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Bad matters made worse

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Abstract

Heart attacks occur when lipoprotein-driven inflammation called atherosclerosis triggers blood clotting in the arteries. It seems that the attacks can, in turn, accelerate atherosclerosis by fanning the inflammation.

Heart attack, or myocardial infarction, is a leading cause of morbidity and mortality worldwide, and people who have had one infarction are at increased risk of another in the first year or so after the attack¹. Myocardial infarction results from acute, occlusive thrombosis (blood clots) within the coronary arteries. These clots form at sites of atherosclerosis, a chronic disease process in which fat and cholesterol build up along the artery walls². Atherosclerosis starts when circulating fat-carrying particles called lipoproteins, most notably low-density lipoprotein (LDL), are retained in the subendothelium, a tissue layer in the artery wall³. This induces an inflammatory response that involves the influx of immune cells called monocytes, which differentiate into other inflammatory-cell types, including phagocytic cells called macrophages and dendritic cells^{3,4}. On page 325 of this issue, Dutta *et al.*⁵ show that in mice with atherosclerosis, myocardial infarction leads to increased monocyte recruitment and enhanced atherosclerosis. If these processes are similarly linked in humans, the findings may have implications for therapeutic strategies in human heart disease.

The idea for this study came from the observation that a high monocyte count in the blood after myocardial infarction is a risk factor for repeat infarction, and that, in mice, infiltrating spleen-derived monocytes have a role in atherosclerosis⁶. If there is a cause-effect relationship between monocyte count and atherosclerosis, this would suggest that the number of circulating monocytes, particularly monocyte subclasses that are especially inflammatory, could be a rate-limiting factor.

To explore these issues, Dutta and colleagues used a mouse model of atherosclerosis in which the mice lack apolipoprotein E (APOE), a protein that facilitates the removal of certain types of atherosclerosis-promoting lipoproteins from the blood. The mice were also fed a high-cholesterol diet. Mice do not normally develop atherosclerosis because they have low levels of atherogenic lipoproteins, but the combination of a high-cholesterol diet and the absence of APOE in this model induces atherosclerosis. However, even this robust model does not cause acute thrombosis and myocardial infarction, probably owing to several physical and biochemical factors. So the authors modelled heart attack in the atherosclerotic mice by clamping shut their left coronary artery.

Within 1–3 weeks after myocardial infarction, the atherosclerotic lesions in the aortas of the ‘heart attack’ mice were approximately 40% larger than those in sham-operated animals, which had atherosclerosis but had not undergone infarction. The mice with infarction also had elevated blood monocyte counts, and the lesions themselves contained greater numbers of inflammatory cells and showed signs of disease progression, including larger regions of

dead cells (necrosis). Furthermore, the authors provide evidence that the sympathetic nervous system (SNS) was activated in the mice following myocardial infarction, and that this led to an expansion of monocytes in their spleens. This was followed by monocyte delivery to the blood (a process called monocytosis) and then to the atherosclerotic lesions (Fig. 1). The SNS is associated with the 'fight or flight response', so it may be that in humans, and perhaps in this mouse model, SNS activation following myocardial infarction is a response to pain, anxiety and an acute decrease in heart function. The authors also showed that splenectomy or drug-induced blockade of the SNS lowered post-infarction monocytosis in the mice, although they did not report whether these interventions affected progression of atherosclerosis *per se*.

Might this process of heightened susceptibility following myocardial infarction also be important in humans? The mouse model used by Dutta *et al.*⁵ has many obvious differences to human disease, most notably the absence of atherosclerosis-driven acute thrombosis or infarction, and the possible confounding effects of the absence of APOE, which has several other biological actions besides lipoprotein clearance. However, the atherogenic process itself is similar to that which occurs in humans, and the links to post-infarction monocytosis and SNS activation in humans add relevance.

Even so, the mechanism underlying post-infarction susceptibility in humans is likely to be multifactorial. For example, heightened systemic and cardiac inflammation could fuel the inflammatory response by mechanisms over and above raising monocyte numbers, and biological changes induced by the occluded artery or by tissue damage sustained in the attack might alter the subendothelium of nearby arteries in ways that promote lipoprotein retention. It should also be remembered that heart attacks often indicate the presence of environmental and/or genetic risk factors, and so are probably a marker of individuals predisposed to accelerated atherosclerosis due to a variety of factors beyond the actual infarction event.

The possibility that an SNS–spleen–monocyte pathway of accelerated atherosclerosis contributes to the increased risk of repeat events after heart attack could add perspective to current therapeutic strategies and suggest new ones. Several clinical trials have shown that post-infarction administration of high doses of statins — drugs that lower blood levels of LDL — have a substantial protective effect against repeat infarction. Reduction of LDL would be expected to interrupt the atherosclerotic process in the post-infarction period, as it does in other settings. However, some researchers interpret this rapid effect of statins as indicative of other mechanisms, such as anti-inflammatory activity, which is known to be a property of statins⁷. Low levels of high-density lipoprotein (HDL), a risk factor for myocardial infarction, have also been linked to increased monocytosis and atherosclerosis⁸, so the current study could inform current human therapeutic trials designed to raise plasma HDL. It would also be interesting to assess whether beta-blocker drugs, which are often given to patients following heart attack, have any effect on monocytosis and atherosclerosis progression.

Finally, although therapeutic strategies aimed at lowering monocyte numbers may have broad benefit in blocking the progression of atherosclerosis, their applicability could be tempered by the fact that post-infarction monocytosis could also have a role in healing the damaged heart muscle⁹ (Fig. 1). Indeed, this previous finding, in the context of Dutta and colleagues' study, raises the fascinating question of why these monocytes help tissue healing in infarcted heart muscle but worsen atherosclerosis. A crucial healing function of monocyte-derived phagocytes is in the clearance of dead cells¹⁰. It is possible that dead cells in atherosclerotic lesions are less easily recognized by the newly arriving phagocytes than are dead cardiac muscle cells. Alternatively, when the post-infarction phagocytic cells enter

the lesions, they may be exposed to factors that impair their ability to clear dead cells — factors that would not be present in the infarcted heart muscle. Thus, although it is likely that inflammation and monocytoysis have several roles in the response to heart attack, further understanding of these processes is needed to intelligently translate these concepts into new therapies.

References

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Figure 1. A cycle of damage and repair

During atherosclerosis, fat-carrying lipoproteins are retained in the artery wall. This induces an inflammatory response that is characterized by an influx of immune cells called monocytes, which differentiate into other inflammatory cells, such as macrophages and dendritic cells. Blood clots at sites of atherosclerosis can block the arteries and cause heart attacks. In a mouse model of atherosclerosis, Dutta *et al.*⁵ show that heart attack activates the sympathetic nervous system (SNS), and that this promotes monocyte production in the spleen. The authors demonstrate that the monocytes move from the spleen to the blood and then to atherosclerotic lesions in the arteries, where they accelerate the progression of these lesions (red arrow). However, monocytes are also likely to be important in the repair of heart muscle tissue (green arrow) following heart attack⁹, and this dual role could complicate attempts to treat post-heart-attack atherosclerosis by targeting monocytes.