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Review

Acute myocardial infarction leads to acceleration of atherosclerosis

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ABSTRACT

Patients who experience acute myocardial infarction (AMI) are at increased risk of recurrent events in the weeks to months following the initial event. The underlying etiology for this vulnerable period following MI is unclear but could be related to the same underlying triggers responsible for the initial MI. Alternatively, the recurrent cardiac event could be promoted by the incident event. For example, several biomarkers reflecting inflammatory activity have been shown to be elevated for weeks to months following MI and this inflammatory response could aggravate existing atherosclerotic lesions by accelerating their growth and/or promoting plaque instability. The purpose of this review is to highlight recent preclinical and clinical studies supporting links between AMI and atherosclerosis and to consider potential therapeutic interventions.

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1. Background

Myocardial infarction (MI) is the leading cause of mortality in many industrialized countries [1]. The substrate for MI is atherosclerosis and MI occurs at the site of pre-existing atherosclerotic lesions, usually following local plaque disruption with subsequent occlusive thrombosis [2]. In general, factors that promote atherosclerosis also promote myocardial infarction [3–8]. While therapeutic targeting of cholesterol with statins has been shown to prevent events and reduce progression of atherosclerosis, it is clear that other lipid-independent factors, such as inflammatory cytokines, also affect progression of atherosclerosis [4,9]. Atherosclerosis may be considered a chronic inflammatory disease with influx of leukocytes leading to plaque growth [10]. Factors that promote leukocyte proinflammatory activity may therefore lead to progression of atherosclerotic plaques. Identification of conditions in which the likelihood of MI is increased may uncover important novel triggers or pathways involved in the progression of atherosclerotic vascular disease.

2. Epidemiology

Survivors of AMI are at increased risk of subsequent MI [11]. As the initial MI identifies a subset of patients at high vascular risk, it may seem obvious that patients with MI are at higher risk than those without MI. However, the risk of recurrent MI is particularly high shortly after the incident event [11]. In the VALIANT [12] study, recurrent MI was studied in over 10,000 patients who had suffered an initial MI that was associated with left ventricular dysfunction or heart failure [11]. In just over 2 years of follow-up, 9.6% ($n = 861$) of patients suffered a recurrent MI. The median time to recurrent MI was 136 days following the initial event. However, the risk for

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recurrent MI was highest in the first month with the rate markedly declining over the first 3 months. The consequences of recurrent MI are particularly hazardous and in this study the mortality rate was 20.5% within 7 days of the MI. Patients who initially survived the recurrent MI continued to be at high risk for mortality with a greater than two-fold increased mortality during the subsequent year compared to patients without recurrent MI. One year mortality was 10.3% for the entire VALIANT cohort while the one year mortality was 38.3% in patients who experienced a recurrent MI. Thus, recurrent MI is common following hemodynamically significant MI's and these recurrent MI's are associated with high mortality rate.

3. Acute MI and biomarkers of inflammation

A broader understanding of the mechanisms underlying recurrent MI is necessary for application of appropriate therapeutic interventions. Current medical interventions such as statins are highly effective in reducing progression of atherosclerosis and also reducing the risk of recurrent MI [6]. Although contemporary medical treatments have reduced the risk of recurrent ischemic events, the risk remains high. For example, in a study of community dwellers from Olmstead County Minnesota, the risk of a recurrent ischemic event during a 3-year period following a MI was about 44% [13]. However, the risk of recurrent MI occurring after an incident MI occurring in 1998 was 32% lower than for subjects whose incident MI occurred in 1979.The ARIC (Atherosclerosis Risk in Communities) study has also suggested a temporal decline in the risk of recurrent MI [14]. Regardless of the year of the incident MI, the risk of a recurrent MI was particularly high in the first year following the incident MI. The high risk of MI in the weeks to months following an incident MI suggests that the myocardial injury secondary to the acute coronary atherothrombosis may have directly affected the subsequent event. It is also possible that unknown pathways responsible for the incident event are simultaneously affecting other lesions and thus causing a series of temporally related events. Biomarkers reflecting inflammatory activity following MI, including C-reactive protein, serum amyloid A, tumor necrosis factor-alpha (TNF-α), CCL2, CCL3, CCL5, CCL18, CXCL8, MIF, C1q/tumor necrosis factor-related protein-3, and others are elevated for days to months following the incident event [15–21] and elevations of many of these predict increased risk of recurrent MI [15,16]. This inflammatory response, in part secondary to the myocardial injury, could trigger leukocyte influx into atherosclerotic plaques and also promote plaque destabilization.

4. Preclinical studies suggesting a causal link between AMI and acceleration of vascular disease

To address the direct role of MI on progression of atherosclerosis, preclinical animal studies involving MI with various inflammatory and/or vascular endpoints have been performed. A myocardial proinflammatory response to MI has been well documented in the literature using preclinical models. In 1998, Ono et al. analyzed a rat model of MI [22]. Following induction of MI, TNF-α, interleukin-1β, and interleukin-6 peaked at 1 week after infarction in the infarct zone and then declined. Gene expression levels of these cytokines in the noninfarcted myocardium remained high up to 20 weeks following the infarct. Although this paper focused on the possible involvement of local cytokine expression towards adverse post-MI remodeling, this myocardial cytokine response could also be responsible for inducing the elevated levels of systemic biomarkers of inflammation reported following MI. The time course is consistent with myocardial expression of cytokines being the origin of the systemic inflammatory response.

The concept that myocardial infarction could affect a vascular process involving an artery remote form the infarct site was demonstrated by Takaoka et al. [23]. This paper focused on the potential contribution of MI on coronary restenosis after angioplasty/stenting. Therefore they used a mouse model of femoral artery injury induced by a spring wire to induce a smooth muscle cell-rich lesion characteristic of lesions responsible for restenosis following stent deployment. Neointimal hyperplasia was quantitated 4 weeks following the injury. These authors found that when MI was induced at the time of femoral injury, the neointimal hyperplastic response was augmented. Bone marrow transplantation with marrow from mice expressing green fluorescent protein (GFP) showed that while GFP positive cells contributed to neointimal hyperplasia following the wire injury alone, the marrow contribution was not directly responsible for the AMI-induced increase in lesion area. Using cDNA arrays, they found several proinflammatory transcripts in the injured femoral artery segments that were increased following AMI. Since some of these upregulated genes were TNF-α − responsive, the authors measured TNF-α mRNA from the infarcted hearts and found it to be elevated up to 28 days following the MI. This was associated with increased expression of the TNF receptor (TNFR1) at the site of femoral artery injury. Pentoxifylline treatment, which the authors showed reduced TNF-α synthesis was effective in blocking the effect of AMI on the augmentation of neointima. Thus, this paper importantly demonstrated that inflammatory pathways activated following MI, and probably originating from injured myocardium, were potent enough to accelerate the response to injury at a remote vascular site. Studies in human patients following MI who received coronary stents have demonstrated that a distinct monocyte subset (CD14 + CD16 + CX3CR1+) is correlated with restenosis within the stented segment [24]. Thus, changes in peripheral blood monocytes following MI may also contribute to adverse vascular events.

Since recurrent CV events following MI most likely reflect effects on the underlying substrate for MI, atherosclerosis, Wright et al. tested the impact of AMI in atherosclerotic-prone mice [25]. In this study, apolipoprotein E-deficient mice on a western diet underwent induction of anterior MI by LAD ligation. Six weeks later, atherosclerosis was compared between mice with MI and mice that underwent a sham LAD ligation procedure. Mice with experimental MI showed a 65% increase in aortic surface area occupied by atherosclerosis and a 2-fold increase in lesion thickness involving the aortic valves compared to sham-operated mice. Histologically, lesions augmented by MI showed large macrophage rich-areas. Consistent with a role of TNF-α, circulating levels of TNF-α were higher in mice with MI compared to sham-operated mice. To determine whether MI-induced changes in leukocytes which might promote leukocyte recruitment to atherosclerotic lesions, leukocyte–endothelial interactions were measured in cremaster venules and found to be increased. Thus, this paper demonstrated that AMI leads to acceleration of atherosclerotic plaque growth and that this is associated with features consistent with enhanced monocyte recruitment.

Most recently, in 2012, Dutta et al. [26] studied the effects of MI on atherosclerosis in apolipoprotein E-deficient mice. As early as 3 weeks following MI, plaque size had increased by 50% and this was associated with greater lesion protease activity and greater lesion area occupied by CD11b+ myeloid cells expressing higher levels of inflammatory genes. In mice following MI, monocytes were increased in the blood and spleen for up to 3 months following the MI, with no change in the bone marrow. These changes were also observed in humans that died following AMI. These observations suggested the spleen might be contributing to the post-MI leukocytosis. To specifically determine the role of the spleen in the augmentation of atherosclerosis following MI, splenectomy was