Published in final edited form as:

Nat Med. 2014 July ; 20(7): 707–708. doi:10.1038/nm.3631.

Stressing out hematopoietic stem cells in cardiovascular disease

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Abstract

Stress has long been thought to be a major contributing factor to cardiovascular disease, although little is known about the underlying cellular mechanisms. A new study illustrates that chronic stress promotes hematopoietic stem cell proliferation in bone marrow, leading to increased leukocyte production, circulation, and recruitment to the vasculature.

Hassled by work deadlines? Have a hectic daily schedule? Struggling to maintain your work-life balance? For most of us, this is the norm. Our daily lives are filled with stressful situations. Many clinical and experimental studies over the past few decades have linked chronic psychosocial stresses to increased incidence of infections ¹ and disease ². Epidemiological studies in humans have linked social stressors to the development of cardiovascular diseases ^{3–5}, including atherosclerosis, myocardial infarction, and stroke. In animal models, Kaplan *et al.* first reported that social stress increased atherosclerosis in monkeys independently of plasma cholesterol levels ⁶. Other studies showed that social stress, but not physical stress, accelerated atherosclerosis development in mice ^{7–9}. However, the mechanisms for how stress makes our cardiovascular system sick are largely unknown. In this issue of Nature Medicine, Heidt *et al.* elegantly show that chronic stress activates (i.e., stresses out) hematopoietic stem cells (HSC) in the bone marrow, causing them to generate increased numbers of leukocytes that travel into the blood circulation and contribute to development of cardiovascular disease (Fig. 1).

In this study, Heidt and colleagues asked if chronic stress could change HSC activity and if so, could this contribute to an increased risk of atherosclerotic plaque development or myocardial infarction? They first explored the impact of stress on myeloid cell production in humans by studying a highly stressed group of individuals: on-duty medical residents working in a hospital intensive care unit (ICU). Compared to being off-duty, medical residents actively working in the ICU had higher perceived stress perception when tested ¹⁰, and examination of their peripheral blood showed an increase in numbers of leukocytes, with higher numbers of neutrophils, monocytes and lymphocytes present.

To further address these findings, the group decided to study stressed mice. They found that chronically stressed mice also had increased numbers of neutrophils, monocytes and lymphocytes in their blood, extending their observations in humans. Further, they discovered that chronic stress caused proliferation of HSC, which increased the numbers of committed myeloid and lymphoid progenitor cells present in mouse bone marrow.

Mechanistically, they focused on the sympathetic nervous system, which produces norepinephrine and other catecholamines during stress¹¹. Norepinephrine release from the sympathetic nervous system has been associated with increased leukocyte trafficking in neuroinflammation¹². Previous studies have shown that norepinephrine also regulates circadian HSC migration¹³. The production of norepinephrine is controlled by the activity of the enzyme tyrosine hydroxylase¹⁴. Heidt and coworkers found increased expression of both tyrosine hydroxylase and norepinephrine in bone marrow of stressed mice. Consistent with the known role of norepinephrine as a primary repressor of synthesis of the chemokine CXCL12, they also reported a drastic reduction in CXCL12 protein in the bone marrow of stressed mice. CXCL12 functions in the bone marrow to control HSC proliferation¹⁵ and retain leukocytes in the bone marrow¹⁶. As a result of reduced CXCL12, bone marrow progenitor cells were able to proliferate excessively, produce more leukocytes and these leukocytes were released more readily into the blood circulation.

β -adrenergic receptor expression on bone marrow niche cells regulates CXCL12 release, which further links the sympathetic nervous system to leukocyte trafficking¹³. Within bone marrow niches, β 2 receptors are highly expressed in osteoblastic lineage cells, while β 3 receptors are highly expressed in mesenchymal stromal cells. Heidt *et al.* focused on β 2 and β 3 adrenergic receptor signaling in the bone marrow as a mechanism to control hematopoiesis in response to stress. The authors found that mice that lacked the β 3-adrenergic receptor (*Adrb3*^{-/-}) were protected against the effects of chronic stress with no changes in HSC proliferation, CXCL12 production, or blood leukocyte numbers. Similarly, treatment of mice with a β 3-adrenergic receptor antagonist protected them against stress-induced changes in hematopoiesis, while treatment with a β 2-adrenergic receptor antagonist had no effect.

Finally, the authors asked how these hematopoietic changes in response to chronic stress impacted atherosclerosis. Would there be an increase in leukocyte supply to the vessel wall and increased atherosclerotic plaque development in response to chronic stress-induced hematopoiesis? Decades of research have shown that monocyte interactions with the vascular endothelium are key early events in atherogenesis, and that high circulating monocyte and neutrophil levels correlate with increased risk of cardiovascular disease.^{17,18} Examination of stressed atherosclerosis-susceptible ApoE^{-/-} mice showed an increase in HSC proliferation, with no changes in body weight or plasma lipoprotein cholesterol levels after 6 weeks of induced stress and high-fat diet feeding. Confirming that stress increased leukocyte recruitment to the vasculature, the authors observed an increase in numbers of neutrophils and Ly6C⁺ classical monocytes recruited to aortas of stressed ApoE^{-/-} mice. Correspondingly, after 6 weeks of chronic stress, fluorescence (FMT/CT) imaging of the mouse aorta showed an increase in plaque protease activity, and analysis of aortic arches showed increased matrix metalloproteinase 14 and myeloperoxidase (a neutrophil marker) content in the plaque. Surprisingly, the authors found that aortic root plaque size as a measure of atherosclerosis did not change in the stressed mice, but the characteristic features of the lesions were dramatically changed. The atherosclerotic lesions in the stressed mice had thinner fibrous caps (likely related to increased protease activity) and larger necrotic

cores, both of which are hallmarks of rupture-prone lesions that cause acute MI or stroke. These stress-induced effects were negated by β 3-adrenoreceptor blocker treatment.

The studies by Heidt *et al.* have clear clinical implications because they suggest that selectively targeting β 3-adrenergic receptors may protect against leukocyte-mediated inflammation associated with atherosclerosis and MI. β 1 and β 2 blockers are routinely used for the prevention and management of MI and stroke. However, β 3-adrenergic receptor blockers currently have limited clinical applications¹⁹. Further studies are needed to determine if selective β 3-blockers could have similar effects in reducing stress-induced leukocyte production in humans, and if so, whether they would be useful future therapies for MI or stroke.

As leukocytes themselves express β -adrenergic receptors, learning how β -adrenergic receptor signaling directly impacts leukocyte function in the vasculature is of interest. Prior studies by Born *et al.* have shown that CD14dim nonclassical monocytes express β 2-adrenergic receptors and rapidly appear in circulation from vascular marginal pools in response to catecholamine release. However, such demargination largely occurs in response to acute stress and is distinct from the bone marrow HSC responses reported by Heidt *et al.* in this issue. Nevertheless, such studies suggest that leukocytes directly respond to stress hormones. In support of the notion that stress can impact the function of leukocytes in the vasculature, recent studies reported that human monocytes isolated from stressed individuals showed elevated pro-inflammatory gene expression²⁰. Further, these investigators found that treatment of stressed mice with the non-selective beta adrenergic receptor blocker propranolol dramatically reduced inflammatory gene expression in monocytes²⁰, suggesting that monocyte inflammatory responses are regulated, at least in part, by stress and beta-adrenergic signaling. Taken together, such studies and the studies by Heidt *et al.* indicate that both the production and trafficking of leukocytes and their functions in the vasculature are impacted by chronic stress.

The work of Heidt *et al.* is a big step in understanding how chronic stress contributes to cardiovascular disease, and the mechanisms explored in this work are likely to be relevant to other diseases that have an inflammatory component. So, slow down, take a deep breath, and relax.

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Fig. 1.