Sympathetic Nervous System
A Crucial Player Modulating Residual Cardiovascular Risk
Mahir Karakas, Wolfgang Koenig

Myocardial Infarction Accelerates Atherosclerosis
Dutta et al

Activation of the sympathetic nervous system after myocardial infarction results in the mobilization of hematopoietic stem cells, causing an inflammatory boost that accelerates atherosclerosis. This may have important implications for future therapeutic interventions targeting inflammatory pathways.

The social and economic impacts of atherosclerosis and subsequent macrovascular clinical manifestations like myocardial infarction (MI) and stroke are immense. Complications of atherosclerosis and MI, such as heart failure, and also recurrent cardiovascular events present a major challenge. They seem to occur more frequently after MI than expected by presumed linear progression of atherosclerosis. In a recent article in Nature, Dutta et al found strong evidence that, like in a vicious cycle, acute MI itself accelerates atherosclerosis by triggering a burst of acute systemic inflammation initiated by progenitor cell mobilization from the bone marrow niche.

The authors present 4 major findings: (1) acute MI (but also stroke) activates the sympathetic nervous system (SNS); (2) this causes the release of upstream progenitor cells from bone marrow niches; (3) these cells are hosted by the spleen leading to amplified extramedullary myelopoiesis; and (4) at the end of this multimodal cascade, there is a strong increase in inflammation in atherosclerotic plaques, leading to increased size and instability.

The authors also show that experimental MI in apolipoprotein E−/− mice activates inflammatory pathways. In serial measurements after coronary ligation, concentrations of cathepsin in aortic plaques and the expression of the inflammatory cytokines interleukin (IL)-6, myeloperoxidase, and matrix metalloproteinase-9 were increased. Consecutively, this was associated with higher vulnerability of atherosclerotic plaque, as demonstrated by decreased thickness of the fibrous cap, and enlarged necrotic cores. Moreover, after MI, the number of macrophages and monocytes, especially the Ly-6C<sup>high</sup> monocyte subset, were increased in the aorta of apolipoprotein E−/− mice and exhibited higher levels of messenger RNAs (mRNAs) encoding the inflammatory genes cathepsin B and IL-1β. Further analyses showed that MI causes extramedullary myelopoiesis. It increased the number of hematopoietic progenitor cells in the spleen but not in the bone marrow. These cells expressed a more pathogenic profile than other myeloid cells. This was essential in terms of acceleration of atherosclerosis, because MI did not cause progression of atherosclerosis in splenectomized mice. For instance, Ly-6C<sup>high</sup> monocytes isolated from the spleen on day 4 after MI expressed 60-fold higher mRNA levels of IL-1β and 6-fold higher mRNA levels of cathepsin B than Ly-6C<sup>low</sup> monocytes isolated from bone marrow. In the next step, the authors found that increased sympathetic tone after MI is directly involved in disease progression by mobilization of upstream progenitor cells from bone marrow niches with high capacity for self-renewal, thereby sustaining the proliferative activity after MI in the spleen. They convincingly could demonstrate that the level of the rate-limiting enzyme of noradrenaline, tyrosine hydroxylase, was increased in bone marrow of mice after MI. Also, levels of mobilization factors like CXCL12 (stromal cell-derived factor-1), angiopoietin, and stem cell factor increased, whereas levels of the adhesion molecule vascular cell adhesion protein-1 decreased after MI. In accordance with these findings, all effects could be reversed by administration of a β-adrenergic receptor blocker, and numbers of progenitor cells in the blood and the spleen thereby were strongly reduced. Furthermore, retrospective analysis in the Pravastatin or Atorvastatin Evaluation and Infection Therapy trial TIMI-22 trial by the present authors revealed that previous β-blocker therapy was associated with reduced number of monocytes after an acute coronary syndrome (Figure).

The rapid activation of the SNS after myocardial ischemia has been known for decades and is believed to represent a compensatory mechanism to improve or maintain cardiac output and systemic blood pressure during episodes of impaired ventricular function. The activation of β-adrenergic receptors in myocardial ischemia increases circulating levels of cyclic adenosine monophosphate and activates protein kinase B, and thereby enhances endothelial nitric oxide synthase phosphorylation and cardioprotective signaling through nitric oxide. Neurohormonal blockade is considered a cornerstone in the treatment of heart failure, and agents inhibiting the renin-angiotensin-aldosterone system have been shown to reduce morbidity and mortality after acute MI, especially in high-risk patients with heart failure. Recently, a Japanese group shed light on another possible underlying mechanism. They revealed a mechanism mediated by the central nervous system in which brain-derived neurotrophic factor promotes survival of cardiomyocytes, increases the expression of...
prosurvival and proangiogenic factors, and thereby has a protective role regarding cardiac remodeling after MI. In line with this finding, previous studies revealed that brain-derived neurotrophic factor promotes neovascularization by induction of vascular endothelial growth factor in response to hypoxic stimuli via the protein kinase B pathway and enhances capillary formation by recruiting proangiogenic hematopoietic cells.\textsuperscript{12–14} The authors showed that the activation of the SNS causes the release of upstream progenitor cells from bone marrow niches by influencing levels of homing and mobilization factors. This seems plausible, and a possible underlying mechanism has been described in 2006 by Katayama et al.\textsuperscript{11} These authors showed that the SNS regulates the egress of stem and progenitor cells from the osteoblastic niche. The stem/progenitor cell retention factor stromal cell-derived factor-1 is strongly expressed in osteoblasts, and norepinephrine signaling controls osteoblast suppression and subsequent downregulation of stromal cell-derived factor-1 in the bone, thereby mobilizing progenitor cells. In this setting, the administration of a β-adrenergic receptor blocker enhanced mobilization of bone marrow-derived progenitor cells in both control and norepinephrine-deficient mice. Subsequently, it has been shown that this catecholaminergic progenitor cell mobilization depends on Wnt stimulation, and recently Dimmelier et al demonstrated that MI-induced activation of Wnt signaling in the bone marrow mobilizes CD34\textsuperscript{+} and CD133\textsuperscript{+} cells.\textsuperscript{12–14} In accompanying experiments in mice, the induction of MI time-dependently increased the number of c-kit+/Sca-1+/lin\textsuperscript{−} cells and colony-forming units in the bone marrow. As described, activation of the SNS activates nitric oxide metabolism. In a mouse model of femoral artery ligation, activation of SNS and increasing levels of norepinephrine enhanced the number of bone marrow-derived cells in ischemic tissue by 70% and promoted their ability to differentiate into cells with endothelial and inflammatory phenotypes.\textsuperscript{15} Angiogenesis and the infiltration of inflammatory cells in hypoxic areas are critical processes in organ response to ischemic injury. A previous study demonstrated that hind limb ischemia increases numbers of both Ly-6C\textsuperscript{high} and Ly-6C\textsuperscript{low} monocytes via monocyte chemotactic protein-1 activation, but vessel growth and blood flow recovery in ischemia are mainly based on Ly-6C\textsuperscript{high} monocytes.\textsuperscript{16} Besides monocytes, hematopoietic progenitor cells are released to the blood in response to inflammation and ischemia. As Si et al\textsuperscript{17} showed, this process depends on the expression of inflammatory cytokines. In aseptic inflammation, only lin\textsuperscript{−}/c-kit\textsuperscript{+} cells from wild-type mice, but not from chemokine knockout mice, were recruited to sites of inflammation.

Given the complex pathophysiology of cardiometabolic disease, various circulating markers representing inflammatory pathways have been investigated regarding their potential to improve risk prediction. Currently, the largest database exists for C-reactive protein, the classical acute phase protein.\textsuperscript{18} C-reactive protein rapidly responds to various upstream pro-inflammatory cytokines like IL-6 and IL-1, is elevated during atherogenesis, serves as a marker of ongoing atherosclerosis, and finally predicts its clinical complications. Among patients with acute MI and stable post-MI patients, there is strong and consistent evidence for C-reactive protein as a predictor of recurrent events.\textsuperscript{19,20} Similarly, circulating levels of myeloperoxidase, also an important player in the acceleration of atherosclerosis after MI, have been shown to predict cardiovascular events.\textsuperscript{21} It has been known that myeloperoxidase is present within atherosclerotic plaque in human arteries and contributes to atherogenesis by catalyzing oxidative reactions in the vascular wall.\textsuperscript{22} The new aspect presented here is that, as evidenced by serial measurements, MI boosts myeloperoxidase concentrations in atherosclerotic plaques.

The authors present a provocative study that may help to understand stem cell niche alterations induced by MI that have a critical impact on the composition and functional activity of mononuclear cells. They expand previous findings and, for the first time ever, show that relocation of c-kit+/Sca-1+/lin\textsuperscript{−} (Flk2\textsuperscript{−}) cells from the bone marrow to the spleen only occurs if mice have undergone coronary ligation. The novelty of the presented work is that it demonstrates that the beneficial short-term effects of SNS activation and progenitor cell mobilization are counterbalanced by adverse long-term effects. Therefore, the study of Dutta et al also may have important clinical implications. Although the administration of bone marrow-derived cells in hematologic disorders demonstrated excellent safety with respect to acute adverse cardiovascular effects, and although this also was demonstrated in controlled clinical trials of acute MI, this might not hold true for the long-term.\textsuperscript{23} Accordingly, retrospective hematologic studies showed that in long-term survivors, the risk for premature atherosclerosis increases over time, especially after allogeneic hematopoietic stem cell transplantation, and it is clearly higher than in the age-adjusted general population.\textsuperscript{24} In the retrospective multicenter European Group of Blood and Marrow Transplantation, the median age at occurrence of a cardiovascular event was fairly low at 54 years, and it was shown that the risk was mainly driven by the presence of ≥2 established cardiovascular risk factors.\textsuperscript{25} Dyslipidemia, diabetes mellitus, physical inactivity, smoking, and arterial hypertension were more common among patients treated with allogeneic hematopoietic stem cell transplantation than among leukemia patients or healthy controls, and they might be promoted by prolonged, intensified immunosuppressive treatment or might be because of late organ effects after transplantation, such as decreased growth hormone secretion in children, or hypothyroidism.
This progenitor cell–mediated inflammation also may explain the heterogeneous results among various cardiovascular cell transplantation trials and the mostly negative midterm results. Moreover, based on the findings in the highlighted article, one may hypothesize that long-term adverse effects of cardiovascular progenitor cell therapy might neutralize its initial benefits or even induce disease progression. In contrast to this hypothesis, 5-year results of the Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction trial, the first randomized study investigating the effects of intracoronary infusion of circulating or bone marrow-derived progenitor cells in 59 patients with successfully reperfused acute MI, showed that although 16 of 55 patients underwent target vessel revascularization, only 2 target vessel revascularizations occurred later than 1 year after cell administration, thus not directly favoring the hypothesis of cell therapy–induced atherosclerotic disease progression.26

Finally, the study provides important information supporting the rationale for several planned or ongoing clinical trials evaluating the inflammation hypothesis in post-MI patients. These trials will test whether anti-inflammatory therapy carries clinical benefit for the high-risk patient with cardiovascular disease. In 2008, the Stabilization of Atherosclerotic plaque by Initiation of Darapladib Therapy (STABILITY) trial (NCT00799903) was initiated. In a randomized, double-blind, placebo-controlled, multicenter clinical outcome trial in 15,828 patients with chronic coronary heart disease, darapladib, a specific inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂) will be assessed in addition to standard coronary heart disease pharmacotherapy, and final results of the study may be available next year. The inhibition of Lp-PLA₂ reduces the generation of proatherogenic and proinflammatory compounds from oxidized low-density lipoprotein cholesterol in the vessel wall, namely lyso-phosphatidylcholine and oxidized free fatty acids, and thus may lead to plaque stabilization. The primary outcome measure is determined as time to first occurrence of any component of the composite of major adverse cardiovascular events, consisting of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. This trial is complemented by the Stabilization of Plaques Using Darapladib–myocardial infarction, and nonfatal stroke. This trial is composed of any component of the composite of major adverse cardio–wall, namely lyso-phosphatidylcholine and oxidized free fatty

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