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Review Article

The role of TANK-binding kinase 1 (TBK1) and C-reactive protein in myocardial infarction inflammatory response

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Abstract
The inflammatory response is an immunobiological defense mechanism triggered by damage to living tissues. Inflammation plays a crucial role in pathogenesis of atherosclerosis and vascular disease. Inflammatory response is the main player in the initiation and progression of atherosclerosis, which in turn leads to occlusion of coronary arteries inducing ischaemic events finally causing injury and consequent death of cardiomyocytes. Despite decades long improvements in diagnosing and treatment of coronary heart disease, questions about how to prevent and/or stop ventricular remodeling in post Myocardial infarction still rises. This paper discusses some recent findings and the role of some inflammatory biomarkers, namely C-reactive protein and TBK1 in Myocardial Infarction and their impact in post myocardial infarction ventricular remodeling due to prolonged inflammatory response. Deeper understanding the role of TBK1 in the inflammatory response post myocardial infarction could be of significant importance to the design of novel therapeutic strategies targeting the resolution of prolonged inflammatory response which takes place post myocardial infarction leading to ventricular remodeling and impaired ventricular function.
Key words: TANK-Binding Kinase 1 (TBK1), C-reactive protein, myocardial infarction, ventricular remodeling, cardiac remodeling, inflammation.

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Introduction

Acute Myocardial Infarction (AMI) is one of the major causes of morbidity and mortality in industrialized countries. Despite the considerable progress over the past decades, in the understanding of its pathophysiologic mechanisms, as well as in its treatment at the acute stage, AMI still carries a great burden to the affected individuals, diminishing significantly the quality of life, and to the health care system.

Acute myocardial infarction results in the activation of the acute phase response-the mobilization and recruitment of leukocytes to the site of infracted myocardium. Furthermore, myocardium that is remote from ischemic zones have also been associated with the activation of pro-inflammatory pathways and infiltration of leukocytes. These responses are increasingly recognized as important in post-infarct ventricular remodeling [1]. Ventricular remodeling is the process by which ventricular size, shape, and function are regulated by mechanical, neuro-hormonal, and genetic factors [2, 3]. Remodeling may be physiological and adaptive during normal growth or pathological due to myocardial infarction, cardiomyopathy, hypertension, or valvular heart disease [4].

Inflammation

Inflammation is a protective immuno-vascular response that involves immune cells, blood vessels, and molecular mediators; it is part of the complex biological response of vascular tissues to harmful stimuli.

It is a non-specific, first-line body defense response to cell injury. Given that the response is the same regardless of the nature of the agent of cell injury. As inflammation is in response to cell injury, the magnitude of the response depends on the degree of damage. The purpose of inflammation is to quickly eliminate the initial cause of injury, stop further cell damage, clear out necrotic cells and damaged tissues to enable completion of the healing process. If the harmful stimuli persists, the inflammatory response becomes chronic preventing the completion of tissue repair, thus causing the inflammatory process to continue leading to further tissue damage.

C-reactive protein

C-reactive protein (CRP) is an acute-phase serum protein and a member of the pentraxin protein family. CRP is a phylogenetically highly conserved plasma protein that participates in the systemic response to inflammation. Its plasma concentration rises during inflammatory states, a characteristic that has long been employed for clinical purposes. Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells in

order to activate the complement system via the First Complement Component, Subcomponent Q (C1Q) complex [5].

Inflammatory markers such as CRP, increase manifold in response to infection and tissue damage and in active diseases states. However, variations within the reference range predict the onset of health events, such as cardiovascular disease and disability, in individuals without an obvious inflammatory stimulus [6].

Innumerous studies have shown CRP to be risk factor and predictor of future cardiovascular events. Individuals who have CRP results at the high end of the normal range have 1.5 to 4 times the risk of experiencing a heart attack as those with hs-CRP values at the low end of the normal range. Lowering of C-reactive protein is associated with a reduction in cardiovascular risk.

C-reactive protein is no longer simply a marker, but is increasingly considered as a mediator of cardiovascular disease. C-reactive protein originates in the liver and its production is stimulated by systemic cytokines (IL-1b, IL-6). Following Acute Myocardial Infarction, serum C-reactive protein increases following cytokines activation and binds to the damaged myocardial cells. Further, it stimulates the complement cascade, which may finally increase the MI size, worsening the overall post-MI outcomes [7-9]. These events suggest that C-reactive protein is not only a sensible inflammatory marker, but should also be considered as a direct inflammatory promoter with pro-atherogenic and pro-thrombotic properties [10, 11, 12]. In fact, C-reactive protein has been shown to be directly correlated to the early and late post-MI morbidity and mortality [13, 14].

Although C-reactive protein is a sensitive marker of inflammation, an elevated C-reactive protein value is not specific for any condition, for example, statin therapy, besides lowering LDL cholesterol, also reduces both C-reactive protein levels and cardiovascular risk. Another example is the effect that exercising has on CRP levels.

TANK-Binding Kinase 1 (TBK1)

Recently, an increasing number of studies have focused on inflammatory diseases. TANK-Binding Kinase 1 (TBK1), also called NF-kB-activating kinase (NAK) and tumor necrosis factor receptor−associated factor 2-associated kinase (T2K), is a serine/threonine-protein kinase that is encoded by the TBK1 gene, which regulates antiviral defense, host-virus interaction, and immunity. Interestingly, high levels of active TBK1 have also been found to be associated with inflammatory diseases, indicating that TBK1 is closely related to inflammatory responses [14].

TBK1 has the ability to regulate the expression of inflammatory mediators such as IL-6, TNF-α, and IFN-β [15, 16, 17]. Taken together, these findings suggest that TBK1 acts as a critical player in various immuno-biological and immuno-pathological events, especially inflammatory responses [10].

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Interferon regulatory factor 3 (IRF-3) activated by various TLRs are the major transcription factors involved in the induction of inflammatory mediators, such as NO, PGE2, and IFN-β. TBK1 is involved in both of these signaling pathways [18, 19, 20]. Following activation of TLRs, TBK1 assembles with TRAF3 and TANK to phosphorylate IRF-3, -5, and -7 at multiple serine and threonine residues [21, 22, 23]. These IRFs ultimately heterodimerize and translocate into the nucleus, where they induce expression of pro-inflammatory genes such as IFN-α/β [24, 25].

Macrophages are one of the major regulators of the inflammation processTBK1 is involved in the TLR3 and TLR4 signaling pathways in macrophages, acting as the central kinase directly related to the production of pro-inflammatory cytokines, such as interferon α/β, IP-10 [26-28].

A great number of studies have reported that TBK1 plays pivotal roles in inflammatory diseases, including atherosclerosis. These cumulative studies may provide the essential clues and insights needed for the development of therapeutic strategies against the various diseases involving TBK1 [29].

Established the significant role of TBK1 in inflammation, an increasing number of compounds that target TBK1 for the treatment of inflammatory diseases have been synthesized. For example, MRT67307 has successfully suppressed TBK1 activity with high specificity, without inhibiting other kinases.

Myocardial Infarction

Atherosclerosis as a persistent arterial disease is characterized by an imbalanced lipid metabolism and maladaptive immune response, resulting in subendothelial lipoprotein retention and endothelial activation with continuous migration of leukocytes and smooth muscle cells to the inflamed intima [30, 31].

Atherosclerosis is considered to be in the genesis of plaque formation, it's well known that it plays an important role in the weakening of the fibrous cap of the advanced plaque, eventually inducing plaque rupture and acute coronary syndromes. The plaque rupture can cause the artery occlusion and if so, the blood flow to the myocardium is compromised

resulting in myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia [32].
An intense organized inflammatory response with release of inflammatory cytokines, platelet activation and leukocytosis is triggered after myocardial ischemia and necrosis, this inflammatory response mediates the healing and scar formation leading ventricular remodeling.

Ventricular remodeling
Sudden coronary artery occlusion results in ischemic related death of cardiomyocytes [33]. The inflammatory response and cytokine release are essential components of the host response to acute myocardial infarction, and play an essential role in cardiac repair [34]. The initial remodeling phase after a myocardial infarction results in repair of the necrotic area and myocardial scarring that may, to a magnitude, be considered beneficial since there is an improvement in or maintenance of left ventricular function and cardiac output. Over time, however, the persistent activation of a variety of inflammatory molecules and pathways, such as the complement system, T cells, and the formation of auto-antibodies causes the heart to undergo remodeling, ventricular mass and volume increase, adversely affecting cardiac function.
Inflammation is the cornerstone of the post-MI healing process, participating in the physiological myocardial scar formation. However, in the case of an exuberant inflammatory reaction, the extent of the primary ischaemically damaged myocardial tissue may paradoxically increase, altering the long-term prognosis. Coronary angiography and percutaneous coronary intervention (PCI) have become the best modalities for the detection and the treatment of AMI. PCI provokes plaque fissuring leading to a vessel wall infiltration of lymphocytes and macrophages, both responsible for the post-PCI local vascular inflammatory response [35].
Frangogiannis et al [36] states that myocardial necrosis induces complement activation and free radical generation, triggering a cytokine cascade initiated by Tumor Necrosis Factor (TNF)-α release. The initiation of reperfusion of the infarcted area is attended by an intense inflammatory reaction. Interleukin (IL)-8 synthesis and C5a activation have a crucial role in recruiting neutrophils in the ischemic and reperfused myocardium.
A number of strategies have been suggested to diminish the harm caused by these inflammatory events but most have failed [37, 38]. The systemic administration of corticosteroids was shown to decrease infarct size in a canine model of experimental myocardial infarction [39]. This evidence led to a clinical study using methylprednisolone to treat patients with acute myocardial infarction, however the results of the trial were catastrophic, leading to an increased incidence of ventricular arrhythmias and extending infarct size [40]
Subsequent investigations suggested that corticosteroids inhibit the inflammatory process by decreasing the number of infiltrating leukocytes, but its effect also delays healing and collagen deposition [41]. At this stage there is a need for a better understanding of the events associated with myocardial ischemia at cellular and molecular levels in order to develop more site-specific interventions that could alleviate inflammatory response.

Conclusion
Various studies have pointed Inflammation as a major player in the pathogenesis of atherosclerosis, inflammation is also responsible for the weakening and rupture of fibrous plaque cap, leading to ischemia and consequently to acute coronary syndrome. Again inflammation plays an important role in cardiac repair and formation scar tissue, initiating cardiac remodeling.
We present a prospective analysis of the association between circulating levels of inflammatory markers, specifically CRP and TBK1 during atherosclerosis, Myocardial infarction and post-MI cardiac remodeling. Recently, potential and promising studies in the role of TBK1 in inflammatory response show that in inhibiting TBK1, there is a significant attenuation in the inflammatory response. However the lack clinical data to support these findings in Acute Myocardial Infarction and post-MI requires further research. We are currently in the process of asserting the correlation between the levels of these two inflammatory markers in Myocardial Infarction patients.

Abbreviation
TBK1: TANK-Binding Kinase 1
AMI: Acute Myocardial Infarction
MI: Myocardial Infarction
CRP: C-Reactive Protein
IL: Interleukin
TNF: Tumor Necrosis Factors
IFN: Interferon
IRF: Interferon Regulatory Factor
TLRs: Toll-like Receptors
NO: Nitric Oxide
TRAF3: TNF Receptor-Associated Factor 3
PCI: Percutaneous Coronary Intervention
TANK: TRAF (TNF (Tumor Necrosis Factor) (Receptor-Associated Factor)
NAK: NF-κB Activating Kinase
PGE2: Prostaglandin E2

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