The Possible Role of Herpesviruses in the Pathogenesis of Coronary Atherosclerosis

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Abstract

Cardiovascular diseases are still the dominant cause of death worldwide. Coronary artery disease (CAD) is the most common type of heart disease and the leading cause of death for both men and women. Coronary atherosclerosis underlies multiple clinical manifestations ranging from asymptomatic to stable angina, acute coronary syndrome, MI, heart failure, and sudden cardiac death. The prerequisites for a closer study of the pathogenesis of the atherosclerotic process were the development of atherosclerotic vascular lesions at a younger age and the rapid progression of the process. Currently, it is generally accepted that CAD is a multifactorial disease. Attention is drawn to hereditary disorders of the receptor apparatus, endothelial dysfunction, and lipid metabolism disorders. In addition, latent viral infections are one of the etiopathogenetic factors in the development of atherosclerosis. A number of scientific studies have confirmed the relationship between infectious agents and the development of atherosclerotic vascular lesions. The viral etiology of the development and progression of atherosclerosis is the subject of debate among scientists around the world. (**International Journal of Biomedicine. 2021;11(4):391-396.**)

Key Words: herpesviruses • coronary atherosclerosis • Toll-like receptors • vascular endothelial cells

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Abbreviations

CAD, coronary artery disease; **CA**, coronary atherosclerosis; **CMV**, cytomegalovirus; **CRP**, C-reactive protein; **EBV**, Epstein-Barr virus; **FCs**, foam cells; **HSV**, herpes simplex virus; **HAV**, hepatitis A virus; **HBV**, hepatitis B virus; **HCV**, hepatitis C virus; **ox-LDL**, oxidized low-density lipoprotein; **MI**, myocardial infarction; **MMP**, matrix metalloproteinases; **SMCs**, smooth muscle cells; **TLRs**, Toll-like receptors; **TNF- α** , tumor necrosis factor-alpha; **VSMCs**, vascular smooth muscle cells; **VECs**, vascular endothelial cells.

Coronary atherosclerosis (CA) is one of the main causes of disability and premature death of people all over the world,⁽¹⁾ the development of which can take many years and not have any pronounced symptoms. The first signs of the problem appear in cases when the pathological process is pronounced. During the past decades, our understanding of the pathophysiology of CAD has undergone a remarkable evolution. There are numerous factors involved in the causation of atherosclerosis. Many studies have found a significant association between atherosclerosis and smoking, sedentary

lifestyle, hypertension, atherogenic dyslipidemia, genetic factors, and life stress.⁽²⁻⁷⁾ However, about 30% of patients with atherosclerosis lack identified risk factors, an observation indicating that additional factors predispose to atherosclerosis.

Injury to the vessel wall and the associated inflammatory response to injury are now generally recognized as the essential components of atherogenesis. Among candidates for triggers are ox-LDL and heat shock proteins. Another candidate trigger of both inflammatory and autoimmune responses may be an infection.⁽⁸⁾

Since the 19th century, it has been suspected that the development of atherosclerotic plaques and their rupture is associated with inflammation caused by infection. The idea that atherosclerosis results from injury to arterial walls traces back to Rudolph Virchow. In 1856, Virchow recognized the inflammatory nature of atherosclerotic plaques.⁽⁹⁾ "In some, particularly violent cases the softening manifests itself even in the arteries, not as the consequence of a really fatty process, but as a direct product of inflammation."^(10,11)

In the last decades, various studies were conducted on the association between CAD and infectious agents, including viruses.⁽¹²⁻¹⁵⁾ In 1983, Fabricant CG et al.⁽¹⁶⁾ showed that repeated experiments have established that infection with Marek's disease herpesvirus (MDV) leads to atherosclerosis in specific pathogen-free normocholesterolemic chickens.

Currently, many viruses are known to be associated with atherosclerosis. A number of herpes viruses have been identified in atherosclerotic coronary arteries.⁽¹⁷⁻¹⁹⁾ These herpes viruses include CMV (human herpesvirus 5),^(20,21) EBV (human herpesvirus 4)⁽²²⁾ and HSV (human herpesvirus 1 and 2).⁽²³⁻²⁵⁾ In addition, the possible role of HAV,⁽²⁶⁾ HBV,⁽²⁷⁾ and HCV^(28,29) in the development of CA was also shown.

Although the evidence is not entirely consistent, infections of vascular wall cells lead to inflammation and atherosclerosis. The mechanism of viral damage to the vascular endothelium is universal.⁽³⁰⁾ All viruses possess pathogen-associated molecular structures, such as lipopolysaccharides, released by viral RNA,⁽³¹⁾ which interact with Toll-like receptors (TLRs) located on the cell membrane of immunocompetent cells. TLRs are major initiators of inflammation. Previous studies involving SNP analysis of TLRs demonstrated that TLRs are involved in the development and progression of diseases like atherosclerosis, cardiac dysfunction in sepsis and congestive heart failure.⁽³⁰⁻³²⁾

TLR2 promotes atherosclerosis in LDL receptor (LDLr)-deficient mice fed a high-fat diet (HFD).⁽³³⁾ In atherosclerosis-susceptible low-density lipoprotein receptor-deficient (Ldlr-/-) mice, complete deficiency of TLR2 led to a reduction in atherosclerosis.⁽³³⁾ In a study by Curtiss et al.,⁽³⁴⁾ deficiency of TLR1 or TLR6 did not diminish HFD-driven disease. When HFD-fed, LDLr-deficient mice were challenged with Pam3 or MALP2, specific exogenous ligands of TLR2/1 or TLR2/6, respectively, atherosclerotic lesions developed with remarkable intensity in the abdominal segment of the descending aorta.

Michelsen et al.⁽³⁵⁾ demonstrated that genetic deficiency of TLR4 was associated with a significant reduction of aortic plaque areas in atherosclerosis-prone, APOE-deficient mice, despite persistent hypercholesterolemia, implying an important role for the innate immune system in atherogenesis.

In a study by Ding Y,⁽³⁶⁾ TLR4 deficiency led to markedly decreased atherosclerosis in obese, TLR4 and LDL receptor double knockout mice. It has been observed that TLR3 has a protective effect on the vascular wall after mechanical and hypercholesterolemia-induced arterial injury. TLR3 plays a critical role in regulating the degradation of the extracellular matrix in lesions, in part by modulation of macrophage MMP-2 and -9 activities.⁽³⁷⁾

Karper et al.⁽³⁸⁾ showed that blocking TLR7 and TLR9 reduced postinterventional vascular remodeling and foam cell accumulation in hypercholesterolemic APOE*3-Leiden mice.

Thus, the mechanisms of atherogenesis induced by TLRs include the dysfunction of vascular cells, the recruitment of macrophages and other immune cells to the site of vascular injury, the formation of foam cells, and the instability of plaques, while the anti-atherosclerotic effect of TLRs is more in line with its evolutionary conservative function.⁽³⁹⁾

However, if the general mechanism of the viral contribution to the pathogenesis of CA seems clear, then the study of the specificity of the effect of a wide variety of viral load on the development of CA is at the early stages of research.⁽¹⁷⁾

For example, CMV is widely distributed, can infect blood vessel wall cells, and exhibit the persistence, latency, and recurrence of infection. The infection can indirectly influence the earliest lesions of atherogenesis consisting of intimal accumulations of FCs and T-lymphocytes intermixed with VSMCs.⁽⁴⁰⁾ Host defenses to extravascular infections are usually associated with the production of proinflammatory cytokines and cellular adhesion molecules, enhancing leukocyte adhesion.

Studies have linked CMV to three arterial diseases: primary atherosclerosis, post-angioplasty restenosis, and posttransplantation arteriosclerosis. The Atherosclerosis Risk in Communities Study showed that high levels of CMV antibodies were significantly associated with CAD incidents (RR=1.76; 95% CI: 1.00-3.11) during a 5-year follow-up period.⁽⁴¹⁾ In contrast, the Cardiovascular Health Study demonstrated that the risk of MI and CAD death was associated with the presence of IgG antibodies to HSV-1 (OR=2.0, 95% CI: 1.1-3.6) but was not associated with the presence of IgG antibodies to CMV (OR=1.2, 95% CI: 0.7-1.9).⁽⁴²⁾ A study by Zhou et al. found that prior infection with CMV was a strong independent risk factor for restenosis after coronary atherectomy.⁽⁴³⁾

Sambiase et al.⁽⁴⁴⁾ showed a direct role for the CMV in the pathogenesis of accelerated graft coronary atherosclerosis. DNA and/or protein of HSV, HIV, CMV, HCV, EBV, as well as influenza, have been found in atherosclerotic plaques.^(13,45)

In experimental studies, it was found that CMV infection can induce severe endothelial dysfunction^(46,47) and altered response to oxidized lipids in the sub-endothelium,⁽⁴⁸⁾ leading to atherosclerosis progression. Thus, replication of CMV in VECs and macrophages⁽⁴⁹⁾ triggers the release of proinflammatory cytokines, adhesion molecules, and MMP, as well as cellular death.⁽⁵⁰⁻⁵³⁾ CMV appears to induce a proliferation of VSMCs by inhibiting the tumor suppression gene p53.^(54,55) CMV and HSV can each have an atherogenic effect, including smooth muscle proliferation, increased expression of cytokines, chemokines, and increased uptake of low-density lipoprotein.⁽⁵⁶⁾

Chanouzas et al.⁽⁵⁷⁾ showed that the host cellular immune response to CMV leads to the expansion of cytotoxic CD4+CD28null T-cells that express endothelial homing markers and are independently linked to increased arterial stiffness, a marker of cardiovascular mortality.

CD4+CD28null T-cells were CMV-specific and expressed a T-helper 1 (Th1) phenotype with high levels of interferon-gamma (IFN- γ) and TNF- α secretion. As known, IFN- γ and TNF- α cytokines mediate inflammation in blood vessel walls through disruption of endothelial junctions and induction of chemokine and adhesion molecule expression on vascular endothelium. This promotes the recruitment and adherence of lymphocytes and monocytes on the inflamed endothelium and facilitates leukocyte transmigration.⁽⁵⁸⁾

Apostolou et al.⁽⁵⁹⁾ reported that acute infection with EBV was associated with atherogenic lipid changes. The results obtained by Gargouri et al.⁽⁶⁰⁾ suggest that lipid peroxidation, protein oxidation, and DNA fragmentation are generally induced during EBV lytic cycle induction.

Many studies have demonstrated possible links between HSV and native atherosclerosis.^(24,61-64) A meta-analysis performed by Wu et al.⁽⁶⁴⁾ indicated that HSV-1 and HSV-2 infections could increase the risk of contracting atherosclerosis. HSV infection of endothelial cells increases endothelial cell synthesis of tissue factor, the rate of thrombin generation on the cell surface, and platelet adherence, while it decreases prostacyclin and thrombomodulin generation.⁽⁶⁵⁻⁶⁷⁾

In 1990, Key et al.⁽⁶⁶⁾ reported two procoagulant consequences of endothelial HSV infection: loss of surface thrombomodulin activity and induction of synthesis of tissue factor, which could contribute to the deposition of thrombi on atherosclerotic plaques and to the "coagulant-necrosis" state.

The nature of the cellular immune response to three human herpesviruses— HSV1, EBV, and CMV—has received considerable attention.⁽⁶⁸⁻⁷¹⁾ Some features of these responses suggest they may have significant modulatory effects on the immune system in totum. CMV DNA is present in atherosclerotic and normal vascular tissue, and the anti-CMV immune response may be increased in the context of severe disease.^(72,73)

The mechanisms whereby CMV might promote atherosclerosis in vivo are not completely clear. Some studies suggest that chronic, unresolved inflammatory responses against latently infected cells distributed systemically or directly in the vessel wall may play a role.^(74,75) Alternatively, immunomodulatory proteins secreted by CMV may alter the VSMC motility or macrophage activation within atherosclerotic lesions.^(76,78) The latent CMV infection is periodically reactivated, resulting in a chronic immune response or inflammatory response that is damaging to the vascular endothelium and inner membrane, resulting in VSMC proliferation and mutation.⁽⁷⁹⁾ The replication of CMV in VECs is the key point of persistent viral infection, transmission, and disease onset, and is the most direct cause of endothelial dysfunction and apoptosis.

The formation of antibody immune complexes of CMV antigen deposited in the vascular wall in the atherosclerotic lesions can induce VECs, macrophages, FCs, VSMCs, and T-lymphocytes to express the monocyte proteins CCL-2, -3, -4, and -5 and macrophage colony-stimulating factor.^(53,82) Moreover, they also stimulate macrophages to produce and release of interleukins IL-1, -6, -8, -10, and -12, TNF- α , and other inflammatory cell factors, which cause cellular

and humoral immune responses, and accelerate the release of CRP to induce an inflammatory chain-reaction.⁽⁷⁸⁾ A study by Izadi et al.⁽⁸⁰⁾ showed that, due to periodic CMV activation in VSMCs caused by local immune responses and inflammation, VSMCs show degeneration and apoptosis caused by inflammatory substances, leading to instability in plaques, which are prone to rupture and bleeding, leading to acute coronary syndrome.

Many viral infections target hemostasis and coagulation, introducing either hemorrhagic or thrombotic complications.⁽⁸¹⁾ There is strong evidence showing abnormal hemostasis linked to inflammation during viral infections in humans.^(21,82-84)

Thus, the biological characteristics of CMV are consistent with the CA pathogenesis.⁽⁷⁸⁾ CMV infects VECs, leading to cellular injury and metabolic changes.⁽⁸⁵⁾ The activation of latent CMV infection can periodically affect VECs and cause high expression of platelet alpha-granule membrane protein-140, E-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecules, coagulation factors, and other tissue factors.⁽⁷⁸⁾ Viruses from VECs then infect VSMCs, and the latent or persistent infection in VSMCs leads to proliferation and the accumulation of cholesterol and cholesterol esters. In infected cells, abnormal apoptotic changes may play an important role in CA pathogenesis.⁽⁸⁶⁾ The latent CMV infection is periodically reactivated, resulting in a chronic immune response or inflammatory response that is damaging to the vascular endothelium and inner membrane, resulting in VSMC proliferation and mutation. Inflammatory factors can stimulate monocytes to chemotaxis to the vascular wall and differentiate into macrophages, and form FCs through phagocytosis of modified lipoproteins, such as ox-LDL.⁽³⁹⁾ With the development of inflammation, activated leukocytes and VECs can release fibroblast growth-regulating factor, induce the phenotype change of VSMCs, migrate from the middle membrane through the inner elastic layer to the subintimal of arteries, and proliferate and express a large number of cytokines and adhesion factors.^(39,62) In the late stage of atherosclerosis, inflammatory cytokines and MMP can degrade extracellular matrix proteins, which make the plaque easy to rupture. In addition, inflammatory cells secrete vascular growth factors, which can promote the formation of blood vessels in the plaque, and eventually lead to MI or stroke.^(39,87) Large cohort studies indicate that seropositivity for CMV or HCV represents an independent risk marker for cardiovascular diseases.^(88,89)

Conclusion

Over the past 30 years, numerous studies provide powerful evidence regarding the involvement of herpesviruses, especially CMV, in the formation of CA. The development of CA is closely related to inflammatory reactions and the immune response, endothelial injury, lipid deposition, metabolic disorders of VSMCs, and coagulation thrombosis. However, the role of viral infection in the development of CA needs further study, since many remaining issues need to be explored and resolved.

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Competing Interests

The authors declare that they have no competing interests.

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