Atheroimmunology: keeping the immune system in atherosclerosis in check

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The immune response is not unlike a game of chess, with white and black pieces playing opposing roles and orchestrating an opening, a middle and an endgame of innate immunity, adaptive immunity and resolution, respectively. After decades of research, the study of atheroimmunology has brought the first therapeutics to the clinic. Can we resynchronize the immune system in atherosclerosis and save the king?

Atherosclerosis is a lipid-driven, non-resolving inflammatory process with features of autoimmunity. In physiological host defence, the immune response is deployed in a spatially and temporally regulated manner, in which acute inflammation reaches its most effective magnitude and is then actively resolved. In atherosclerosis and other chronic inflammatory diseases, this biphasic process of inflammation and resolution is lost, and the immune system is effectively out of sync. This situation leads to the concurrent activation of both pro-inflammatory and anti-inflammatory pathways and a bewildering heterogeneity of immune cell states in the atherosclerotic plaque[1,2], resembling the intricate balance of power of pieces on a chessboard.

Low-dose colchicine (an anti-inflammatory agent that is approved by the FDA) and canakinumab (a monoclonal antibody against IL-1β) are effective for the secondary prevention of cardiovascular events in patients with residual inflammatory risk, as detected by high-sensitivity assay for plasma C-reactive protein levels, despite guideline-

recommended treatment (lipid-lowering and blood pressure-lowering drugs) for traditional cardiovascular risk factors. With the advent of clinical trials demonstrating the clinical potential of targeting the immune system in atherosclerosis, advances over the next 5 years will have a transformative effect on the way that we conceptualize and treat this condition. The five Review articles[3-7] in this Focus issue of *Nature Reviews Cardiology*, marking the 20th anniversary of the journal, herald a deepening of the discussion on how and why we need to target the immune system in atherosclerosis.

Although the presence of immune cells had been observed in atherosclerotic plaques since the time of Rudolf Virchow (1821–1902), the field of 'atheroimmunology' — the role of the immune system in atherosclerosis — was set in motion when Göran Hansson isolated T cells from human atherosclerotic plaques and demonstrated that antigen presentation occurred in human atherosclerotic lesions. Soon after, Attilio Maseri and Paul Ridker developed the study of systemic inflammation in acute coronary syndromes and cardiovascular risk, respectively. Next, the role of innate immunity in atherosclerosis came to the fore. Cytokines such as IL-1β were shown to induce important changes in vascular smooth muscle cells, and the production of IL-1β in the atherosclerotic plaque was later shown to be derived from inflammasome activation in macrophages by cholesterol crystals (see Fig. 1 and the accompanying references in the Supplementary information). These studies laid the foundation for the CANTOS trial[8], which showed that the blockade of IL-1β with canakinumab reduced the risk of cardiovascular events in a secondary prevention setting, particularly in patients who had a significant reduction in plasma levels of C-reactive protein in response to therapy. The interaction between inflammation and lipid metabolism is crucial to the establishment of pro-inflammatory, lipid-associated macrophages[1].

Activation of the adaptive branch of the immune system and autoimmunity features of atherosclerosis also became evident[3], including restricted T-cell receptor usage and the

generation of autoantibodies against lipoproteins, signifying a degree of loss of tolerance to lipoproteins during atherogenesis. B cells have an important role in atherogenesis[9], and selectively targeting these cells might offer therapeutic options. Immune checkpoints such as CD40 emerged as being central in regulating the immunological synapse (the interface between an antigen-presenting cell and a lymphocyte) and driving atherogenesis[10]. Previously, we generally conceptualized immune cells as being foreign to the vessel wall and instinctively categorized them as being aggressive. We now know that immune cells are integral to the vessel wall in both health and disease and contribute to vascular homeostasis. For example, regulatory T lymphocytes modulate atherogenesis and can be therapeutically harnessed[11]; macrophages oversee the clearance of apoptotic cells in atherosclerotic lesions via efferocytosis[6], preventing the formation of the necrotic core[12]; and vascular tissue-resident macrophages have anti-atherogenic functions[13].

Inflammation of the vessel wall is not unique to atherosclerosis, and vasculitis is an important component of other chronic inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus. In their Review[3], Porsch and Binder highlight the existence of shared pathways in both atherosclerosis and autoimmune diseases. Shared pathways might indicate a shared pharmacopoeia, although whether the atherosclerosis that is driven by autoimmune syndromes is different from the atherosclerosis that develops in the general population is not known. The clinical association between autoimmune diseases and atherosclerosis emphasizes the importance of systemic inflammation and its prothrombotic effects as a contributor to atherogenesis in its own right. The systemic, low-grade inflammation that occurs in cardiometabolic disease is not simply a reflection of vascular inflammation and atherosclerotic plaque wash-out, but is highly dependent on multiorgan crosstalk, integrating metabolic and renal disease and insulin resistance. In their Review[4], Maffia et al. discuss the ever-expanding role of the complement system in inflammation and

atherosclerosis and the differential effect on atherogenesis of targeting components of plasma-operative complement, such as C5 (which is proatherogenic) compared with local cell-autonomous C3 (which supports efferocytosis).

Local inflammation in the atherosclerotic vessel wall and plaque is driven by highly specialized vascular immune cells, such as vascular tissue-resident macrophages[1,13] and lymphoid subsets, which differ from those found in peripheral blood[2] and whose mechanisms of tissue adaptation are not fully defined. The interacting but not univocal roles of systemic and local inflammation are often conflated, with the assumption that both can be treated therapeutically in a single stroke. This approach is translationally unhelpful because it is too simplistic. The systemic and local compartments of the immune response need to be selectively targeted and monitored for maximal efficacy in clinical trials. Persistent leukocyte recruitment is an important feature of atherosclerotic plaques. In their Review[5], Döring et al. discuss how chemokines and their heterodimerization can be targeted to avoid the amplification of atheroinflammation and how specialized pro-resolving mediators can offer useful pharmacological targets to stop excessive recruitment of leukocytes.

A strong theme explored in this Focus issue on atheroimmunology is how to preserve vascular homeostasis by promoting local endogenous protective mechanisms. In their Review[6], Adkar and Leeper analyse in detail how cell death programmes drive sterile inflammation in the atherosclerotic plaque and how clearance of apoptotic and necrotic cells via efferocytic pathways is regulated by potentially targetable ‘eat me’ and ‘don’t eat me’ signals. Efferocytosis is linked not only to complement biology[4] but also to the establishment of appropriately resolving macrophages and the release of anti-inflammatory cytokines. In their Review[7], Fredman and Serhan build further on this concept by detailing the biology and targeting of specialized pro-resolving mediators, a superfamily of locally acting, short-lived

autacoids that have efficacy in reducing atherogenesis in mouse models and which potentially provide an avenue to restore physiological regulation of inflammation.

The immune system is diffuse in its architecture and operates through a network of cells, tissues and organs. As in a game of chess, we need to track and tackle all the key pieces of this decentralized system simultaneously, in an ever-changing context of the lifestyle–gene interactions that lead to the risk of atherosclerotic cardiovascular disease. The epidemics of diabetes mellitus and obesity, and the ensuing low-grade, systemic inflammation, coupled with better management of plasma lipid levels, have produced a shift in the cardiovascular exposome, making the study of atheroimmunology more relevant than ever before. The CANTOS trial[8] has indicated that in atherosclerotic cardiovascular disease, as in autoimmune diseases, there are responders and non-responders to biologic agents. This concept needs be integrated into the design of clinical trials to monitor early treatment efficacy and allow patient selection. Dissecting the differences between the physiological roles of the vascular immune system and the damage caused by its pathogenic excess will help to identify the pathways whose inhibition confers substantial benefit and which outweighs the potential risks of immunosuppression and susceptibility to infection. Promoting endogenous protective mechanisms and cells might achieve the goal of tissue specificity and selectivity. This objective will require knowledge of immune cell diversity, tissue-specific immunity and multiorgan communication networks. The game of chess continues.

References

1 Dib, L. *et al.* Lipid-associated macrophages transition to an inflammatory state in human atherosclerosis increasing the risk of cerebrovascular complications. *Nat. Cardiovasc. Res.* **2**, 656–672 (2023).

2 Fernandez, D. M. *et al.* Single-cell immune landscape of human atherosclerotic plaques. *Nat. Med.* **25**, 1576–1588 (2019).

3 Porsch, F. & Binder, C. J. Autoimmune diseases and atherosclerotic cardiovascular disease. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-024-01045-7 (2024).

4 Maffia, P., Mauro, C., Case, A. & Kemper, C. Canonical and non-canonical roles of complement in atherosclerosis. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-024-01016-y (2024).
5 Doring, Y., van der Vorst, E. P. C. & Weber, C. Targeting immune cell recruitment in atherosclerosis. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-024-01023-z (2024).
6 Adkar, S. S. & Leeper, N. J. Efferocytosis in atherosclerosis. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-024-01037-7 (2024).
7 Fredman, G. & Serhan, C. N. Specialized pro-resolving mediators in vascular inflammation and atherosclerotic cardiovascular disease. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-023-00984-x (2024).
8 Ridker, P. M. *et al.* Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N. Engl. J. Med.* **377**, 1119–1131 (2017).
9 Tsiantoulas, D. *et al.* APRIL limits atherosclerosis by binding to heparan sulfate proteoglycans. *Nature* **597**, 92–96 (2021).
10 Lutgens, E. *et al.* Requirement for CD154 in the progression of atherosclerosis. *Nat. Med.* **5**, 1313–1316 (1999).
11 Ait-Oufella, H. *et al.* Natural regulatory T cells control the development of atherosclerosis in mice. *Nat. Med.* **12**, 178–180 (2006).
12 Gerlach, B. D. *et al.* Efferocytosis induces macrophage proliferation to help resolve tissue injury. *Cell Metab.* **33**, 2445–2463.e8 (2021).
13 Park, I. *et al.* C-type lectin receptor CLEC4A2 promotes tissue adaptation of macrophages and protects against atherosclerosis. *Nat. Commun.* **13**, 215 (2022).

Competing interests

The authors declare no competing interests.

Supplementary information

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Fig. 1 | Milestones in atheroimmunology research. The timeline shows selected scientific and clinical milestones since the late 1980s that have shaped our understanding of the roles of the immune system in atherosclerosis. See the Supplementary information for references.

Optional pull-quotes

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