

<https://doi.org/10.29001/2073-8552-2021-36-2-14-22>

УДК 616.13-004.6:612.017:[616.988:578]

Атеросклероз. Макрофаги. Вирусные инфекции

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Аннотация

Появление новой коронавирусной инфекции обострило актуальность существующих вопросов и привело к появлению новых, связанных с влиянием вирусов на атеросклеротический процесс и развитие сердечно-сосудистых осложнений. Как известно, атеросклероз является многофакторным, липид-контролируемым системным воспалительным процессом. Известен ряд вирусов, ассоциированных с поддержанием воспаления за счет долгосрочной персистенции и репликации вирусов в макрофагах, что изменяет их пластичность. Используя различные механизмы воздействия на макрофаги, вирусы могут вызывать проатерогенный цитокиновый ответ. Недостаточно данных относительно влияния вирусных инфекций на изменение пластичности моноцитов/макрофагов и возможностей контроля воспаления в атерогенезе. Сохраняется вопрос является ли причинной или ассоциативной связь между вирусными заболеваниями и атеросклерозом. В данном обзоре мы обобщаем и анализируем связанные с вирусами механизмы, способствующие развитию атеросклероза.

Ключевые слова:	атеросклероз, вирусные инфекции, воспаление, макрофаги, латентные вирусные инфекции, осложнения атеросклероза.
Конфликт интересов:	авторы заявляют об отсутствии конфликта интересов.
Прозрачность финансовой деятельности:	никто из авторов не имеет финансовой заинтересованности в представленных материалах.
Для цитирования:	Рябов В.В., Алексеева Я.В., Гомбожапова А.Э., Соколова Я.В., Карпов Р.С. Атеросклероз. Макрофаги. Вирусные инфекции. <i>Сибирский журнал клинической и экспериментальной медицины</i> . 2021;36(2):14–22. https://doi.org/10.29001/2073-8552-2021-36-2-14-22 .

Atherosclerosis. Macrophages. Viral infections

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Abstract

The emergence of new COVID-19 infection aggravated the existing issues and gave rise to new challenges associated with the impact of viruses on the atherosclerotic process and development of cardiovascular complications. Atherosclerosis is

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a multifactorial disease and its progression is largely determined by dyslipidemia and chronic low-grade systemic vascular inflammation. There are a number of viruses known to be involved in maintaining the inflammatory state through the prolonged viral persistence and replication in the macrophages whose plasticity changes due to the infection. The viruses can trigger the pro-atherogenic cytokine response through the diverse macrophage-dependent mechanisms. There is lack of data regarding impact of viral infections on the monocyte/macrophage plasticity and possible control of inflammation in atherogenesis. It is still unclear whether the relationships between the viral diseases and atherosclerosis are causal or merely associative. In this review, we summarize and critically analyze the current state of knowledge regarding the virus-related mechanisms promoting atherosclerosis.

Keywords:	atherosclerosis, viral infections, inflammation, macrophages, latent viral infection, atherosclerosis complications.
Conflict of interest:	the authors do not declare a conflict of interest.
Financial disclosure:	no author has a financial or property interest in any material or method mentioned.
For citation:	Ryabov V.V., Alekseeva Y.V., Gombozhapova A.E., Sokolova Y.V., Karpov R.S. Atherosclerosis. Macrophages. Viral infections. <i>The Siberian Journal of Clinical and Experimental Medicine</i> . 2021;36(2):14–22. https://doi.org/10.29001/2073-8552-2021-36-2-14-22 .

Introduction

Atherosclerosis is a multifactorial lipid-driven systemic inflammatory process [1]. Despite the advances in studying atherosclerosis, we are still far from reaching clear understanding of the mechanisms provoking plaque rupture, the role of plasticity of monocytes/macrophages, and the potential to control inflammation in atherogenesis. The emergence of new Coronavirus (2019-nCoV, COVID-19) has led to increased recognition of a significant role of viral infections in the onset and progression of atherosclerosis [2]. Moreover, the COVID-19 pandemic gave rise to new questions concerning the impact of viruses on the immune cells, especially macrophages.

The macrophages are multifunctional cells able to phagocyte modified low-density lipoproteins and to polarize towards either pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes [2–4]. Despite the ongoing research on macrophage role in the progression of atherosclerotic lesion, the underlying mechanisms in the development of complicated and unstable plaques remain unclear [3]. There is a theory considering the ability of macrophages to change their programmed differentiation upon interaction with lipoproteins. Coronary angiography data obtained in routine clinical settings indicate that up to 14% patients suffer from myocardial infarction with nonobstructive coronary arteries (MINOCA) [5]. It is important to elucidate the mechanisms of the development of unstable atherosclerotic plaques in this cohort of patients and to identify targets that can be modified in order to prevent recurrent events.

Macrophages are the promising targets for research because there is a potential for directing their differentiation towards a required cellular subpopulation. Furthermore, there is evidence that macrophage plasticity is modified by various infectious agents contributing to viral persistence, reproduction, and migration to other tissues [6]. The ability of macrophages to act as a reservoir for the infectious agents potentially altering the activity of nuclear receptors and cytokine and coagulation responses has once again renewed interest in the viral hypothesis of atherogenesis. Research on the relationships between viruses and the atherosclerotic process became more relevant after the success of studies investigating the effects of viruses on

cancer progression [7, 8]. A striking example is the creation of human papillomavirus vaccine for the prevention of cervical cancer [9]. The following question arises: does the absence of such a breakthrough in the investigation of interactions between the atherosclerotic process and viruses indicate the absence of a relationship or does it simply mean that there are barriers, which still do not allow us to demonstrate such a connection? However, ongoing research provides indisputable evidence of a link between index vascular events and viral infections [10]. Numerous case-control and cohort studies demonstrated that the influenza vaccine has a pronounced protective effect against major vascular events, reducing the incidence of these cases by 20–70% in primary and secondary prevention settings [11]. Similar conclusions were obtained when studying the effects of herpes zoster on the destabilization of atherosclerotic plaques [10]. Given the results of these studies, is it possible to suggest that the next step in the treatment of atherosclerosis will be the emergence of a vaccine? In this review, we have gathered evidence of both direct and indirect effects of viruses on the pathogenesis of atherosclerosis, as well as the role of macrophages in the development and progression of this disease.

Concepts of atherosclerosis

There are several theories of atherosclerosis [1, 7]. One of the original theories refers to the infiltration concept focusing on the interconnection between atheroma development and the processes of infiltration, imbibition, and perfusion of the blood vessels by lipids. Based on the theory of infiltration, the cholesterol-associated concept was proposed by the Russian pathomorphologist N. Anichkov in 1913 [7].

The epidemiological studies have been performed to search for a confirmation of cholesterol-associated theory. In 1948, the Framingham Heart Study proved the essential role of hypercholesterolemia in the occurrence of coronary artery disease (CAD) [11]. Monitoring of 5,000 subjects for over 30 years showed that the risk of morbidity and mortality caused by CAD is twice as high as in cases where the serum cholesterol level is 6.5 mmol/L and higher, compared with the cases where serum cholesterol level is less than 5.2 mmol/L [12]. Performed epidemiological studies have also proved the relationships between the decreased level of total cholesterol

and its atherogenic fractions (LDL) with reduced risk of CAD development. Obtained data led to the development of lipid-lowering drugs, which affected the main pathogenic factor in the atherosclerosis progression, and the era of statins began after the completion of Scandinavian Simvastatin Survival Study (4S) [13].

The results of numerous clinical studies demonstrated a significant reduction of cardiovascular morbidity and mortality in the individuals administered with statins for primary and secondary prevention [14]. Today, HMG-CoA reductase inhibitors or statins are the first line therapy for atherogenic dyslipidemia. However, in some cases, an appropriate response to statins therapy is absent or insufficient. Thereby, a search for new targets continues. Recently, a new class of lipid-lowering drugs, inhibitors of the proprotein convertase subtilisin/kexin type 9 (PCSK9), has been created. These drugs contribute to reducing the rates of serum cholesterol and its fractions through inhibition of the PCSK9 protein, which in turn, is involved in the regulation of LDL receptor expressions [15].

Alongside the study of hypercholesterolemia influence, the role of vascular wall in atherogenesis was vigorously investigated [1, 16]. W. Meyer (1949) and H. Bredt (1969) found that the vascular endothelial damage is the first stage in the initiation of atherosclerotic process further followed by infiltration of the vascular wall with lipids [17–20]. According to the response-to-injury hypothesis proposed by R. Ross and J. Glomset in 1973, endothelial lesion triggers a chain of events such as platelet adhesion, platelet secretion of growth factors, smooth muscle cell proliferation, and monocyte migration.

The revision of vascular wall involvement in the formation of atherosclerotic plaques led to the development of N.N. Anichkov's infiltration theory and further creation of an infiltration-combinational concept, which, along with hypercholesterolemia, considers other factors damaging to the vascular wall [1, 17, 18]. The most widely observed risk factors of atherosclerosis are hypertension, hyperglycemia, obesity, smoking, and heredity [16]. However, the relationships between the incidence of cardiovascular complications and viral infections may also play an essential role beyond the traditional risk factors [18], but data in this area remain extremely controversial.

Regardless of a trigger that causes vascular wall damage, it leads to the activation of inflammation. Disruption of endothelial structure and function causes the migration of monocytes, which further transform into the macrophages and finally into the foam cells due to phagocytosis of atherogenic lipoproteins. In addition to the phagocytosis of oxidized low-density lipoproteins, the inflammatory cells secrete pro-inflammatory cytokines, chemotaxins, and growth factors, which promote the persistent inflammatory fibroproliferative reaction in the vessels [20]. In this regard, atherosclerosis has been considered a state of chronic sterile inflammation. The severity of atherosclerotic plaque infiltration by the inflammatory cells is associated with the burden of atherosclerosis, hyperproduction of a wide range of cytokines and chemokines with pro-inflammatory activities, and increases in the serum concentrations of immunological biomarkers, primarily of high sensitive C-reactive protein (hsCRP) and interleukin 6 (IL-6). These processes correlate with the worsening of atherosclerotic vascular lesion and the development of cardiovascular complications irrespective of serum concentration of lipids and confirm the key role of inflammation in atherogenesis [19, 21–25].

In search for new means of influencing atherosclerosis, researchers proposed to inhibit the pro-inflammatory cytokines in order to treat atherosclerosis. Indeed, Canakinumab, a monoclonal antibody inhibiting IL-1 β , and Colchicine were tested in the recently completed the CANTOS and COLCOT trials. These trials showed a significant reduction in the frequency of combined endpoint compared with placebo and provided evidence for a decrease in the number of cardiovascular events by inhibiting the inflammatory response [26].

The role of macrophages in the atherosclerosis progress

The key cells of atherogenesis are the macrophages that perform a protective function as the scavenger cells phagocytosing atherogenic lipoproteins. Being present at all stages of atherosclerotic process, the macrophages become the main source of inflammatory mediators. In addition, the macrophages lead to atheroma instability due to the production of matrix metalloproteinases [27]. The macrophages have become a subject of scientific interest due to their ability to be polarized into two directions. The classical path of differentiation results in the formation of the first type of cells, M1. The second type of macrophage, M2, forms due to the activation of the alternative pathway. The process of differentiation into the various functional types of macrophages (M1/M2) depends on multiple cytokines [27, 28].

The macrophage polarization towards M1 direction is accompanied by the secretion of proinflammatory mediators such as IL-1 β , IL-6, sTLR, TNF- α , matrix metalloproteinases, chemokines, and platelet growth factors, which initiate and maintain inflammation in the atheroma [29]. There are also alternative ways for the activation of macrophages (M2 phenotype), which, vice versa, are capable of suppressing inflammation in the atherosclerotic plaque. The associated IL-10 blocks the formation of M1 macrophage phenotype fulfilling a protective and restrictive role in the progression of atherogenesis [30].

The results of experimental works performed on mice show that the M2 phenotype of macrophages is suppressed with the predominance of pro-inflammatory signals. The introduction of IL-13, a cytokine activating polarization in the alternative way, leads to formation of M2 macrophages, which contribute to the inhibition of inflammation in the atheromas and thereby positively influence the course of atherosclerotic process [30–32]. Macrophage plasticity is regulated based on the principle of negative feedback [33]. The development of strategies for depletion or inactivation of macrophages involved in the proinflammatory cytokine responses may potentially modulate the atherosclerotic process.

Effects of latent viral infections on macrophages

Circulating monocytes and macrophages perform many functions including the involvement in protecting the body against viral infections. However, the contact of the virus with the monocyte/macrophage does not always lead to the elimination of the infection. To date, it has been proven that more than 35 viral agents belonging to 13 different families are capable of persistence in the inflammatory cells [30]. Using monocytes/macrophages as a reservoir, the viral agents can be activated due to their reduced immunoreactivity and spread to target cells [31]. The interaction between the viruses and monocytes/macrophages activates the signaling pathways leading to the production of pro-inflammatory cytokines, thereby causing cell polarization along the classical pathway

maintaining chronic inflammation in the presence of latent infection. The presence of risk factors combined with an increased level of pro-inflammatory cytokines contributes to the progression of atherosclerotic process [28, 29].

Latent viral infections and atherosclerosis

The development of advanced technologies, which were previously unavailable, resulted in an increasing interest in the viral hypothesis of atherogenesis. According to this hypothesis, viral infections can cause both the development and destabilization of atherosclerotic plaques leading to cardiovascular events [29–34]. This idea still remains controversial and requires further investigation. One of the challenges consists in the multifactorial nature of proatherogenic properties of viral agents. The presence of more than one latent infection also complicates the identification of a correlation between the viruses and atherosclerosis [35]. In addition to direct viral effects on the endothelium, many viruses mediate indirect effects on the vascular wall through

the activation of a systemic inflammatory response [36]. Today, there is a large range of infections associated with the development of atherosclerosis [37]. These include the following viruses: Herpesviridae family viruses, enteroviruses, hepatitis viruses, influenza viruses, human immunodeficiency virus, and human papillomavirus. Bacterial infections also play a role, but this review focuses on the role of viruses in the development of atherosclerosis [33–42].

Viruses of the Herpesviridae family

Members of the Herpesviridae family are distinguished by their high prevalence, pantropism to tissues as well as their capacity for lifelong persistence. The Herpesviridae family consists of three subfamilies, namely: alpha herpesviruses, beta herpesviruses, and gamma herpesviruses [40]. They differ by the affinity to certain cell types and the spectrum of activity. Eight types of this virus are pathogenic to humans [41]. General characteristics of the members of the Herpesviruses family are presented in Table 1.

Table 1. General characteristics of Herpesviruses

Name	Sub-family	Type of infected cells		Effect on a cell during lytic infection	Disease
		Lytic infection	Latent infection		
Herpes simplex virus type 1 (HSV 1)	Alpha	Epithelial, endothelial and smooth muscle cells	Neurons	Cytolysis	Oral (herpetic stomatitis, labial herpes), less often, genital herpes, ophthalmic herpes, herpetic meningoencephalitis, pneumonitis, ganglionitis, autoimmune lesions of the nervous system
Herpes simplex virus type 2 (HSV 2)	Alpha	Epithelial, endothelial and smooth muscle cells	Neurons	Cytolysis	Oral, but more often genital herpes, neonatal herpes
Varicella virus	Alpha	Epithelial and endothelial cells	Neurons	Cytolysis	Varicella zoster as well as ganglionitis, acute demyelinating inflammatory polyneuropathy (Guillain–Barre syndrome)
Cytomegalovirus (CMV, HSV type 5)	Beta	Hematopoietic, epithelial, endothelial, smooth muscle cells and fibroblasts	Macrophages, lymphocytes, epithelial cells	Cytomegaly	Congenital lesions of the CNS, retinopathy, sialadenitis. When generalizing CMV infection: cytomegalovirus, hepatitis, cytomegalovirus, pneumonitis; cytomegaly in immunodeficiency and in patients after an organ transplant; mononucleosis syndrome; retinitis, colitis or neuroinfection with AIDS as well demyelinating diseases of the nervous system
Herpes simplex virus type 6 (HSV 6)	Beta	CD4+ cells, myeloid cells	Monocytes, macrophages	Cytomegaly	Acute skin lesions in children (roseola infantum) or exanthema
Herpes simplex virus type 7 (HSV 7)	Beta	T- and B-lymphocytes	T-lymphocytes	Cytomegaly	Is a likely cause of chronic syndrome fatigue and can also cause lymphoproliferative diseases. Often coexists with Herpesvirus type 6
Epstein-Barr virus (EBV, HSV type 4)	Gamma	T and B lymphocytes, epithelial and smooth muscle cells	B-lymphocytes	Lymphoproliferative disorders	Infectious mononucleosis, Burkitt's lymphoma, CNS lymphomas in patients with immunodeficiency, post-transplant syndrome lymphoproliferative syndrome, nasopharyngeal carcinoma, hairy leukoplakia of the tongue, possibly also chronic fatigue syndrome besides hypothalamic syndrome, autoimmune processes, lesions of the endocrine organs
Herpes simplex virus type 8 (HSV 8) CD19	Gamma	CD19+ B-lymphocytes, salivary gland epithelium	Plasmacytoid dendritic cells	Lymphoproliferative disorders	Kaposi's sarcoma in HIV-seronegative people, Kaposi's sarcoma associated with HIV infection and AIDS, lymphoproliferative diseases: primary exudate lymphoma, multifocal Castleman disease

Herpes simplex virus (HSV) type 1 and 2

Active studies of HSV effects on atherosclerosis began in 1970s when atherosclerotic-like changes were found in the microscopy of arteries of hens suffering from Marek's disease [42]. The hypothesis that HSV types 1 and 2 can activate the processes of atherogenesis, coagulation, and platelet aggregation was put forward. The ongoing work is still controversial. However, increasing number of studies confirm the relationships between HSV and atherogenesis. In 2016, Y.P. Wu et al. performed a meta-analysis of 17 studies investigating the associations of HSV with atherosclerosis. The results showed that the infections with HSV type 1 and

type 2 are associated with an increased risk of developing both atherosclerosis (mainly type 1 HSV) and coronary events (HSV type 1 and type 2) [43–45].

The mechanisms of atherogenic HSV effects are very diverse [39] and implicated in the modulation of all elements of atherogenesis including vascular endothelium, smooth muscle cells, and lipoproteins. Endothelial dysfunction during HSV infection occurs in three ways. The first pathway is associated with a decrease in the synthesis and surface expression of heparin sulfate-proteoglycan and thrombomodulin by endothelial cells. The second mechanism initiates the expression of glycoprotein C on the

surface of the endothelium forming the site of attachment for prothrombinase, thereby enhancing the production of thrombin and the adhesion of platelets. The third mechanism enhances the migration and adhesion of the inflammatory cells by increasing the expression of Fc-receptor, C3b binding, and viral glycoprotein E [43]. The effects of HSV infection on cholesterol metabolism have been poorly studied, but the changes contributing to the progression of atherosclerosis have been identified. HSV type 1 increases the activity of HMG-CoA reductase and reduces the hydrolysis of cholesterol while increasing its synthesis. It was also found that type 1 HSV increases binding of lipoproteins to LDL receptors. Data showed that HSV can trigger smooth muscle cells proliferation and contribute to the accumulation of lipids in the cells [30]. The HSV-infected cells express receptors that can bind to monocytes, thereby increasing inflammation and increasing the likelihood of plaque instability. Moreover, HSV increases adhesion and platelet aggregation of the infected cells *in vitro* [30].

Epstein-Barr virus

There are plenty of publications demonstrating the relationships between atherosclerosis and the Epstein-Barr virus (EBV). Detection of antibodies to EBV reaches 90–95% in the adult population, which is demonstrated by the widespread prevalence of this infection. Most frequently, EBV is asymptomatic and persistent for a long time in the human body. However, by reducing the reactivity of the organism, the viral infection is capable of activation. Primarily, EBV affects B-lymphocytes, although this virus has been recently detected in the monocytes/macrophages, vascular endothelial cells, bone marrow cells, and the epithelial cells of the gastric mucosa, larynx, urethra, cervical canal, and vagina [46, 47]. B-lymphocytes are supposed to transport the virus into the endothelium and epithelium through the monocytes/macrophages, contributing to its further spread [48]. In addition to direct infection and the damage of vascular endothelium through cytolysis during the transition to the lytic form of infection, there is an indirect mechanism that implements acute ischemic events. Indeed, studies conducted by Philip F. Binkley *et al.* showed that, upon reactivation of the latent EBV infection, the enzyme deoxyuridine triphosphate nucleotidohydrolase (dUTPase) is synthesized activating the monocytes and macrophages and triggering a cascade of pro-inflammatory cytokines involving IL-6. The dUTPase affects the endothelium by increasing the expression of ICAM-1 and, thereby, enhancing the adhesion of the immune cells. This mechanism of action is potentially involved in the atherosclerosis progression and atheroma instability [47, 48].

Cytomegalovirus

Studies focusing on the role of cytomegalovirus (CMV) infection in atherogenesis remain controversial [49, 50]. The earliest evidence of the presence of CMV-specific nucleic acid fragments derived from progressive atherosclerotic plaques has been demonstrated using *in-situ* hybridization. The results of the work were demonstrated by electron microscopy, and subsequent studies supported them with *in-situ* dot-blot hybridization technology, polymerase chain reaction, and the study of the level of IgM antibodies against CMV. Some researchers identified the presence and replication of CMV directly in atherosclerotic plaques, suggesting a direct effect of the virus on the development of atherosclerosis. Later, re-

searchers proposed hypotheses that CMV is involved in the activation of endothelial cell apoptosis through the CMV-specific antibodies. Data showed that CMV infection is associated with three vascular diseases: primary atherosclerosis, restenosis after balloon angioplasty, and post-transplantation atherosclerosis. However, the results, generated by different research groups, still contradict each other. For instance, despite all positive results, M.C. Borgia studied 152 individuals and did not find any positive correlation between the development of atherosclerotic plaque instability and persistent systemic CMV infection [50].

However, the study of CMV infection is associated with a number of difficulties. The main challenge, which may cause contradictory results, is the ability of CMV to persist in a macroorganism for a long time. The interaction of CMV with monocytes through the protein receptors, $\beta 1$ and $\beta 3$ integrins, and epidermal growth factor EGFR increases cell motility and also promotes the migration of monocytes into the tissues and their transformation into the macrophages. Despite the lack of viral gene expression, individual studies observed changes caused by the activation of infected monocytes, which led to the formation of the pro-inflammatory monocyte/macrophage phenotype contributing to the spread of viral infection and triggering the pro-inflammatory cytokine cascade [51].

According to Koon-Chu Yaiw *et al.*, one of the mechanisms of CMV involvement in atherosclerosis consists in the induction of mRNA expression for 5-lipoxygenase, which, in turn, catalyzes the conversion of arachidonic acid to leukotrienes. This process triggers local inflammation in the vascular wall and leads to the further progression of cardiovascular pathology. Moreover, according to this study, inflammation itself can also become a trigger for CMV reactivation, release from the latent state, and further replication [52].

Another possible mechanism is proposed by M. Rabczyński *et al.* who demonstrated the relationships between the infectious process and atherosclerosis through heat shock proteins (HSPs). Antibodies against CMV are able to recognize certain epitopes of human HSPs and thus cause autoimmune reactions damaging to the vascular endothelium. The hypothesis, put forward by A. Assinger, suggests a possible effect of the virus on the platelets. CMV is able to transmit activating signals that stimulate the migration of the leukocytes through the activation of TLR-2 platelet receptors [53].

Enteroviruses

Enterovirus infections are characterized by tropism for cardiomyocytes. However, they are also considered triggers of the atherosclerotic process. Members of this family are ubiquitous and distinguished by a widespread virus infection among a healthy population. Enteroviruses are RNA-containing viruses of the Picornaviridae family of the Enterovirus genus. In the traditional classification, four groups of enteroviruses are recognized including polioviruses, Coxsackie viruses type A and B, and ECHO viruses (Enteric Cytopathic Human Orphan) [54] (Table 2).

In 2003, a group of researchers from different countries led by Maria M. Zanone found out that type B Coxsackieviruses are associated with the increased release of adhesive molecules such as ICAM-1 and VCAM-1, especially during the first 40 days of infection. ICAM-1 leads to an increase in leukocyte adhesion whereas VCAM-1 leads to an increase in lymphocyte and monocyte counts.

Table 2. General characteristics of the representatives of Enteroviruses

Name	Group	Serotypes	Tropism	Effect on cells	Forms of damage	Disease
Poliovirus		1 (the highest pathogenicity)	Grey matter of the spinal cord (motoneurons) and brainstem (motor cranial nerve nuclei) brain membranes	Pycnosis, degenerative changes, eosinophilic inclusions, Crystalline viruses. Cell death	Inapparent Abortive Meningeal Paralytic	Poliomyelitis
		2 (medium pathogenicity)				
		3 (least pathogenicity)				
Coxsackie	A	23	Peripheral nerve endings	Complete cell degeneration, pycnosis of the nucleus and cytoplasm, viral plaques (cytopathic effect)	Diffuse myositis with trophic paralysis (newborn mice)	Serous meningitis (2-4, 6,7,9,10), Herpangina (2-6,8,10), Acute pharyngitis (10,21), Exanthema of the mouth and limbs (5,16), poliomyelitis similar diseases (1,2,5,7-9,21), Hepatitis (4,9,20)
	B	6	Multi-organ tropism	Well multiplied in cell culture	Spastic paralysis (newborn mice)	Encephalitis, myocarditis, peri-endocarditis, sporadic paralysis, poliomyelitis
ECHO		33	Polytropism, including the central nervous system, striated muscles, intestines.	Degeneration Cytopathic effect	Myositis and paralysis (mouse)	Liver failure, SARS, aseptic meningitis, polio-like diseases, fulminant encephalomyocarditis in newborns

The microcirculatory endothelium can hide the presence of a viral infection for a long time, increasing the number of adhesion molecules and the synthesis of cytokines. The hypothesis of this study was based on the assumption that the endothelium of large epicardial vessels and the microcirculation reacts differently to viral infection. In addition, the response to different strains of the virus may also vary. In this regard, the purpose of the work was to study the susceptibility of the human endothelium to different subtypes of Coxsackieviruses, in particular, CVB-3, -4, and -5. The immunophenotypes of infected cells (adhesion molecules and HLA), costimulation, and the duration of infection persistence were analyzed. Data showed that the microcirculatory endothelium plays a decisive role in determining the tropism of viruses and further pathogenesis of the disease [55, 56]. In regard to the damaging effects of Coxsackieviruses on the endothelium, the researchers believe that autoimmune reactions may be caused by viral load through the mechanisms related to molecular mimicry. Viruses can induce both the expression of HLA II molecules on the cell surface making them targets for recognition and the activation of autoreactive T-cells. There are data suggesting the role of Coxsackieviruses as the mediators of cytotoxic effects. This, in turn, can cause the progression of the disease and sustain infection in the body for a long time [56]. The persistence of infection is confirmed by previous *in vivo* studies of the heart, skeletal muscles, the central nervous system, and *in vitro* studies of human kidney cells, vascular endothelium, and pancreatic islets [57]. The presence of infection in these cultures was associated with the enhanced production of such cytokines as platelet growth factor A/B, tissue growth factor beta 1/2, tumor necrosis factor alpha, and interferon alpha [56, 57].

HIV infection

The unprecedented growth of HIV infection has led to a significant accumulation of the information about the structure of the pathogen, the course of the disease, and the complications associated with it. One of the discoveries was the detection of the relationships between the virus and progression of atherosclerosis [36]. Cardiovascular complications in HIV-infected patients develop at a young

age and the atherosclerotic process rapidly progresses often in the form of multi-vessel coronary artery disease. It is important to note that the risk of cardiovascular events is high in both men and women. Several studies investigating the effects of HIV on the progression of atherosclerosis in women show that HIV infection is an independent risk factor for early cardiovascular events in non-menopausal women. One study showed that the number of RNA copies exceeding 500 is associated with an extremely high risk of ischemic events [58, 59].

The causative agent of HIV infection belongs to the family Retroviridae characterized by T-lymphotropic effects on the host organism. The viral genome is represented by RNA; however, a distinctive feature of the virus is the ability to synthesize DNA on an RNA template using the reverse transcriptase enzyme. There is a suggestion that the macrophages play a dominant role as a source of HIV. These cells become a cause of tissue damage at the late stages of disease progression after depletion of CD4+ T-cell pool. One experimental trial showed a close link between HIV and macrophages [58].

Immunodeficiency virus promotes all mechanisms of atherogenesis. HIV infection causes inflammation whereas immunodeficiency leads to hypercoagulation, dyslipidemia, insulin resistance, and endothelial dysfunction. Damage to the endothelium is associated with a direct toxic effect of the virus. An increase in IL-6 in the mononuclear cells leads to the initiation and maintenance of chronic inflammation in atherosclerotic plaque [59].

Influenza A virus

Acute infections can also lead to atheroma instability. The relationship between the influenza virus and myocardial infarction has been actively studied. Influenza virus belongs to the RNA-containing viruses of the Orthomyxoviridae family represented by 3 genera: A, B, and C. The influenza virus A is the most pathogenic and the most studied in the concept of atherosclerosis progression.

The first assumptions about possible relationships between viral infections and cardiovascular events were made back in 1900 during the flu pandemic in Europe and the United States when cardiovascular mortality sharply

increased. This hypothesis finds more and more evidence in the ongoing research. According to the results of meta-analysis, there is a significant association of the influenza A virus with the development of instability of an atherosclerotic plaque. Ten out of 14 completed studies showed that the number of hospitalizations for acute myocardial infarction increases during influenza pandemic [60]. Given the availability of influenza vaccine, it was essential to track how its use affected the development of acute myocardial infarction. To achieve this goal, researchers studied the effects of the vaccination against influenza A virus on the incidence of myocardial infarction. The studies showed that the vaccination against influenza A reduced the risk of myocardial infarction by 29%, being second only to statins in preventing the development of cardiovascular events [60].

Influenza virus affects several elements of atherosclerosis resulting in atheroma destabilization. Upon onset, viremia exerts a cytotoxic effect on the macrophages and vascular endothelium. In addition to the direct mechanism of atherosclerotic plaque destabilization, studies identified the mechanism enhancing inflammation via the cytokines IL-6 and TNF- α , which, in turn, increase damage to the endothelial

wall. Changes in the coagulation due to increases in thrombin and fibrinogen lead to the development of hypercoagulation status [60].

Conclusion

In summary, it is vital to improve our understanding of the inflammatory nature of atherosclerotic disease and develop targeted therapies affecting the inflammatory process. The activation of pro-inflammatory cytokine cascades by monocytes and macrophages is the most universal mechanism of atherosclerotic process. New data emerge showing the involvement of monocytes and macrophages in the proatherogenic effects of viruses. Being a reservoir for various viral agents, these inflammatory cells not only become a source of chronic inflammation but also can contribute to spreading the viruses to other organs and tissues. The study of relationships between the viruses, macrophages, and atherosclerosis is a new and promising area of research, which may explain pivotal questions regarding etiology and pathogenesis of atherosclerotic process. It may ultimately contribute to discovering new targets for prevention and treatment of atherosclerosis.

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Information on author contributions

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Ryabov V.V. – supervision and methodology.
Alekseeva Ya.V., Sokolova Ya.V., and Gombozhapova A.E. – writing the review.
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Received March 16, 2021

Поступила 16.03.2021