*). After the signaling for the beginning of the inflammatory process, the complement system will participate in the immune response, but it's important for the explanation of the autoimmune process of atherosclerosis. The focus is to show the adaptive immune response, specifically a humoral arm, to talk about this autoimmune reaction. When the death of nonspecific cells of the innate immune system occurs, the antigen is presented to the adaptive immune system. In consequence, it activates the CD4 lymphocyte through the first signal (MHC2 with the TCR) and second signal with (B7 and CD28) activated. There is release of the cytokine IL-2, exerting paracrine and autocrine activation so that more lymphocytes proliferate. IL-2 will also differentiate into TH1, with a pro-inflammatory response, increasing the number of natural killer (NK) cells and the complement system. (*Wolf; Ley 2019*).

Both CD4 and IL-2 will release IL-4, in order to differentiate into TH2 and will secrete IL-4, causing the B lymphocyte to transform into a plasma cell and secrete antibodies. The antibodies will bind to SELF structures (the artery in question) and are then classified as IgG autoantibodies against LDL that is located inside the artery, oxidized LDL and apoprotein B of

the atherosclerotic plaque. This antibody will mark the plaque, recruiting cells, generating an exacerbated immune response, which will increasingly swell the plaque, due to the infiltration of cells of the adaptive immune system (B and T cells) and innate immune system, obstructing more and more the vessel and providing a higher risk of complications, such as thrombosis. (*Wolf; Ley 2019*). These processes sustain a complex and persistent inflammatory microenvironment consisting of macrophages, T cells, NK cells, NK cells, B lymphocytes, and neutrophils. *(Frostegård, 2013)*.

Medial smooth muscle cells migrate into the intima and develop a more synthetic phenotype, producing matrix components. As the atherosclerotic plaque grows, a fibrous cap develops to cover it and dying in addition to dead cells accumulate, many of which are derived from foam cells. In advancement, microvessels develop into the plaque, which can be seen as part of normal aging but is also a feared complication of atherosclerosis. *(Frostegård, 2013)*.

The new vessels covering the atherosclerotic plaque usually rupture, and platelet-attracting factors are released. Platelets arrive to clot (form the platelet plug) of the injured vessel and this causes partial or total obstruction of the vessel. *(Frostegård, 2013)* . If the obstruction is only partial, because of the blood flow and activated immunocompetent cells are abundant, this platelet plug can break off and travel towards smaller vessels. As a consequence, the thrombus will be trapped in this smaller vessel, leading to narrowing or occlusion of a blood vessel, which is the common cause of complications of atherosclerosis, causing tissue hypoxia and even death depending on the occlusion site. (*Ilhan; Kalkanli 2015*).

Recent studies have shown that pyroptosis, which was initially found to function as an innate immune effector mechanism to facilitate host defense against pathogenic microorganisms, is also involved in the initiation, progression and complications of atherosclerosis that involves endothelial cells, pro-inflammatory leukocyte and smooth muscle cells. Pyroptosis is a newly discovered form of programmed cell death, characterized by cell swelling, the protrusion of large bubbles from the plasma membrane and cell lysis. This death pathway is mediated by the pore formation of gasdermin D, which is activated by human caspase-1/caspase-4/caspase-5), and followed with the releasing of both cell contents and proinflammatory cytokines. Currently, there are still some limitations in the studies of pyroptosis in atherosclerosis but researches are being done to solve those. *(Qian et al. 2021)*.

Although the classical perception is that autoimmunity is pathogenic in its own, autoimmunity against apoprotein B (apoB), Ox-LDL, and other antigens involving CD4+ helper T cells instructs myeloid cells and antigen-specific antibodies that modify directly the pathogenicity of these antigens. So, one can have atheroprotective characteristics. Thus, the adaptive immune system in atherosclerosis can be pro- or anti-inflammatory (atherogenic) and with the progression of the disease and inflammation, it is not known why, but the protective immune response

undergoes a change in functionality and if converts to pathogenic. The ability of immune cells to adapt to the tissues, creates a highly specialized and complex plaque microenvironment, a feature highlighted by the heterogeneity of regulatory T cells, whose nuances and impact on the disease have yet to be fully discovered. (*Wolf; Ley 2019*).

The evolution of genetic techniques to map the cellular and molecular composition of atherosclerotic tissue has already provided a first atlas of immunological alterations associated with clinical complications in humans. As a result, causal relations between plaque heterogeneity are being established, in addition to understanding disease progression and the specific effects of cardiovascular risk factors, defective regression, and the cellular mechanisms that drive clinical cardiovascular outcomes. In this way, they brought capabilities to solve some complexities of atherosclerotic disease and offer opportunities to test new candidate immunotherapies. (*Wolf; Ley 2019*).

The roles of immune and inflammatory modulators in the formation and development of atherosclerosis have provided a deeper insight into these mechanisms and thus the understanding, diagnosis and prognosis of the disease. Therefore, controlling the immune reactions of an organism through an immunomodulatory agent that adjusts them to the desired level is the main objective of some clinical studies to control atherosclerosis (*Ilhan; Kalkanli 2015*), but limitations in the predictive power of animal models and lack of an understanding complete understanding of the role of autoantibodies, B and T lymphocytes present obstacles to clinical translation. (*Wolf; Ley 2019*).

Single-cell technologies have the potential to advance our basic knowledge of the complex immune mechanisms underlying atherosclerosis directly in humans. The analysis of experimental atherosclerosis with the use of the same single-cell tools offers the unique opportunity to build an immune atlas of experimental and human disease that will aid in the validation of human mechanisms in relevant mouse models. Paired with cell-based, pooled single-cell CRISPR screens to identify the specific function of several genes and proteins on heterogeneous immune cells, single-cell studies offer new opportunities for molecular-targeted drug development. The growing adoption of immune monitoring tools such as mass cytometry in ongoing clinical trials shows the importance of how immune cells respond to new drugs and highlights that a similar approach might aid in the discovery of new precise immunotherapies and drug discovery. *(Fernandez; Giannarelli 2021)*.

Most antiatherosclerotic drugs in current clinical use target hyperlipidemia and several other drugs have also been investigated in clinical trials as anti-inflammatory agents (the development of some of these agents has been terminated but others remain in development). Most of the tested drugs have shown a limited ability to reverse atherosclerosis. Interestingly, recombinant IL-19 was shown to reduce atherosclerosis development in a time - and dose - dependent manner. Traditionally, IL-19 was thought to be expressed in only immune cells, but studies revealed that IL-19 is also expressed in multiple atherosclerotic plaque cell types, but not normal arteries. IL-19 reduces the

development of atherosclerosis via multiple mechanisms, including balancing cholesterol metabolism, enhancing Th2 immune cell polarization, reducing the inflammatory response and reducing the proliferation, migration and chemotaxis of vascular smooth muscle cells. Clinical studies have primarily aimed to achieve regression and/or stabilization of atherosclerotic plaques, with regression in particular indicating a very good drug response. Thi way, it's proposed that IL-19 is a promising biomarker and target for the diagnosis and treatment of atherosclerosis, but more studies and research are needed before materializing and signing the idea. *(Engelen et al. 2022)*.

Also, a large number of preclinical studies are demonstrating an atheroprotective effect of immunization with LDL antigens and that has sparked the idea of developing a vaccine against atherosclerosis. In particular immunization approaches with ox-LDL and oxidation-specific epitopes trigger robust and lasting antibody responses that correlate with atheroprotection, so, active vaccination strategies may represent a realistic alternative. *(Porsch et al. 2021)*.

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We conclude that atherosclerosis is a disease triggered by multiple factors, including environmental, genetic and the well-cited immune factors. This pathology manifests itself primarily through an inflammatory process mediated especially by cells of the innate and adaptive immune system, something that previously went unnoticed. Recent studies report the detailed role of the inflammasome in the activation process of pro-inflammatory factors such as IL-1β and IL-18, which potentiate acute inflammation in the body.

Even with the knowledge of the strong role of the autoimmune system in atherosclerosis, it is still not completely understood how it changes from an anti-inflammatory to a pro-inflammatory factor. Thus, despite the great development experienced in recent years, further studies are still needed, especially through genetic techniques, to properly understand the development of the disease. In this manner, it will be possible to immunomodulate atherosclerosis and develop better and more efficient techniques for prognosis, diagnosis and treatment.

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