

Reconsidering the Mechanisms of Acute Coronary Syndrome

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Abstract

The main mechanism of Acute Coronary Syndrome (ACS) has been thought to be thrombus formation accompanying the rupture of coronary atheroma (plaque). However, in the present day when Low-Density Lipoprotein (LDL) cholesterol can be reduced by HMG-CoA reductase inhibitors (statins), thrombosis due to "erosion" and not rupture of plaques is attracting attention as an important mechanism of ACS. ACS due to eroded plaques involves inflammation and immunity, particularly Neutrophil Extracellular Traps (NETs). Therefore, it is necessary to reevaluate whether invasive treatments and antithrombotic therapy that have been used for ACS due to plaque rupture are most suitable and to investigate new personalized treatments. In the future, personalized treatments corresponding to different mechanisms of ACS should be investigated and drugs that inhibit the formation of NETs may become a treatment option.

Introduction

Treatment for a certain disease may change associated pathological state or mechanisms. HMG-CoA reductase inhibitors (statins) prevent the progression of arteriosclerosis by controlling Low-Density Lipoprotein (LDL) cholesterol and therefore prevent cardiovascular adverse events. The number of Acute Coronary Syndrome (ACS) caused by coronary atheroma (plaque) rupture is also reduced by the shrinkage of the lipid core of the coronary atheroma. Moreover, a shift in the mechanisms of ACS has occurred, i.e., even when plaque rupture can be avoided, prolonged inflammation and immune response due to erosion cause thrombosis leading to the development of ACS. This review focuses on neutrophils, particularly the formation of Neutrophil Extracellular Traps (NETs) as a factor for the progression of eroded plaques to thrombosis and describes new strategies for the treatment of ACS in the future.

Changes in the mechanisms of ACS

Acute Coronary Syndrome (ACS) is a syndrome in which the rupture of coronary atheroma (plaque) and accompanying thrombus formation rapidly narrow and obstruct the lumen of a coronary artery resulting in ischemia and necrosis of the myocardium [1,2]. In the early phase of arteriosclerosis, plaques are formed by intimal thickening, lipid deposition, and macrophage infiltration. However, the vascular lumen is maintained by the positive remodeling of the outer diameter. If further growth of plaques causes decompensation, the vascular lumen is narrowed, and severe stenosis causes angina of effort. In such development and progression of arteriosclerosis, inflammation plays an important role [3]. In the process, a vulnerable plaque consisting of a necrotic core rich in lipid components with cholesterol crystals, inflammatory cell infiltration, and a thin fibrous capsule covering the necrotic core is formed in a coronary artery, and thrombus formation due to rupture of the plaque is thought to cause ACS [4]. However, a pathological state in which a thrombus is formed in a coronary artery without obvious plaque rupture has been found [5]. Such a pathological state has become recognized as "erosion," which causes thrombus formation through vascular endothelial cell impairment or deficiency. Previously, treatment focused on the stabilization of unstable plaques that may rupture. The main treatment was lipid-lowering therapy using HMG-CoA reductase inhibitors (statins). With the use of these drugs, significant decrease in the number of ACS patients was observed particularly in Europe and the United States. However, lesions of thrombotic obstruction developing from eroded plaques without rupture gradually started to attract attention [6-9]. Table 1 shows the characteristics of ruptured plaques and eroded plaques. In the statin era, a target disease for treatment that attracted attention was acute ST-segment elevation myocardial infarction caused by the rupture of unstable plaques accompanying hyper-LDL-cholesterolemia. With widespread administration of lipid-lowering therapy with statin formulations, the number of patients with acute myocardial infarction caused by such a mechanism has decreased. However, the proportion of patients with acute non-ST-segment elevation myocardial infarction in whom no hyper-LDL-cholesterolemia or ruptured plaque was observed has increased, and mechanisms through which eroded plaques cause thrombotic obstruction have attracted attention (Figure 1).

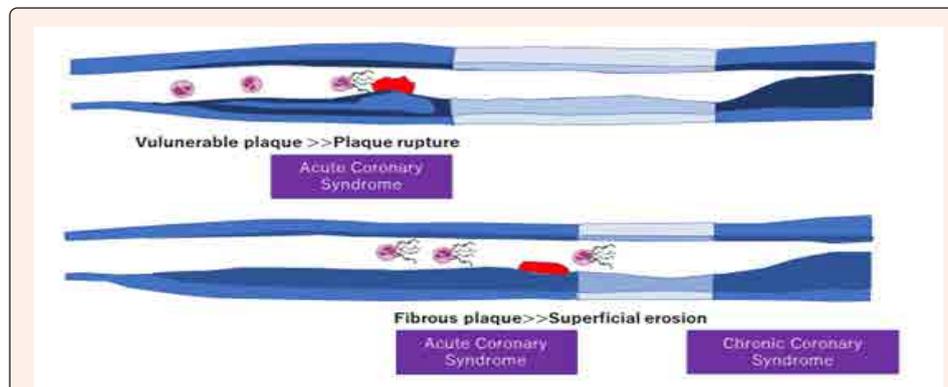


Figure 1: Due to statin therapy, the pathological basis of acute coronary syndrome of plaque rupture has changed to plaque erosion

Table 1: Comparison of ruptured plaques and eroded plaques

		Ruptured plaques	Eroded plaques
Histological characteristics	Morphology	Thin capsule, large lipid core	Homogeneous fibrous plaques
	Plaque components	Rich in lipid	Mainly proteoglycan and glycosaminoglycan
	Thrombus	Rich in fibrin (red thrombus)	Rich in platelet (white thrombus)
	Apoptosis	Smooth muscle cells	Endothelial cells
	Immune cell components	Abundant (macrophages predominate)	Scarce (neutrophils predominate)
Clinical picture	Gender	More common in men	More common in women
	Lipid profile	Hyper-LDL-cholesterolemia	Hypertriglyceridemia
	Electrocardiogram	ST-segment elevation	Non-ST-segment elevation

Neutrophils and thrombosis in ACS

A concept of “inflammation” in the development of arteriosclerosis proposed by Peter Libby [10] directed attention to immune cells such as monocytes/macrophages and lymphocytes [11], which resulted in the CANTOS and COLCOT studies [12,13]. In ACS, neutrophils and the degranulation of neutrophils were detected in thrombi collected during thrombus aspiration therapy in emergency coronary artery revascularization, indicating the involvement of neutrophils in the development of ACS [14,15]. Previously, peripheral blood neutrophils were thought to be a homogeneous cell population. However, the dynamic analysis of them and detailed analyses of surface marker and transcription factor expression have revealed that they are a heterogeneous cell population with various characteristics [16-18]. In particular, the formation of Neutrophil Extracellular Traps (NETs) that Brinkmann et al. reported in 2004 as a new functional morphology of neutrophils which captures and kills bacteria [19] expanded its research target to sterile immunity, resulting in the analysis of its roles in the development of arteriosclerosis. However, since the concept of plaque rupture was previously thought to be the main pathogenesis of ACS, the formation of NETs by neutrophils was regarded as a bystander in terms of thrombus formation after plaque rupture, not as an important factor for the development of ACS. For the formation of obstructive thrombi due to the rupture of unstable plaques, it is known that the release of tissue factor and platelet aggregation due to the exposure of subintimal extracellular matrix to blood components after rupture cause thrombus formation. However, there are few reports of direct involvement of neutrophils and NETs. However, Quillard et al. reported enhanced formation of NETs in eroded plaques obtained by carotid endarterectomy in humans, showing the involvement of NETs in the formation of obstructive thrombi from eroded plaques [20].

Treatment for ACS based on the pathogenesis

Jia et al. reported treatment of patients with ACS accompanied by erosion, which was defined by optical coherence tomography, with anticoagulants/antiplatelet therapy instead of mechanical revascularization. Approximately 80% of the patients showed more than 50% reduction in the number of thrombi after 1 month. More than 1/3 of the patients had no detectable thrombus after 1 month. This study proposed that the appropriateness of mechanical revascularization for ACS due to eroded plaques needs to be reevaluated [21,22]. The formation of NETs is involved in the development of ACS due to eroded plaques and is attracting attention as a new therapeutic target. The effects of drugs that inhibit the formation of NETs are being investigated. However, there is concern that the original role of the formation of NETs, i.e., protecting the host from pathogenic bacteria, may be lost. Mechanisms through which the formation of NETs is induced are complex and have not been adequately elucidated. We hope that specific factors that affect the formation of NETs in the development of cardiovascular disease are identified and the importance of the formation of NETs at each stage of the disease is determined, which will translate into selective treatments becoming available.

Conclusion

In the era of strict lipid management, the progression from eroded plaques to thrombosis is attracting attention as a mechanism of the development of ACS, and the involvement of immunity, particularly Neutrophil Extracellular Traps (NETs), in

the process has been reported. In the future, personalized treatments corresponding to different mechanisms of ACS will be investigated and drugs that inhibit the formation of NETs may become a treatment option.

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