



Inflammation in atherosclerosis: casualty or causality?

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The past 30 years have seen dramatic advances in molecular immunology resulting in the delivery of transformational disease-modifying therapies for rheumatoid arthritis and other ailments in which inflammation plays a pathogenic role. This therapeutic revolution has had little impact on our specialty, apart from highlighting that suppressing inflammation can increase the incidence of cardiovascular events! I find this surprising because inflammation is such a prominent histopathological feature of complex atherosclerosis; epitomized by the foam cell. The difficulty is we are still not sure if this inflammation is adaptive, maladaptive, or merely a bystander.

In reading through this issue I was reminded of a visit to Germany that coincided with an industrial accident during which toxic effluent had polluted the Rhine. There was an amusing anecdote circulating among my colleagues that the manager of the factory suspected of causing the accident had tried to blame the dead fish, "it's not our chemicals that have caused the damage but those stinking dead fish". This issue of *Heart and Metabolism* is grappling with a similar issue, are foam cells and other manifestations of inflammation merely dead fish?

A good place to start this issue is the article "Macrophages: cause or cure in atherosclerosis?" by Martin Bennett. The article provides a clear and concise overview of macrophage biology and highlights recent advances in our understanding of subtypes with specific properties. These macrophage subtypes may have diametrically opposing effects on atherosclerotic plaque progression, causing divergent findings and confusing the unwary. Complicating matters further is the ability of a macrophage to morph between types. Conse-

quently, macrophages can both promote and prevent atherosclerotic plaque progression.

The other article that provides an improved understanding of basic immunology is the Refresher corner by Sidney Shaw on innate immunity. This article deals with the subject of sterile inflammation triggered by damage to normal cellular constituents. As a result of this damage, cellular lipids, proteins and nucleotides are changed to resemble those found in pathogens. These danger-associated molecular patterns are then recognized by the primitive innate immune system, principally through five families of receptors that are described in detail. The activation of these receptors then triggers a shared proinflammatory signalling network outlined in Figure 1. Once again it is unclear if such inflammation is harmful, and there seems little doubt that in many circumstances, such as immediately after acute myocardial infarction, it is required for tissue clearance and mature scar formation.

Despite the uncertain role inflammation plays in atherosclerosis much effort is being expended to image the vasculature in order to identify plaques vulnerable to rupture. Such plaques are metabolically active and this may manifest through high glucose utilization and/or active calcium deposition. These processes may be visualized using positron emitting ^{18}F as a sodium salt (behaves like calcium) or covalently linked to deoxyglucose (behaves like glucose). Positron emission tomography lacks spatial resolution and does not highlight the adjacent "cold" tissue needed for anatomical interpretation of the images. As described in the article by Drs Joshi, Chowdhury and Rudd, this can be provided quickly and at high resolution by coincident computed tomography scanning. Such techniques are

now being used as surrogate endpoints in clinical trials of agents that may protect against atherothrombosis as efficacy can be inferred in advance of the investment needed to deliver a phase III trial with relevant clinical endpoints such as myocardial infarction, stroke and the need for revascularization.

Such trials bring us nicely on to the articles "The role of inflammation in atherosclerosis: what we have learned from clinical trials" by M. Al-Hawwas and J.-F. Tanguay and "Secretory phospholipase: a potential target for cardiovascular therapies" by S. J. Nicholls and M. Duong. The article by Drs Al-Hawwas and Tanguay provides a comprehensive overview of phase II/III clinical trials currently being undertaken that involve anti-inflammatory strategies. The article by S. J. Nicholls and M. Duong is similar but concentrates on the phospholipase inhibitors. What is clear is that inflammation is a very active area of research, with a number of companies convinced it plays a pathogenic role in atherosclerosis. As explained by Drs Al-Hawwas

and Tanguay, our current standard treatments, such as statins, probably work partly by suppressing inflammation. New agents would thus have to show benefit over and above the standard therapies that may already be acting on these pathways. Furthermore, as also discussed by Drs Al-Hawwas and Tanguay, standard anti-inflammatory drugs such as non steroidal anti-inflammatory drugs and prednisolone seem to increase, rather than decrease, cardiovascular risk.

I realise that the flavour of this Editorial is sceptical and questions the view that inflammation plays the role of bad guy in atherosclerosis. The best evidence for this comes from the Case report by Catriona Maybury and Catherine Smith and from the article by Malek Al-Hawwas and Jean-François Tanguay. Both sets of authors point out that chronic inflammatory disease is associated with accelerated atherosclerosis. This is best illustrated by allograft vasculopathy affecting the transplanted heart. Perhaps inflammatory cells are not that fishy after all? ■