PERSPECTIVE

Coronary artery disease
What is the role of inflammation?

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The increasing evidence that inflammation plays a crucial role in atherosclerosis has led to considerable interest in potential implications for clinical practice. These include the role of inflammatory markers in predicting CVD risk and the development of novel therapies to target vascular inflammation.

Key points

- **Cardiovascular event rates remain high despite currently available therapies to lower blood pressure and reduce cholesterol.**
- **Inflammation plays a crucial role in atherosclerosis.**
- **There is great interest in the role of inflammatory markers on cardiovascular disease risk.**
- **Imaging modalities have been developed to both identify and quantify inflammation in atherosclerotic plaques.**
- **Novel agents targeting specific inflammatory mediators have not yet proved beneficial, but several large trials are ongoing.**

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Over the course of the past three decades, randomised controlled trials have shown that lowering blood pressure and cholesterol levels have a favourable impact on cardiovascular events.[1-6] Accordingly, these measures have been increasingly integrated into our approach to both primary and secondary prevention. However, there continues to be a high rate of cardiovascular events despite these interventions. This suggests that additional targets must be identified to achieve more effective reductions in cardiovascular risk in individuals with traditional risk factors that are well controlled.

Role of inflammation in atherosclerosis

A large body of experimental evidence has elegantly defined the role of inflammation in the pathogenesis of atherosclerosis.[7] In the early stages of the disease process, expression of proinflammatory adhesion molecules and chemokines are evident on the endothelium.[8] These factors promote the adhesion of circulating monocytes and their ultimate migration into the artery wall.[9] Under the control of a range of stimulating factors, these monocytes become macrophages, which engulf oxidised lipid to become foam cells, the cellular hallmark of the growing atherosclerotic plaque.[10] Foam cells play a pivotal role in the orchestration of plaque formation by elaborating a series of factors that promote ongoing accumulation of lipid and inflammatory and smooth muscle cells within the vessel wall.[11] In parallel, a strong fibrous cap is formed through the synthesis of collagen overlying the mature plaque.

For patients with acute ischaemic syndromes, a series of events takes place that transforms this mature plaque to an unstable one, evidenced by the breakdown of the fibrous cap and contact between circulating blood and plaque contents.[12] This is a highly thrombogenic environment, leading to activation of platelets and the coagulation cascade, luminal thrombosis and compromise of the vascular supply to the tissue bed. Pathology studies have demonstrated that unstable plaques typically contain more lipid, inflammatory and necrotic

material than plaques that do not rupture and remain clinically silent.[13]

In addition to the important role played by the monocyte/macrophage system in this series of events, there is increasing recognition that other inflammatory cells, including neutrophils, lymphocytes and mast cells, are also contributors to the progression of atherosclerotic disease. The understanding of how these inflammatory cells enter the artery wall has become increasingly complex. In addition to the traditional view that this influx typically involves migration across the endothelium, there is increasing interest in the role that the adventitial and adipose tissue surrounding the blood vessel plays in this process. In fact, it may be that a considerable amount of the inflammatory activity responsible for the ultimate progression of atherosclerotic disease is generated from outside the blood vessels.[14]

Inflammatory markers and cardiovascular risk

As pathology reports have provided increasing evidence for the role of inflammation in the disease process, there has been considerable interest in the potential implications for clinical practice. Several groups have investigated the role of circulating inflammatory markers in the prediction of cardiovascular risk. Measurements of C-reactive protein (CRP) using a high-sensitivity assay have been widely used in this research, with consistent reports that elevated CRP levels are associated with an increased risk of cardiovascular events in primary and secondary prevention settings.[15] Such observations have been translated to clinical trials, which have demonstrated that the clinical benefits of statins and aspirin are much greater in patients with elevated CRP levels at baseline and that the degree of CRP lowering is associated with the extent of their benefit.[16,17] This provided the impetus to perform the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, in which rosuvastatin was found prospectively to produce cardiovascular benefit in lower-risk patients with elevated CRP levels.[18]

It remains to be determined whether CRP plays a role in the disease process or simply reflects a marker of systemic inflammation. Nevertheless, there has been considerable interest in the investigation of circulating markers of factors that do play a role in inflammation within the artery wall, such as myeloperoxidase and secretory phospholipase A2, as alternative risk prediction markers.

Novel imaging modalities to detect inflammation

In addition to the study of inflammatory factors within the blood, novel imaging approaches have been developed to characterise the inflammatory activity within the plaque. Given the fundamental role of inflammation in distinguishing a stable from an unstable plaque, invasive (intravascular ultrasound, optical coherence tomography, near infrared spectroscopy) and noninvasive (magnetic resonance imaging, computed tomography) imaging modalities have been used to distinguish inflammatory components within atherosclerotic plaques.[19-25] Hybrid imaging with computed tomography to localise plaque and measure fluorodeoxyglucose uptake permits evaluation of the degree of inflammatory activity within that lesion.[26] Although this imaging technique is well validated in histology studies, how this will be implemented in clinical practice is unclear.

Novel therapies to reduce vascular inflammation

Given the diverse evidence implicating inflammation in atherosclerosis, there is hope that a novel antiatherosclerotic therapies that directly target one of these molecular pathways can be developed. Several established treatments for patients with atherosclerosis, including aspirin, ACE inhibitors and statins, have anti-inflammatory properties in addition to their respective antiplatelet, antihypertensive and lipid-modifying properties. However, to what extent their clinical benefit is attributable to their anti-inflammatory effects alone is yet to be established.

In recent years, several agents that target inflammatory mediators of atherosclerosis, have progressed in clinical development but not all findings have been positive. Secretory phospholipase A2 (sPLA2) generates bioactive mediators of inflammation in the artery wall, with evidence of a pathological role in the disease process and reports that systemic levels predict cardiovascular risk.[27,28] An outcome trial in patients with acute coronary syndrome recently showed that the sPLA2 inhibitor, varespladib, not only did not reduce cardiovascular events, but in fact increased the rate of myocardial infarction.[29] Similarly, darapladib, which targets the lipoprotein associated form of phospholipase A2, was found to have no clinical benefit in patients with either stable coronary artery disease[30] or acute coronary syndromes (unpublished outcome data from the SOLID-TIMI 52 trial).[31]

A number of large clinical trials continue to proceed evaluating the impact of alternative approaches to targeting inflammation, including interleukin-1 antagonists and methotrexate. It remains to be determined whether they will work, whether inflammation is too complex to treat in patients with atherosclerosis and whether the correct patient in which to use such agents can be identified.

Conclusion

The large residual risk despite successful targeting of the major traditional cardiovascular risk factors highlights the need to develop better risk markers and approaches to both disease prevention and treatment. The inflammation story has been fascinating to observe because it has revealed elegant insights into the mechanisms underlying cardiovascular disease. How it translates to interventions that change health outcomes remains to be determined. **CT**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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