Chapter

Correlations between Inflammation and Thrombosis in the Pathogeny of Myocardial Infarction

Iris Bararu Bojan, Oana-Viola Badulescu, Maria Vladeanu, Andrei Bojan and Manuela Ciocoiu

Abstract

Atherosclerosis is the main cause of myocardial infarction. This process involves a complex interplay between metabolic pathways governing lipid deposition, inflammatory and immune responses to oxidized lipids, and endothelial dysfunction. Myocardial infarction appears when these processes culminate with a thrombotic event. Markers of inflammation, such as C-reactive protein (CRP), myeloperoxidase (MPO) and leukocyte levels are strong predictors of cardiovascular death, myocardial infarction, and stroke. This process involves a complex interplay between metabolic pathways governing lipid deposition, inflammatory and immune responses to oxidized lipids, and endothelial dysfunction. Myocardial infarction appears when these processes culminate with a thrombotic event. Markers of inflammation, such as C-reactive protein (CRP), myeloperoxidase (MPO) and leukocyte levels are strong predictors of cardiovascular death, myocardial infarction, and stroke. This review will summarize the molecular and cellular links between inflammation and thrombosis in the context of myocardial infarction, which support the concept of a thrombo inflammatory state leading to the vessel obstruction and to the subsequent myocardial necrosis.

Keywords: thrombosis, inflammation, atherosclerosis

1. Introduction

Myocardial infarction is a form of coronary artery disease, in which the occlusion of the coronary artery induces ischemia of the subsequent territory and eventually leads to the destruction of up to a billion myocardic cells.

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As the human heart cannot regenerate, the acute myocardial infarction is associated with the destruction of large proportion of myocardium that will lead to the development of a collagen scar. This process is associated with an evident inflammatory reaction. This inflammatory reaction will lead to the chemotaxis of leukocytes that will be preferentially localized at the border of the necrotic myocardium. These leukocytes may lead to cytotoxic reactions that can increase the injured zone [2].

2. The role of inflammation in myocardial infarction

The acute pro-inflammatory process triggered by the onset of myocardial infarction consists in multiple processes such as the production of reactive oxygen species and DAMPs (damage associated molecular patterns) which are in fact the substrate for PRRs (pattern recognition receptors). These processes will eventually lead to the formation of cytokines and chemokines that will mediate the attraction of thee inflammatory cells to the border zone of the myocardial infarction.

After the onset of a myocardial infarction the healing process involves three important phases: the inflammatory response, the proliferation and in the end the maturation.

During the inflammatory response the necrotic cardiomyocytes release danger signals, called alarmins that will signalize some particular types of receptors called TLRs (toll-like receptors) and RAGE (receptor for advanced glycation end products), thus stimulating the immune cells, the endothelial ones and the fibroblasts to secrete chemokines and cytokines. The inflammatory phase is also characterized by the activation of the complement cascade. The complement cascade can be activated in three different manners: the classic pathway, the lectin and the alternate way [1–3]. These pathways all lead to the common pathway that results in opsonization, subsequent inflammation attracting others phagocytes, or activation of thee cell killing membrane attack complex – **Figure 1**.

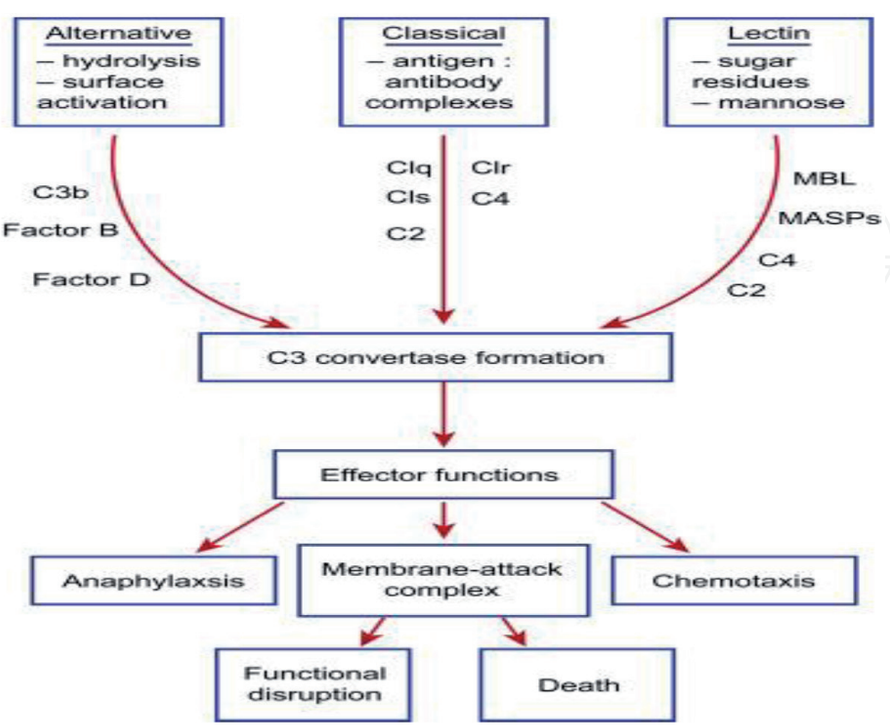

Figure 1.
The complement cascade – https://www.sciencedirect.com/topics/medicine-and-dentistry/complement-system.

The inflammatory process and the activation of the complement cascade determine the release of pro-inflammatory cytokines, such as Tumor Necrosis Factor (TNF)-α, IL-1β and IL-6.

A key role in the activation of the inflammatory reaction is played by the IL-1 signaling pathway. This pathway stimulates the production of chemokines by fibroblasts and leukocytes, but inhibits the conversion of fibroblasts in myofibroblasts. Damaged myocardial cells release IL-1α, while IL-1β is upregulated after infarction. An important key for this mechanism is represented by the inflammasome, which triggers the activation of caspase-1 and thus transforms active pro-IL-1β into IL-1β. It was shown that the inflammasome can be found both in myocardial and in interstitial cells in the ischemic myocardium. The pharmacological blockage of IL-1 or the genetic inhibition proved to reduce left ventricle remodelation after myocardial infarction [4, 5].

IL-6 is associated with both pro and anti-inflammatory effects. Myocardial infarction is associated with increased circulating IL-6. Some studies showed that the genetic polymorphisms of the IL-6 receptor signaling pathway may lead to a diminished plasma level of high-sensitivity C-reactive protein (hs-CRP) and thus may lead to the decrease of cardiovascular risk [6].

The post-infarction inflammatory response determines a chemokine upregulation, which are responsible for the recruitment of other leukocytes in the infarcted area.

The neutrophils are activated by CXC chemokines containing the Glu-Leu-Arg sequence (the ELR motif), such as CXCL8/IL-8, while the CC chemokines, such as monocyte chemo attractant protein-(MCP)-1/CCL2 and CCL7 attract monocytes. The phagocytosis is activated and the necrotic detritus is eliminated, so that the healing process may start. When the infiltrated neutrophils enter the apoptotic process, the inflammatory phase comes to an end [7].

From this moment on the apoptotic cells are scavenged by professional phagocytes, thus leading to a process called efferocytosis. This phase consists in the release of cytokines with anti-inflammatory effect such as IL-10 and TGF-β. These mediators induce an endogenous intracellular signal, such as Interleukin-receptor associated kinase-M that inhibits the pro-inflammatory process in the healing areas of the myocardium. The inhibition of inflammatory signaling and the removal of the inflammatory infiltrate is determined by the presence of inhibitory leukocyte, such as anti-inflammatory monocyte subpopulations and regulatory T cells [8].

The remaining cardiomyocytes in the infarct border zone secrete mediators with anti-inflammatory properties that lead to the diminishment of the affected area. If the inflammatory response is unrestrained or is very expansive, the result will consist in rapid left ventricle remodeling, which can be implicated in inducing heart failure in patients surviving an acute myocardial infarction.

When the proliferative phase of myocardial infarction has begun, the diminishment of pro-inflammatory molecules such as IL-1β and Interferon-γ-inducible Protein (IP)-10 causes the transformation of fibroblasts in myofibroblasts. These compounds have an extensive endoplasmic reticulum and possess a contractile protein that is called α-smooth muscle actin (α-SMA) and are capable of inducing an increased synthesis of matrix protein [7–9].

When the proliferative phase comes to an end, the mature scar starts to form. The myofibroblasts enter apoptosis and matrix cross-linking occurs. This mechanism seems to be mediated by the removal of growth factors, the inhibition of TGF-β mediated response and the modification of the composition of the matrix.

In the remaining healthy myocardium the fibroblasts may rest chronically active as s result of a pressure overload. This will induce the fibrosis of the myocardium and will lead to diastolic dysfunction.

As inflammation plays a key-role in the pathogenesis of myocardial infarction, some authors thought that giving anti-inflammatory therapy to patients with acute coronary syndrome would be beneficial, but the results proved that treatment with corticosteroids or with NSAIDs is associated with a worsened outcome. Due to the non-selective inhibition of the inflammatory cascade, these drugs have potentially catastrophic consequences. Therefore the current guidelines are against the use of broad range anti-inflammatory therapy in patients with acute coronary syndrome [10, 11].

A better understanding of the process of inflammation in myocardial infarction leads to the conclusion that targeted inhibition of selected inflammatory routes may add up to the protection of the vulnerable myocardium without harming the reparative response. There are studies that showed that a targeted neutralization of specific inflammatory mediators such as chemokines and cytokines can reduce the size of the infarction.

3. The role of thrombosis in myocardial infarction

Inflammation is responsible for inducing an active atheroclerotic plaque, but this plaque is not sufficient to induce a myocardial. After the plaque has ruptured, the hemostatic balance is impaired, thus leading to coronary thrombosis. The alterations of the hemostatic balance consist in increased platelet adhesion, coagulation cascade activation and subsequent. Over-activated procoagulation determines a thrombophillic status that can be acquired from complex patterns of inheritance or environmental risk factors.

The thrombotic events may be caused by an increase of different coagulation factors. Plasmatic fibrinogen is an important cardiovascular risk factor. It was proven that increased levels of Interleukin 6, may lead to an increased hepatic synthesis of fibrinogen, thus representing an important link between inflammation and thrombophilic status.

Thrombin or FIIa is a serin protease which has an important clotting effect. The importance of thrombin in the clotting anomalies is rather disputed. Some studies have shown that the concentration of thrombin in patients with coronary artery disease is normal and that it does not represent a predicting factor for vascular complications, while other researchers have stipulated that thrombin is one of the most important factors responsible for the thrombotic complications. Nevertheless, increased levels of thrombin are associated with the presence of denser thrombus structures, with a diminished permeability, which is resistant to fibrinolysis [12–14].

Clotting factor XIII is involved in hemostasis, fibrinolysis, vascular remodeling and tissue repair. It is important to do the genotyping of factor XIII in order to assess the prothrombotic status because the existing data in the literature rest unclear. Clotting factor XIII is a pro-transglutaminase with tetrameric structure consisting of two active subunits A and two inhibitory/protective subunits B. The clotting factor XIII genotyping has shown that mixed FXIII heterozygous mutants (formed from a wild allele and a mutant one) were associated with increased levels of total and LDL-cholesterol and with elevated concentrations of CRP, while the other genotypes of clotting factor XIII have not been correlated with these changes [15–18].

From our personal experience, from a clinical study including 60 patients with myocardial infarction, we found out that 25% of patients had heterozygous mutants of factor XIII (wild type + mutant type), the majority of them being elderly men. Almost one third of the patients with PAI-1 4G/4G genotype and a quarter of those with genotype 5G/5G were associated with heterozygous mutants of FXIII

(WT + MT); the combined 4G/5G genotype was associated only with wild-type FXIII. The clotting factor XIII genotyping realized during the current research has shown that mixed FXIII heterozygous mutants (formed from a wild allele and a mutant one) were associated with increased levels of total and LDL cholesterol and with elevated concentrations of C-reactive protein, while the other genotypes of clotting factor XIII have not been correlated with these changes – **Figure 2**.

These genomic changes appear to be responsible for the decreased permeability of the formed thrombus and for the inhibition of the fibrinolysis process, which explains the higher incidence of acute coronary syndromes and complex coronary artery lesions in type 2 diabetic patients [19, 20].

The atherothrombotic complications may be caused also by a modification in fibrinolysis. The fibrinolysis is initiated by the conversion of plasminogen in plasmin, a process which is mediated mainly by the tisular plasminogen activator (tPA).

The plasminogen activator inhibitor type 1 (PAI-1) is the primary inhibitor of the fibrinolysis, which acts by forming a complex with tPA. PAI-1 gene is situated on the 7th chromosome and contains 8 introns and 9 exons. The effect of PAI-1 is the down-regulation of the fibrinolytic process as it inhibits the transformation of plasminogen to plasmin regulated by tissue-plasminogen activator and urokinase [21–23].

PAI-1 levels are proportional with the degree of the inflammatory process, induce atherosclerosis and are linked to the presence of metabolic syndrome. Obesity and diabetes mellitus type 2 are pathological conditions associated with increased PAI-1 levels that may lead to extensive atherosclerosis. Human CD 34+ cells exert high levels of PAI-1 especially in patients with diabetes and micro vascular complications. High levels of PAI-1 are associated with visceral adiposity because this molecule is produced by ectopic fat depots. The inflammatory state conferred by the high PAI-1 levels cause a dysfunctional activity of the cytokines (IL-8, leukotriene B4) and can determine impaired monocyte migration [24].

There are 5 polymorphisms of the PAI-1 gene: 675 4G/5G, 844 A > G, Ala15Thr, Val17Ile and Asn195Ile. The 4G/5G polymorphism (the deletion/insertion of guanosine in the 675 position of the PAI-1 gene promoter) is a major genetic determinant of PAI-1 levels. Some authors have suggested that the 4G allele association with other thrombophilic defects (factor V Leiden, prothrombin mutation, hyperhomocysteinemia, and decreased activity of protein C or S) increases the risk of thrombosis. In patients with coronary artery disease the presence of PAI-1 4G/4G genotype was associated with an increased risk of sudden death. When PAI-1 has an increased activity, the high circulating levels of PAI-1 may induce the persistence of microthrombi, therefore leading to a prothrombotic state in an early myorcardial infarction please, which will affect the short-term outcome of patients with acute coronary syndrome. Even more PAI-1 levels are linked to the degree of myocardial fibrosis that can lead to detrimental left ventricle remodeling and poor long-term prognosis [25–28].

From our personal experience from a research involving 60 patients with acute coronary syndrome, we found out that the majority of patients had the 4G/4G

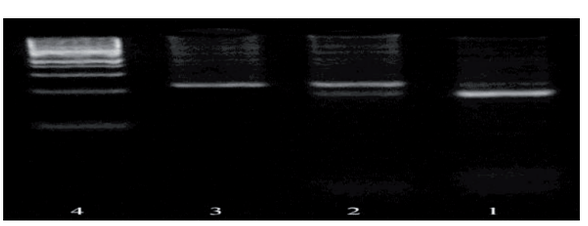

Figure 2.
Identification of factor XIII Val34Leu polymorphism.

genotype, which was associated with elevated levels of glycated hemoglobin and with a high concentration of LDL cholesterol and fibrinogen and with multivessel atherosclerosis, while the other genotypes of PAI-1 were not correlated with these changes – **Figures 3** and **4**.

In our studied group, 65% of patients had the PAI-1 4G/4G genotype, while 15% of patients had a heterozygote 4G/5G genotype. Not only did PAI-1 4G/4G genotype associate more frequently with atherogenic dyslipidemia, but it also showed a slight direct correlation with the inflammatory parameters – **Figure 5**.

As a consequence we can assume that the prothrombotic status found in patients with myocardial infarction seems to be modulated by the genomic polymorphism of clotting factor XIII, which is responsible for the formation of a more stable cruoric thrombus which is more resistant to fibrinolysis. Even more, these patients show a deficiency of the endogenous fibrinolysis, which predisposes the development of a thrombophilic status. This decrease in the thrombolytic process seems to derive from the genomic polymorphism of plasminogen activator inhibitor type 1. The most common genotype of PAI-1 associated with an increased cardiovascular risk is PAI-1 4G genotype. These polymorphisms are correlated with the presence of metabolic disorders and an abnormal inflammatory process in patients with acute coronary syndrome, thereby inducing an increased cardiovascular risk in these patients.

Fibrinogen and PAI polimorphism

Genotype	N	Mean	Std. Deviation	Std. Error	CI 95%		Min	Max	Test t-Student p
					-95%CI	+95%CI			
PAI-1									
4G	39	5.43	0.92	0.18	5.06	5.80	3.81	7.32	**0.037**
5G	12	5.59	0.46	0.16	5.20	5.97	5..00	6.21	
4G/5G	9	6.42	0.58	0.24	5.81	7.02	5.90	7.20	

Figure 3.
The relationship between PAI-1 polymorphism and the plasmatic level of fibrinogen.

LDL Cholesterol and the genomic polimorphism

Genotype	N	Mean	Std. Deviation	Std. Error	CI 95%		Min	Max	Test t-Student p
					-95%CI	+95%CI			
PAI-1									
4G	39	199.00	29.72	5.83	187.00	211.00	136	240	**0.037**
5G	12	200.38	42.91	15.17	164.51	236.24	150	265	
4G/5G	9	161.67	20.48	8.36	140.17	183.16	131	180	

Figure 4.
The relationship between PAI-1 polymorphism and the plasmatic level of LDL-cholesterol.

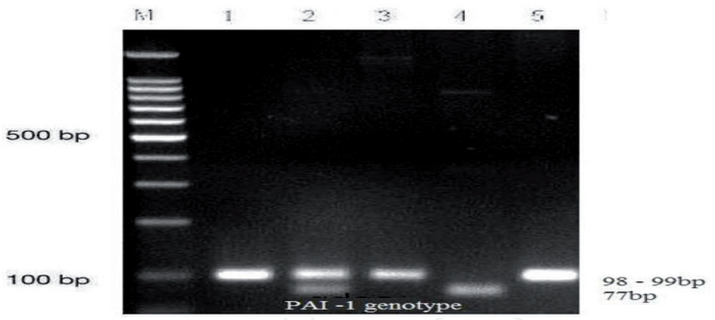

Figure 5.
Identification of PAI-1 polymorphism.

In conclusion, a better understanding of the inflammatory and thrombotic processes that lead to myocardial infarction can help improve the manner of treatment for this patients, thus increasing their quality of life and their prognostic.

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