WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 9, 68-74. Research Article ISSN 2277– 7105

# PHYSIOLOGICAL ROLE OF IMMUNOLOGICAL AND METHODOLOGICAL PROCESSES IN THE PATHOGENESIS OF ATHEROSCLEROSIS

**D. A. Ochilova***

Department of Physiology of Bukhara State Medical Institute candidate of Medical Sciences.

Article Received on
03 July 2020,

Revised on 24 July 2020,
Accepted on 14 Aug. 2020,

DOI: 10.20959/wjpr20209-18033

***Corresponding Author**
**D. A. Ochilova**
Department of Physiology of Bukhara State Medical Institute candidate of Medical Sciences.

## SUMMARY

Cardiovascular diseases attract a lot of attention from researchers around the world due to the high risk of severe complications such as ischemia, heart attacks and strokes. The morphological basis of most of these diseases is atherosclerosis of the arteries. Atherosclerosis is a complex, multi-stage pathological process that develops mainly in the elastic (aorta, branches of its arc) and muscularly elastic (arteries of the heart, brain, etc.) type. the Problem of atherosclerosis is one of the most urgent in modern medicine due to its wide prevalence and severity of adverse outcomes. In modern studies of the progressive development of atherosclerotic plaques, great importance is given to inflammation, since the main cells involved in this process are found in the atherosclerotic lesion itself-monocytes/macrophages and T – lymphocytes, which produce factors for regulating the inflammatory response. Penetration into the subendothelial space of monocytes, their subsequent differentiation into macrophages and activation are the key moments of initiation of atherogenesis and development of atherosclerotic plaque.

**KEYWORDS:** atherosclerotic p, macrophages M1 and M2, T-lymphocytes, monocytes, cytokine.

## RELEVANCE

Atherosclerosis occurs due to a violation of lipid metabolism and is accompanied by the deposition of cholesterol and certain lipoprotein fractions (LP) in the intima. Deposits are formed in the form of atheromatous plaques, which are characterized by a special microanatomy. Inside the plaque is a nucleus consisting of a cluster of necrotic masses

(Mangan and Wahl, 1991), extracellular and intracellular lipids, as well as macrophages (MF), T - lymphocytes (T-LC), foamy and smooth muscle cells (MMC). Above this formation is a connective tissue fibrous covering containing MF and a specialized type of MMC.[1] The subsequent growth of fibrous tissue (sclerosis) and calcification of the vessel wall lead to a slowly progressive deformation and narrowing of the lumen up to occlusion. Such changes in the artery that feeds an organ gradually lead to insufficient blood supply, and when occluded, lead to the formation of foci of necrosis (heart attack and stroke) or gangrene.[6]

The main risk factors contributing to atherosclerosis development are increases in the plasma cholesterol by increasing the level of low-density lipoproteins, reduced levels of high-density lipoproteins, modification of lipoproteins (mdlp) – oxidation, glycosylation, etc., T-cell immune response, viral and chlamydiosis infection. The Association of atherosclerosis with these factors gave rise to the formulation of a hypothesis of the response to damage, which explains the development of atherosclerotic lesions.[7,8]

In recent years, the modern scientific literature has formed an idea of the so-called divergent polarization of macrophages, the essence of which is that macrophages, both in vitro and in vivo, depending on the signals they receive, can show not only Pro -, but also anti-inflammatory activity. In this regard, there are two polar phenotypes of activated macrophages, designated, respectively, as M1 and M2. This polar division of the macrophage population corresponds to the classification of activated T-lymphocytes into Th1 and Th2 subtypes, and emphasizes the connection of the MF of a certain phenotype with the implementation of the corresponding immune response. In the classical activation pathway, native macrophages in response to the action of Pro – inflammatory factors-interferon (Ifny), tumor necrosis factor (TNFa) and lipopolysaccharide (LPS) acquire the "Pro-inflammatory" M1 phenotype, which is characterized by increased secretion of various Pro – inflammatory cytokines, mainly interleukin IL-12 and MCP1 (monocyte-chemotactic factor 1) and low-IL-10. Thus, M1 macrophages initiate an inflammatory response, during which they exhibit high cytotoxic and bactericidal activity and support a Th1-dependent immune response (8). Relatively recently discovered alternative activation of macrophages in the" anti-inflammatory " phenotype of M2 occurs under the influence of other factors, as a result of such activation, several functional subtypes appear among M2 macrophages: M2a occurs in response to 8 stimulation of IL-4 and IL-13; M2b – in response to the action of immune

complexes, LPS and/or IL-1β; and M2c MF – under the action of IL-10, transforming growth factor beta (TGF - β) and glucocorticoids.[11] These subtypes of M2 macrophages differ in a set of surface markers and secreted cytokines. Thus, for M2a macrophages, the characteristic surface marker is CD206 (mannose receptor), for M2b – CD86 (a costimulating molecule to the main histocompatibility complex (GKGS) of class II) and gkgs protein molecules of class II, and for M2C – CD163 (hemoglobin-haptoglobin receptor). All these subtypes of M2 macrophages produce high levels of IL-10 and low IL-12; MF M2a and M2C, in addition to the above factors, secrete high levels of CCL18 and TGF-β; the m2b – chemokine subtype is CCL1 (chemoattractant for monocytes, B-lymphocytes, and dendritic cells), and M2a is also CCL24 (chemoattractant for eosinophils and T-lymphocytes) (Mantovani et al., 2004). Currently, it is believed that macrophages with the M2a phenotype exhibit anti-inflammatory, and M2b/C – regulatory functional activity (Lusta and Nutov, 2014). In General, the M2 macrophage subpopulation stimulates angiogenesis, tissue rearrangement and repair by activating fibroblasts and smooth muscle cells to proliferate and synthesize the intercellular matrix (Wynn, 2004). Along with the fact that M2 macrophages support a Th2-dependent immune response (mainly in some allergic reactions, parasitic infections), attract eosinophils to the focus of inflammation, their main task is to help suppress the inflammatory response and restore tissue.[1]

It is important to note that polar phenotypes of M1 and M2 macrophages most likely represent extreme States of metabolic and functional polarization of macrophages, along with which most likely there is at least a number of intermediate States (phenotypic continuum) (3,5,9). currently, research is being conducted on the functional role of M1 and M2 macrophage subpopulations in tumor growth and various pathologies accompanied by acute and chronic inflammation, including atherosclerosis. Recent studies have shown the simultaneous presence of both Pro-and anti-inflammatory macrophages in various endarterectomized samples of human arteries, as well as in aortic plaques in mice with experimental atherosclerosis.[4,9] Macrophages mediate their participation in atherogenesis by secreting a wide range of cytokines that affect the proliferative behavior and functional activity of plaque cells.[5] however, the role of specialized subpopulations of M1 and M2 macrophages in the process of initiation, progressive development, and destabilization of atherosclerotic plaque is still practically unknown.

To understand the molecular and cellular mechanisms that accompany the progressive development of atherosclerotic plaque in the intima of arteries, as well as the specific role in these processes of phenotypically and functionally different subpopulations of macrophages, it is essential to study the topography of the distribution of these subpopulations at different stages of development of atherosclerotic lesions and the spectrum of cytokines and other regulatory molecules synthesized by them. The lack of information in this field determines the relevance of the present study.

**The Purpose and Objectives of Work**

The purpose of this work is to study the role of subpopulations of Pro - and anti-inflammatory Macrophages in the processes of initial and progressive development of atherosclerotic lesions, as well as their destabilization in human arteries.

**Research Methodology and Methods**

Was examined 260 patients with atherosclerosis, among them 140 with atherosclerotic coronary artery disease, ischemic heart disease (AKA (IHD)) were hospitalized in kardiologicheskom branch of the Bukhara branch of the Republican research center of emergency medical care and 120 people with obliterating atherosclerosis of vessels of lower extremities (OANC), without clinical manifestations of CHD in the Department of vascular surgery Bukhara clinical hospital № 2. Among the surveyed, there were 220 men (84.6%) and 40 women (15.4%). The age of the subjects was 57.2 ±2.7 years (from 45 to 89 years).

The control group consisted of 50 practically healthy donors (30-50 years old), comparable by gender, without clinical manifestations of atherosclerosis, acute and chronic diseases in the acute phase, who do not smoke, do not use any medications, and do not abuse alcohol.

**1) Experimental section**

The experiment was conducted on 55 white male Wistar rats weighing 250-350 grams for six months, in strict compliance with the requirements of the European Convention (Strasbourg, 1986) on the content, feeding and care of experimental animals, as well as their withdrawal from the experiment with subsequent disposal. The experiments were based on the requirements of the world society for the protection of animals (WSPA) and the European Convention for the protection of experimental animals 86/609.

**All animals were divided into 5 groups**

- Group 1-15 animals were on a fat diet (modeling hyperlipidemia + hypothyroidism)
- Group 2-25 animals - (complex model: hyperlipidemia, hypothyroidism and arterial hypertension);
- Group 3 - 15 animals (healthy rats), fed regular food in accordance with the standards of the rat diet.

After 2, 4 and 6 months of observation, 5 animals from each group were removed from the experiment under ether anesthesia, by decapitation. At the end of the experiment, the remaining 10 animals from group 2 received pathogenetic therapy: administration of amino-dioxo-tetrahydro-phthalazindione sodium dihydrate (Galavit)-(group 4 - 5 rats) and polysaccharide glycogen - like 1,4; 1 .b-a-e-glucan isolated from the far Eastern mussel Crenomytilus grayanus (mytilan) - (group 5 - 5 rats), in order to assess their immunopathogenetic efficiency in a complex model of atherosclerosis. At the end of experimental therapy, the animals were removed from the experiment.

The clinical and experimental study was approved by the interdisciplinary ethics Committee of the Bukhara state medical Institute (Protocol No. 2, dated 06.02.2013).

To achieve these goals and objectives, a comprehensive (clinical, immunological, biochemical, and functional) examination of patients with atherosclerosis was performed. Observation of animals included: assessment of their condition, behavior, motor activity, measurement of blood pressure.

The ELISA method was used to determine cytokines, cytokine receptors, markers of extracellular matrix degradation, adipokines - in patients with atherosclerosis, and to determine cytokines, MMR-9 - in animals. The condition of blood vessels (aorta and femoral arteries) in rats was assessed using magnetic resonance imaging, histochemical and histological methods. The morphological structure of the liver of animals was evaluated using the histological method. A spectrophotometric method was used to determine the indicators of total oxidant and antioxidant activity of blood serum and arterial wall of animals. The total blood cholesterol of the examined patients and the lipid profile of the blood of animals were assessed using the colorimetric method.

## RESEARCH RESULT

Patients with as have an imbalance of cytokine regulation: an increase in serum levels of IL-6 (3.2 times) was determined, the content of TGF-p2 and soluble cytokine receptors increased less: TNF - aRI, TNF-aR II, IL-2R, and a decrease in the concentration of IL-2 and IL-10 (2.7-3 times) compared to the control ($p<0.05$) (Experience). Changes in the content of other cytokines studied were characterized by a tendency to increase without statistically significant differences. An increase in the content of soluble TNF-all type receptors is a compensation mechanism consisting in binding of a proinflammatory cytokine with subsequent inhibition of its biological activity.[13] The high level of IL-6 in as reflects the Pro-inflammatory activity of immunocompetent cells, which is consistent with the literature data

## CONCLUSION

In this regard, our study was aimed at conducting a comparative analysis of the distribution of macrophage subpopulations Pro-inflammatory MF and anti-inflammatory MF and factors that characterize their functional activity (Pro - and anti-inflammatory cytokines, as well as enzymes involved in the reorganization of the connective tissue matrix) in various types of atherosclerotic lesions of human carotid arteries and to study the participation of these subpopulations of macrophages in the process of destabilization of atherosclerotic plaque.

## REFERENCES

1. Uyemura K., Demer L. L., Castle S. C., Jullien D., Berliner J. A., Gately M. K., Warrier R. R., Pham N., Fogelman A. M., Modlin R. L. Cross-regulatory roles of interleukin (IL)-12 and IL-10 in atherosclerosis // Journal of Clinical Investigation, 1996; 97(9): 2130.
2. Van Lieshout A. W. T., Fransen J., Flendrie M., Eijsbouts A. M., van den Hoogen F. H., van Riel P. L., Radstake T. R. Circulating levels of the chemokine CCL18 but not CXCL16 are elevated and correlate with disease activity in rheumatoid arthritis // Annals of the rheumatic diseases, 2007; 66(10): 1334-1338.
3. Van Tits L. J. H., Stienstra R., van Lent P. L., Netea M. G., Joosten L. A. B., Stalenhoef A. F. H. Oxidized LDL enhances pro-inflammatory responses of alternatively activated M2 macrophages: a crucial role for Krüppel-like factor 2 // Atherosclerosis, 2011; 214(2): 345-349.
4. Vega M.A., Corbí A.L. Human macrophage activation: Too many functions and phenotypes for a single cell type // Inmunología, 2006; 25: 248-272.

5. Virmani R., Guagliumi G., Farb A., Musumeci G., Grieco N., Motta T., Mihalcsik L., Tespili M., Valsecchi O., Kolodgie F. D. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent should we be cautious? //Circulation, 2004; 109(6): 701-705.
6. Virmani R., Kolodgie F.D., Burke A.P., Farb A., Schwartz S.M. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions // Arterioscler Thromb Vasc Biol., 2000; 20(5): 1262-1275.
7. Wågsäter D., Zhu C., Björkegren J., Skogsberg J., Eriksson P. MMP-2 and MMP-9 are prominent matrix metalloproteinases during atherosclerosis development in the Ldlr-/-Apob100/100 mouse //International journal of molecular medicine, 2011; 2(2): 247-253.
8. Wang X. J., Han G., Owens P., Siddiqui Y., Li A. G. Role of TGFβ-mediated inflammation in cutaneous wound healing // Journal of Investigative Dermatology Symposium Proceedings. – Nature Publishing Group, 2006; 11(1): 112-117.
9. Wilson H. M. Macrophages heterogeneity in atherosclerosis - implications for therapy // J Cell Mol Med., 2010; 14(8): 2055-2065.
10. Wolfs I. M., Donners M. M., de Winther M. P. Differentiation factors and cytokines in the atherosclerotic plaque micro-environment as a trigger for macrophage polarization // Thromb Haemost, 2011; 106(5): 763-771.
11. D. A. Ochilova, N. G. Rakhmonkulova, Sh. H. Sobirov // Features of the Course of Hypertension Disease in People with Dyslipidemia/ American Journal of Medicine and Medical Sciences, 2020; 10(2). DOI: 10.5923/j.ajmms.20201002.02