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Место липидной теории в истории изучения атеросклероза

С. Н. Котляров✉

Рязанский государственный медицинский университет имени академика И. П. Павлова, Рязань, Российская Федерация

АННОТАЦИЯ

Введение. Несмотря на значительные успехи последних десятилетий в изучении атеросклероза, ассоциированные с ним заболевания все еще являются одной из ведущих проблем современного западного общества. В непростой истории изучения атеросклероза предлагались различные теории, которые пытались объяснить его природу в соответствии с уровнем научных знаний тех лет.

Цель. Провести анализ места липидных нарушений в различных теориях атерогенеза, которые были предложены в разные исторические периоды и которые сформировали текущее понимание его природы и являются основой для будущих исследований.

Липидная теория, предложенная более ста лет назад, и сегодня является основой для профилактики и лечения атеросклероза. Полученные впоследствии данные о роли нарушения функции эндотелия, значении иммунных клеток и механизмов врожденной иммунной системы, а также о важности нарушений сосудистой гемодинамики сформировали сегодняшнее понимание патогенеза атеросклероза, которое рассматривает его как сложную цепь иммунных и метаболических событий, происходящих в течение многих лет с участием различных клеток сосудистой стенки и кровотока. Многие из полученных на сегодняшний день данных о патогенезе атеросклероза пока не имеют терапевтического применения и являются перспективными направлениями будущих исследований.

Заключение. Липидная теория атерогенеза прошла сложный путь от понимания роли липидов в качестве простого субстрата для развития атеросклероза до того, что они выполняют сложные иммунные и метаболические функции и являются важной диагностической и терапевтической целью.

Ключевые слова: *атеросклероз; липидная теория; холестерин; эндотелиальная дисфункция; макрофаги; врожденная иммунная система; липидные медиаторы*

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Place of Lipid Theory in History of Study of Atherosclerosis

Stanislav N. Kotlyarov✉

Ryazan State Medical University, Ryazan, Russian Federation

ABSTRACT

INTRODUCTION: Despite the significant advances in the study of atherosclerosis in recent decades, the diseases associated with it still remain one of the leading problems of modern Western society. In the complicated history of the study of atherosclerosis, various theories have been proposed that attempted to explain its nature from positions of the scientific knowledge of those years.

AIM: To analyze the place of lipid disorders in various theories of atherogenesis that have been proposed in different historic periods and have shaped the current understanding of its nature and are the basis for future research.

The lipid theory, proposed more than a hundred years ago, is still the basis for the prevention and treatment of atherosclerosis. Subsequent findings on the role of endothelial dysfunction, on the importance of immune cells and innate immune mechanisms, and the importance of vascular hemodynamic disturbances, have shaped today's understanding of the pathogenesis of atherosclerosis, which regards it as a complex chain of immune and metabolic events occurring over many years and involving various cells of the vascular wall and the bloodstream. Much of the data on the pathogenesis of atherosclerosis obtained to date have no therapeutic application and are promising areas for future research.

CONCLUSION: The lipid theory of atherogenesis has passed a complicated way from understanding the role of lipids as a simple substrate for development of atherosclerosis to the fact of their performing complex immune and metabolic functions and being an important diagnostic and therapeutic target.

Keywords: *atherosclerosis; lipid theory; cholesterol; endothelial dysfunction; macrophages; innate immune system; lipid mediators*

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ECO•VECTOR

LIST OF ABBREVIATIONS

ABCA1 — ATP binding cassette subfamily A member 1
ABCG1 — ATP binding cassette subfamily G member 1
AS — atherosclerosis
CS — cholesterol
eNOS — endothelial nitric oxide synthase
HDLs — high density lipoproteins
LDLs — low density lipoproteins
SPM — specialized pro-resolving mediators

INTRODUCTION

Atherosclerosis (AS) is one of the key problems of our time due to its significant contribution to the morbidity and mortality structure of the population of many countries [1]. Indeed, atherosclerotic cardiovascular diseases, such as coronary heart disease [2], cerebral stroke [3] and AS of the lower limb arteries [4], remain the leading causes of temporary and permanent incapacity for work, and present a heavy economic and social burden for patients, their families and even for healthcare system as a whole [5]. These and other problems associated with AS undoubtedly emphasize the need to better study its causes, mechanisms and pathogenetic factors, which can be the targets for therapeutic intervention. In this context, AS is an actively studied problem, and the information available today considerably expanded understanding of its nature, but is insufficient to provide a comprehensive solution to either the problem of early diagnosis, or effective treatment for all patients. In the controversial history of the study of AS, various concepts have been proposed that explained various pathogenetic factors of the disease from positions of the scientific knowledge of that time.

The **aim** of this study to analyze the place of lipid disorders in various theories of atherogenesis that have been proposed in different historical periods and formed the current understanding of its nature and are the basis for future studies.

Lipid Theory of Atherogenesis

The word ‘atherosclerosis’ was first introduced by a German pathologist F. J. Marchand in 1904 and suggests the *lipid base* in the lesion foci [6]. The lipid theory of atherogenesis proposed by a Russian scientist Nikolai N. Anitschkow in 1913 [7] still remains one of the key concepts and underlies the current therapeutic and preventive strategies. The lipid theory rests on the results of studied conducted by N. N. Anitschkow and colleagues. In those experiments, rabbits were introduced cholesterol (CS) through the stomach, and in several months, cholesterol deposits were found in their arteries resembling lesions in human AS. N. N. Anitschkow was inspired to conduct these studies by the experiments of another Russian scientist — Aleksandr I. Ignatovsky who tried to obtain AS in rabbits by feeding them with a mixture of eggs and milk [8]. Although the scientist obtained the desired result, he incorrectly linked it to the presence of proteins in these products. N. N. Anitschkow and colleagues took those results into consideration and modeled the experiment that proved the connection of AS development with egg yolk and cholesterol present in it. Besides, later N. N. Anitschkow first described lipid-laden macrophages the so-called *foam cells* or *cholesterol esterasophagocytes*, as he called them (cholesterin-esterphagozyten). However, the authors could not completely understand the nature of these cells.

Twelve years after the publication of his key work, N. N. Anitschkow wrote: ‘It appeared that cholesterol, experimentally introduced in an organism, always forms deposits in strictly determined, sort of, predisposed to this, areas, including the arterial walls, and giving a typical picture of atherosclerosis. It was further found that cholesterol forms deposits not only in cells, but along with cells and often primarily, in the intercellular intermediate substance, as well as in fibers and on the surface of connective tissue fibers. It is this latter process, that is, deposition of lipoids in the interstitial substance of arterial walls, that is most important in the pathogenesis of AS’ [9].

On the basis of the available data and the results of his experiments, N. N. Anitschkow came to the conclusion that ‘lipoids’ ‘precipitate’ within the walls of arteries, like other colloidal substances, and that cells of the ‘reticuloendothelial system’ also participate in this process. Thus, the primary understanding was of

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the ***infiltrative nature of AS*** with CS being a passive substrate. Further experiments on dogs and rats did not give the same results as modeling of AS on rabbits, and his conclusions were rejected for some time [10, 11].

Study of Role of Lipoproteins

Изучение путей биосинтеза ХС являлось следующимThe study of the pathways of cholesterol biosynthesis was the next important step in understanding atherogenesis. Significant advances in the study of the pathways of cholesterol synthesis were achieved in the 1950s. The most notable were the works of K. Bloch and F. Lynen, who received the Nobel Prize in Physiology or Medicine in 1964 for their discoveries [12, 13]. Of particular interest among these studies is the description of 3-hydroxy-3-methylglutaryl coenzyme A (beta-hydroxy-beta-methyl-glutaryl coenzyme A, HMG-CoA) reductase in cholesterol biosynthesis by F. Lynen and N. L. Bucher l [13]. The data obtained by the authors attracted attention to HMG-CoA reductase as an enzyme that controls the rate of cholesterol biosynthesis, which was of enormous importance in the future.

The next important milestone that strengthened the lipid theory of atherogenesis was the isolation and characterization of low-density lipoproteins (LDLs) in the late 1940s and 1950s. J. W. Gofman, a physician and physicist at the University of California, Berkeley, used the recently invented analytical ultracentrifuge to separate plasma lipoproteins [14]. Gofman chose to study heart disease because he was intrigued by early studies in Russia indicating a link between AS and blood cholesterol levels. Together with a team that included his long-time colleagues F. T. Lindgren and A. V. Nichols, he isolated and characterized two main fractions based on density: LDLs and high-density lipoproteins (HDLs) [15]. In May 2007, the Journal of Clinical Lipidology republished his classic article on the work of his laboratory from 1949 to 1955 and assigned J. W. Gofman the title of 'Father of Clinical Lipidology' [16].

The concept of oxidized modification of LDLs has become another important part of the lipid theory of atherogenesis. The prehistory of this discovery started in 1979, when a young Norwegian researcher T. Henriksen noted that under certain conditions LDLs were toxic to the culture of endothelial cells and even led to their death. Although subsequent works showed that the initial results were associated with peculiarities of preparation of samples in the presence of oxygen leading to oxidative transformation of LDLs, the concept of oxidatively modified LDLs itself became a part of the current understanding of AS [17].

A therapeutic milestone for the lipid theory began with the identification of the inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase in 1976 by A. Endo from Sankyo company (Tokyo, Japan). This discovery paved the way for a new class of drugs known as statins [18]. Endo's statin, *compactin*, was isolated from *Penicillium citrinum* culture, and in 1987, *mevinolin* (also known as *lovastatin* or Mevacor®, Merck company) isolated from *Aspergillus terreus* culture, became the first statin approved for human use [18]. Statins remain the key drugs for prevention and treatment for AS today.

Studies of Lipid Composition of Membranes

Further studies facilitated expanding the understanding of the role of lipids beyond being simple morphological basis for AS [19]. The current concept suggests that lipids are important participants in many molecular cellular mechanisms. It is known that the plasma membrane of cells, which separates their cytoplasm from the external environment, is not just a mechanical barrier, but also performs key functions for the life of the cell, since it regulates the transport of substances, interactions with other cells, etc. [20]. According to the accepted model of a fluid mosaic proposed by S. J. Singer and G. L. Nicolson in the early 1970s [21], the plasma membrane of cells is represented by a complex combination of various lipids, which render it the necessary biophysical properties, such as viscosity and fluidity [22]. In this case, it is believed that the membrane has a liquid-ordered phase and a disordered phase. The ordered phase is characterized by denser packing of lipids and is known as 'lipid rafts', which are rich in cholesterol and function as dynamic signaling platforms.

The ***concept of lipid rafts*** was proposed in 1988 by K. Simons and G. van Meer [23]. CS is involved in maintaining the spatial structure of the plasma membrane, which is due to the chemical structure of its molecule and its spatial location in the plasma membrane. Changes in CS content in the plasma membrane affect the structure of the latter, its biophysical properties and functions. CS can also directly interact with specific protein sites and affect the lateral diffusion of proteins, due to which it can participate in the regulation of the function of membrane proteins. This is due to the fact that in order to perform their specific function, proteins must have a specific conformation, which can only be achieved in an optimal microenvironment, so the lipid composition of this microenvironment is of critical importance. In this regard, a decrease in the reverse transport of cholesterol in AS and its accumulation in macrophages and lipid rafts can contribute to their proinflammatory activation, among other things, through the activation of membrane receptors of the innate immune system involved in atherogenesis.

It is suggested that lipid rafts exist in planar and caveolar forms (caveolae). Caveolae, first described in

the early 1950s, by 1990s were referred to lipid rafts, which increased interest in them as dynamic signal platforms. One of the best-known functions of caveolae in the endothelial cells includes participation in regulation of endothelial NO synthase, a key source of nitric oxide, which is an important hemodynamic regulator in the arteries, and impairment of which bioavailability in the endothelial dysfunction is considered a key pathogenetic mechanism of AC [24–26]. The caveolae structure is supported by several proteins required for formation and stabilization of caveolae, including the structural protein caveolin-1 and the adapter protein cavin-1 [27]. Caveolin-1 negatively affects the activity of endothelial nitric oxide synthase (eNOS) via a direct interaction with the enzyme, which limits nitric oxide production [28]. Derangement of caveolae structure affects eNOC activation and vascular reactivity [[29]. It is interesting, but the deficit of Abca1 and Abcg1 transporters in endothelial cells reduces CS efflux from these cells, which reduces eNOS activity and enhances inflammation, adhesion of monocytes and infiltration of monocytes into atherosclerotic plaques [30]. These data enhance the understanding of the relationship between eNOC activity, caveolar lipid rafts and CS levels in them.

Apart from participation in the organizing membrane molecular processes, caveolae are considered as a reserve of the plasma membrane surface, which enables endothelial cells to rapidly change the cell surface area [31]. Thus, rapid flattening of caveolae is considered to be a mechanism of rapid increase in the surface area of endothelial cells, preventing damage to the cell membrane in case of change in the vessel geometry, e.g., when blood pressure changes [32].

There is convincing evidence of association of vascular hemodynamics with localization of atherosclerotic lesions [33, 34]. It is known that in straight regions of arteries, the blood flows in laminar pattern, that is, in layers parallel to the vessel wall with high shear stress. It is suggested that curvatures, stenosis or branching of arteries are associated with formation of disordered chaotic turbulent blood flows [35]. These patterns are characterized by non-uniform distribution of low shear stresses, the parameter characterizing the force exerted on the endothelium by the boundary blood flow. It is generally accepted to consider laminar blood flow physiological, and the appearance of turbulence as an atherogenic factor [36]. Experimental data show that in response to changes in the shear stresses, the lipid order in the plasma membranes of endothelial cells undergoes changes, which affect some physical properties of the plasma membrane, such as fluidity and viscosity [37]. Shear stress in laminar flow results in a rapid reduction in the lipid order of the plasma membrane, with the most pronounced changes in the ordered phases, shifting caveolae to liquid disordered state [38]. The decrease in lipid order is dependent on the intensity of shear stress and is reversible. These biophysical characteristics of plasma membranes are part of the mechanical transduction mechanism in endothelial cells, which mediates their response to changes in vascular hemodynamics. Indeed, endothelial cells sense changes in vascular hemodynamic parameters, including shear stress, and respond to these changes by polarization, which involves a change in cell orientation in the direction of blood flow. Polarization involves changes in the arrangement of cell organelles, changes in the cell cytoskeleton, and changes in the composition and structure of plasma membranes [39]. Some known data also indicate that caveolae can function as platforms on which shear stress-sensitive receptors function, i. e., act as platforms for mechano-detection and transduction [40].

Thus, understanding of the role of lipids as structural and functional units of molecular cellular events determines the current position of lipids in the development of AS. To note, the lipid raft concept is a subject of discussion, since some of its statements raise questions in the expert community concerning dimensions of these rafts, their lifetime and also the boundaries between ordered and disordered lipid phases.

Study of Role of Inflammation in Atherogenesis

There is increasing evidence about inflammation being an important part of atherogenesis. Indeed, monocytes migrating from the bloodstream, penetrate under the endothelium and induce inflammation, the same as tissue microphages that make the second macrophage pool in the atherosclerotic plaque. The progression of AS is in many aspects associated with the absorption of lipoproteins by macrophages and their transformation to foam cells, which were described by N. N. Anitschkow. It is believed that lipid (cholesterol) overload of macrophages and the absorption of oxidatively modified LDLs launch inflammatory reactions. Inflammatory activation of macrophages is also promoted by their cholesterol overload resulting from disruption of reverse cholesterol transport with the involvement of ABCA1 (ATP binding cassette subfamily A member 1) and ABCG1 (ATP binding cassette subfamily G member 1) transporters. Under normal conditions, these transporters export CS from macrophages to the extracellular acceptors forming HDLs, a decrease in the level of which is another AS predictor.

Inflammation is a universal mechanism activated in response to a variety of infectious and non-infectious tissue damages. The innate immune system, the evolutionarily ancient arm of immunity, possesses a multiplicity of overlapping tools to initiate and maintain

inflammation. The accumulated data show that in the inflammation process, there is not only a phase of initiation, but also a phase of active resolution. The resolution phase of inflammation is mediated by a number of biological factors and is coordinated with the phase of inflammation, which jointly play an important role in providing immune homeostasis of tissues. This coordination permits the body to control inflammation to minimize tissue damage [41].

The key role in both maintenance and resolution of inflammation is played by bioactive lipids, derivatives of fatty acids. They participate in the regulation of numerous processes associated with inflammation and can be actively involved in the pathogenesis of AS. Leukotrienes are considered important participants of the inflammation in AS. In turn, representatives of the family of lipid mediators, which were termed specialized pro-resolving mediators (SPM), play a role in active resolution of inflammation. AS is characterized by imbalance between the production of proinflammatory and specialized pro-resolving lipid mediators, which leads to persistent inflammation [42].

The presence of SPM in the vasculature and their role in AS were first reported in 1992 by C. N. Serhan and colleagues, who showed that coronary artery angioplasty promotes the release of peptide leukotrienes and lipoxin A4 into the arterial lumen [40]. These results laid the foundation for the hypothesis that an imbalance of lipid mediators such as SPM and leukotrienes may contribute to the development of AS. In 1996, a number of studies provided insight into possible mechanisms. It was shown that rabbits fed a high-fat, high-cholesterol diet but with increased expression of 15-lipoxygenase (a key enzyme in SPM biosynthesis) in monocytes/macrophages, were resistant to the progression of AS [43]. Leukocytes from rabbits with increased expression of 15-lipoxygenase were characterized by increased production of lipoxins, promoting increased anti-inflammatory activity [44]. Currently, SPMs are an actively studied topic, and the therapeutic potential of SPMs is also being assessed, including the possibility of using their synthetic analogues in AS.

Thus, lipid mediators participate both in activation and maintenance of inflammation in the vessel wall in AS, and can promote the resolution of this inflammation. According to this concept, progression of AS depends on the balance between pro- and anti-inflammatory mediators. Upon that, the biosynthesis pathways of these lipid mediators intersect and have intercellular nature, which further enhances the understanding of the complexity of the problem and significance of searching keys to its solution.

CONCLUSION

The data accumulated to date, evidence that atherosclerosis is the result of a complex chain of events occurring both within and outside the vessel wall. These events include hemodynamic changes in blood flow, disorders in the blood lipid profile, endothelial dysfunction, local and systemic inflammation, with the participation of various mechanisms of the innate immune system.

The lipid theory of atherogenesis was one of the earliest, and today its understanding has expanded significantly beyond a simple mechanical interpretation of the processes occurring in the vessel wall. The information obtained in recent years has shown the multifaceted role of lipids and lipid mediators as participants in the structural, metabolic, and immune mechanisms associated with atherogenesis. A better understanding of these mechanisms will improve the quality of diagnosis and treatment for all patients.

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ОБ АВТОРЕ

Котляров Станислав Николаевич, д.м.н., доцент;
ORCID: https://orcid.org/0000-0002-7083-2692;
eLibrary SPIN: 3341-9391; e-mail: 79065410775@yandex.ru

AUTHOR'S INFO

Stanislav N. Kotlyarov, MD, Dr. Sci. (Med.), Associate Professor;
ORCID: https://orcid.org/0000-0002-7083-2692;
eLibrary SPIN: 3341-9391; e-mail: 79065410775@yandex.ru

* Автор, ответственный за переписку / Corresponding author