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Article

MYOCARDITIS: INFLAMMATION OF THE HEART MUSCLE CAUSED BY INFECTIONS

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ABSTRACT

Myocarditis is a disease of the heart muscle that may also affect young people. Myocarditis is an inflammation of the myocardium that often heals spontaneously, but can also occur in mild and severe forms. In severe forms, there is an alteration of the electrocardiogram, heart failure, low blood pressure, chest pain, and shortness of breath. In addition, some protein levels are elevated, such as Troponin. Myocarditis can be caused by infection with viruses, bacteria, fungi, and parasites that induce inflammation of the myocardium. Both the innate and acquired immune systems are involved in this disease. Microorganisms can reach the heart through circulation, the respiratory tract, the gastrointestinal tract, or other routes. Viral myocarditis is one of the most common forms and occurs when viruses infect cardiomyocytes through specific receptors such as the coxsackie-adenovirus receptor (CAR), Toll-like receptor (TLR), or the ICAM-1 receptor. Receptor activation leads to NF-kB signaling with production of inflammatory cytokines (IL-1β, IL-6, TNF). Various T cells are activated, including CD8+ cells that target and destroy infected cardiomyocytes with activation of NLRP3 that triggers caspase-1, causing the synthesis of inflammatory cytokines. The virus enters the cell and uses viral proteases such as 2A and 3C to perform cytopathic effects, while bacteria can release superantigens that trigger excessive immune activation. These infections interfere with mitochondrial metabolism, induce inflammation, and can cause fibrosis.

KEYWORDS: *Myocarditis, heart, muscle, cardiomyocyte, microorganism, infection*

INTRODUCTION

Myocarditis is inflammation that specifically affects the heart muscle, the myocardium. It is a disease that tends to affect young people and can occur almost completely without symptoms, often healing without sequelae, even if it can present itself in a very serious form. Since it is life-threatening in severe forms, diagnosing this disease early and formulating an adequate treatment plan is very important.

The symptoms of myocarditis are very variable in severity and type. In the mild form, there may be only a slight fever and tiredness, while in the severe form, there may be heart failure, low blood pressure, chest pain, shortness of breath and loss of appetite. In severe forms, tachycardia or heart block may also occur, with a significant drop in blood pressure and shock that requires hospitalization in intensive care. The patient affected by severe myocarditis presents alterations in the electrocardiogram, with the presence of high levels of some proteins in the bloodstream, including Troponine, a protein normally contained in myocardial cells.

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The defining diagnostic test for this pathology is myocardial tissue biopsy, which is an invasive test that is rarely performed. More often, in myocarditis, a frequent and routine diagnostic test uses magnetic resonance imaging (MRI), which is not invasive and detects the possible presence of inflammation of the myocardium.

DISCUSSION

Myocarditis can have many causes, including infections (1). Other forms of myocarditis may be induced by certain drugs, exposure to toxins, hypersensitivity, autoimmunity, or the presence of systemic diseases. Infectious myocarditis is an inflammatory disease of the myocardial muscle caused by infectious agents such as viruses, bacteria, fungi, and parasites (2,3). The biological and biochemical mechanisms of infectious myocarditis involve several complex processes, including pathogen invasion, immune system activation, and tissue damage.

Molecular and biochemical pathways involved in myocarditis lead to immune responses, oxidative stress, and damage caused by microorganisms including viruses (Coxsackievirus B, adenovirus, influenza virus, cytomegalovirus, and SARS-CoV-2), bacteria (Streptococcus pyogenes, Corynebacterium diphtheriae, and Borrelia burgdorferi), fungi (Aspergillus and Candida), and parasites (Trypanosoma cruzi and Toxoplasma gondii) (4).

The infection begins with the entry of infectious agents, which enter the body through the respiratory tract, gastrointestinal system, or other routes. These infectious agents reach the heart through the ematic circulation. For example, one of the most common forms of myocarditis is the viral form, which occurs when viruses infect cardiomyocytes through specific receptors such as the coxsackie-adenovirus receptor (CAR) (5). Normally, the virus enters cardiac cells using cellular receptors, including ICAM-1, and replicates. The intracellular virus changes the physiological condition of the cell, causing cytotoxic effects, cell lysis, and the release of damage-associated molecular patterns (DAMPs) (6). The pathogenic virus activates the innate immune response that recognizes viral RNA/DNA or bacterial components via pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) (7). These effects activate signaling pathways, including NF-κB, which lead to the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF (8) (Fig.1). The response to microorganisms activates immune and inflammatory pathways with the involvement of PRRs. TLRs recognize microbial components including viral RNAs and bacterial lipopolysaccharides (LPS). In particular, TLR3, TLR4, and TLR7 play an important role in recognizing viral and bacterial infections in myocarditis (9).

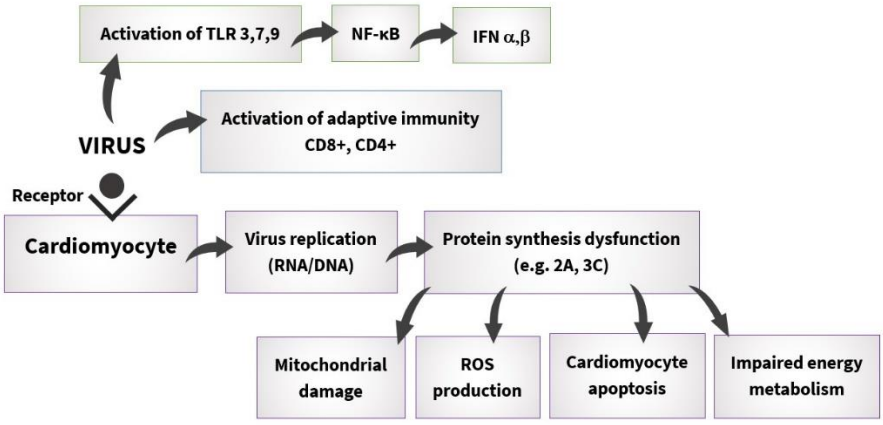

Fig. 1. *The virus binds the cardiomyocyte receptor which induces several biological effects including virus replication and impaired protein synthesis (2A and 3C) which can result in mitochondrial damage, the production of reactive oxygen species (ROS), cardiomyocyte apoptosis, and impaired energy metabolism. In addition, the virus activates adaptive immune responses involving CD8+ and CD4+ cells and also activates Toll-like receptors (TLRs) 3, 7, and 9, inducing NF-kB that promotes interferon (IFN) α and β generation which reacts against the virus.*

Virus-infected cardiomyocytes are recognized as non-self and attacked by immune cells, including natural killer (NK) cells and macrophages, causing cellular damage and tissue inflammation (10). Microorganisms can activate the adaptive immune response, where antigen-presenting cells (APCs) activate T cells and B cells. A subclass of T cells, CD8+ cytotoxic T cells, target and destroy infected cardiomyocytes, while helper T cells generate and release pro- inflammatory cytokines that feed the immune and inflammatory network. In some cases, autoimmune reactions can occur with antibodies that attack self-antigens such as cardiac myosin, leading to chronic inflammation.

While cytokines IL-1 and TNF promote inflammation and cardiac dysfunction, interferon (IFN)-α, -β, and -γ help in viral clearance, but can also cause tissue damage. In inflammation, there is activation of NLRP3 which triggers caspase-1, causing the synthesis of IL-1 and IL-18 and increasing the inflammatory response (11). The adaptive immune response involves cytotoxic T cells that directly attack infected cardiomyocytes, while CD4+ helper T cells (Th17) release pro-inflammatory cytokines such as IFN-γ and IL-17 (12). However, in this immune and inflammatory network, regulatory T cells (Tregs) are also produced that counteract excessive inflammation.

In viral pathogenesis, certain viruses, such as Coxsackievirus B, use the Coxsackievirus and Adenovirus Receptor (CAR) to enter cardiomyocytes. Once the virus has entered the cell, it uses viral proteases such as 2A and 3C to carry out cytopathic effects, apoptosis, and cell death. The antiviral response is mediated by IFN via JAK-STAT signaling.

Bacteria carry out pathogenic effects through toxins by inhibiting protein synthesis in cardiomyocytes. Some bacteria such as Streptococcus pyogenes release superantigens that trigger excessive immune activation, while lipopolysaccharide (LPS) from Gram-negative bacteria activates TLR4, triggering inflammatory cascades and NF-κB (13). Bacterial infections increase oxidative stress and produce reactive oxygen species (ROS) and nitric oxide (NO), impairing mitochondrial function and leading to cardiac dysfunction (11).

Furthermore, parasitic infections can infect cardiac cells and disrupt mitochondrial metabolism (14). All these different types of infections that affect cardiomyocytes may induce chronic inflammation that can lead to cardiomyopathy and fibrosis (15).

CONCLUSIONS

Microbial myocarditis is a direct infection of microbes in cardiomyocytes that causes an immune and inflammatory response with oxidative stress and fibrosis. The immune response involves both innate and adaptive cells. Specific inflammatory and molecular pathways are targeted in myocarditis with activation of inflammatory cytokines, binding of TLRs, and production of ROS. A better understanding of these reactions may provide more specific therapeutic strategies for the treatment of myocarditis.

Conflict of interest

The authors declare that they have no conflict of interest.

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