

# Role of complement factors and their inhibitors in the myocardial infarction

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## Abstract

The complement system, discovered over one hundred years ago, is a major component of innate mechanisms of immune responses. A group of approximately 40 proteins that comprise the complement system, participates in the defense of the host against various agents, e.g. microorganisms, through facilitation of phagocytosis and enhancement of ongoing inflammatory reaction. There are three complement activation pathways: conventional, alternative and lectin pathway. Activation of the complement system results in formation of membrane attacking complex (MAC) and death of the lytic target cell. Complement activation and MAC formation are regulated by specific cellular and serum proteins. It is constitutively active and potentially could damage the body own cells. Cells of ischemic myocardium become foreign cells for the immune system for antigenic reasons. This results in activation of the complement system and formation and deposition of MAC that damages myocardial cells. By binding their surface, it exacerbates myocardial injury caused by infarction. The aim of this paper is to elaborate on the role of complements and their inhibitors in etiology of myocardial infarction basing on literature data concerning this condition.

**Key words:** myocardial infarction, complement system, immune response, inhibitor.

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Cardiovascular diseases and ischemic heart disease in particular with its extreme form – myocardial infarction, are responsible for approximately 40% of deaths in Poland and worldwide and therefore constitute one of the main problems of contemporary medicine. Despite widespread information, e.g. in the media, and multiple scientific publications, many aspects of these disorders remain unclear. Multiple factors can exacerbate ischemic heart disease, resulting in myocardial infarction: complete occlusion of an artery by a clot resulting from a ruptured atherosclerotic plaque [1]; an embolus originating from thrombi formed on the left ventricular valves; sudden increase of myocardial oxygen demand with coexisting impairment of coronary reserve; arteritis [2, 3]. At the current stage of development of biomedical sciences, the disease progression is thought to be modulated by multiple immunological, biochemical and biophysical factors determined by genetic and environmental circumstances [4].

Damage of the barrier between cardiomyocyte cytoplasm and extracellular environment resulting from ischemia is an important factor for the involvement of

immunological mechanisms. Synthesis of ATP that is required for preservation of integrity of the cellular membrane and lysosomal membranes, is reduced, resulting in sarcolemmal damage. The mechanism of ionic exchange is disturbed, what results in inhibition of metabolite removal with subsequent accumulation of lactate, phosphate, ammonium and sodium ions in the cardiomyocytes. Increased osmotic pressure results in edema and cardiomyocyte rupture. Increased sarcolemmal permeability is also caused by the presence of superoxide and hydroxyl free radicals in higher amounts in the ischemic myocardium with simultaneous reduction of contents of inactivators [5]. The surface of all myocardial cells undergoes modification as a result of expression of adhesion molecules. Adhesion molecules are expressed at the border between the endothelium and necrotic cardiomyocytes, both on the surface of the endothelium as well as in the plasma, as soluble adhesion molecules [6]. Platelet endothelial cell adhesion molecule-1 (PECAM-1), also known as CD31, is also expressed on endothelial cells. These molecules are located on side surfaces of endothelial cells but also exist on peripheral blood

monocytes/macrophages, neutrophils and lymphocytes. CD31 located on side surfaces of endothelial cells acts to allow leukocyte migration between these cells [7]. Results of studies performed on animal models involving blockade of PECAM-1 with specific antibodies, demonstrated that leukocyte migration is inhibited during inflammation. Therefore, CD31 blockade in the ischemic myocardium could prevent post-myocardial infarction injury of the myocardium, most probably by inhibiting transendothelial neutrophil migration [8-10].

Neutrophil and monocyte/macrophage migration to ischemic sites is initiated by chemotactic activity of complement factors – predominantly C3a and C5a – on these cells. An infiltration of migrating cells is a response to ischemia-triggered changes. This phenomenon was described for the first time by Mallory *et al.* in 1939 [11]. Inflammatory mediators that are released in the ischemic area as well as secreted by damaged cells, stimulate phagocytic cells and these may remove damaged and healthy cells found in the infarcted zone. Myocardial cell destruction during reperfusion by neutrophils results from their adhesion to each other. It is mediated by ICAM-1 molecule, expressed on cardiomyocyte surface [12]. Its increased expression occurs within the first 36 hours, i.e. during an acute inflammatory response that leukocytes are involved in [13]. Migrating cells undergo activation, resulting in formation

of an inflammatory infiltration in the ischemic myocardium related to stimulation of the cytokine network. Scientific reports published over the recent years in the area of cytokine-mediated regulatory mechanisms, did not fully elucidate their role in the ischemia [14].

Cells of ischemic myocardium acquire foreign antigenic profile for the immune system, what results in complement activation and formation of a membrane attacking complex that damages myocardial cells (Fig. 1). By binding their surfaces, it exacerbates the infarction-related injury. Formation and deposition of large amounts of MAC on the cardiomyocyte surface are caused by the loss of protective CD59 antigen – protectin that by binding C8 complement factor from the C5b678 complex, blocks binding of C9, which makes MAC formation impossible [15-17]. Studies performed on experimental animal models of myocardial infarction demonstrated a potential pathophysiological role of activation of the complement system as a result of tissue ischemia. Complement elimination as well as injection of a recombinant soluble receptor for C1 complement factor was shown to reduce the size of tissue injury [5, 18, 19]. Blockade of neutrophil adhesion or reduction of the monocyte/macrophage number by monoclonal antibodies in the initial phase of reperfusion could be one of the possible means for reduction of the ischemic area [11, 20].

As mentioned above, myocardial infarction is one of the most common causes of death. Its pathomechanism remains unclear despite the fact that many research studies have been conducted to understand it. Basing on the research report, immune reactions in the myocardium are thought to play an ever increasing role. There are no detailed studies on the role of the complement system and its inhibitors in the development and pathogenesis of myocardial infarction in available literature. Only few studies focus on a wider context – integration between cellular and humoral immune response [15, 21-26]. The significant and sometimes decisive role of the complement system in the pathogenesis of myocardial infarction seems highly probable and simultaneously is attractive from a therapeutic point of view. The continuous development of civilization is accompanied by a marked increase of prevalence of cardiovascular diseases and cardiovascular mortality. Considering the fact that activation of the complement system exacerbates pathological changes resulting from vascular atherosclerosis and myocardial infarction, use of inhibitors of this system is being considered. Due to this fact studies of the complement system in the context of myocardial infarction as well as other pathological changes should be continued and extended, using modern research techniques in the hope that they will contribute to the effective fight against diseases that modern medicine is largely helpless against.

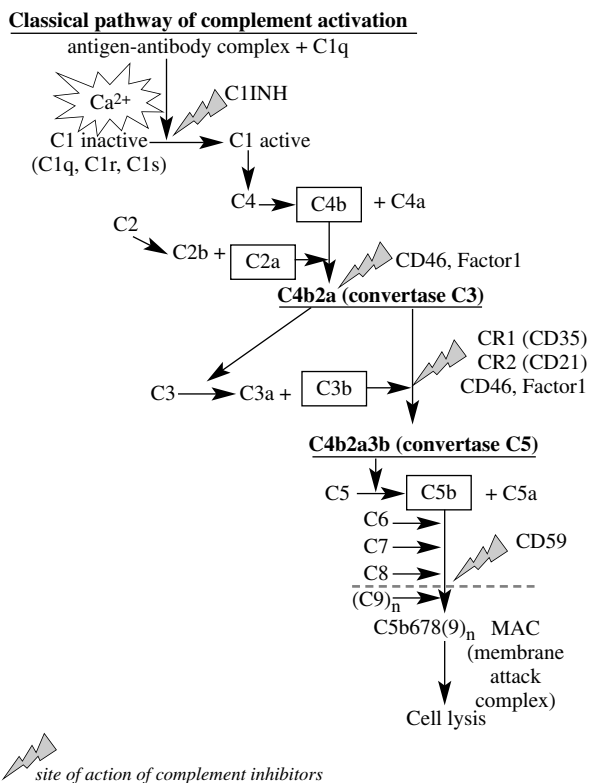


Fig. 1. Activation of the complement system

The authors declare no conflict of interest.

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