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RESEARCH HIGHLIGHT

Immunotherapy for atherosclerosis by targeting pro-inflammatory T cells

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Recent advancements in atherosclerosis management have shifted focus beyond lipid-lowering strategies towards addressing residual inflammatory risks associated with major adverse cardiovascular events. In a recent *Cell Research* paper, Fan et al. reported that anti-PD-1 monoclonal antibody therapy reduces atherosclerosis plaque size and modulates inflammation by serving as a surrogate PD-1 ligand through interaction with myeloid-expressed Fc gamma receptors.

Atherosclerosis is a chronic inflammatory disease of the arteries that leads to major adverse cardiovascular events (MACEs) including ischemic heart disease and stroke.[1] Despite advancements in lipid-lowering therapies, a significant residual risk of MACEs persists, underscoring the need for innovative treatment strategies.[1] Recent research has shifted focus to the role of adaptive immunity in atherosclerosis, with T-cells emerging as pivotal players in disease progression.[2–4] Immunotherapy has revolutionized oncology and is now set to bring its transformative potential to atherosclerosis management. Studies have demonstrated the intricate dance between lipids and inflammation, hinting at a nuanced interdependency rather than a simple cause-and-effect relationship. For example, the CANTOS trial, which targeted inflammation with the interleukin-1β inhibitor canakinumab, marked a milestone in validating the inflammatory hypothesis of atherothrombosis.[5] Tolerogenic and antibody-based vaccines to self-epitopes have shown promise in mouse experiments.[6,7] Based on extensive preclinical data and emerging clinical insights, the recent study leveraging anti-PD-1 monoclonal antibodies suggest a potential new treatment paradigm in cardiovascular medicine.[8] In tumor patients with existing atherosclerosis, anti-PD-1 monoclonal antibody therapy significantly reduced atherosclerotic plaque size.

In a retrospective cohort study involving tumor patients with existing atherosclerosis, anti-PD-1 monoclonal antibody therapy coincided with a significant reduction in atherosclerosis plaque size. This discovery was the first to suggest the potential of repurposed oncological treatments for cardiovascular disease management, indicating that immunotherapeutic strategies could transcend their anticancer applications.

The research provided an in-depth single-cell RNA sequencing-based atlas of T-cells in human atherosclerosis plaques. It revealed diverse phenotypes and underscored the presence of plaque-specific, pro-inflammatory T-cells that could be valuable targets for immunomodulation.

Through comprehensive single-cell analyses, a subset of atherosclerosis plaque-specific PD-1+ T-cells was identified. These cells exhibited an activated and pro-inflammatory phenotype, starkly different from the exhausted T-cells characteristically found in tumor microenvironments. This suggested a unique opportunity to modulate these T-cells to mitigate atherosclerosis progression.

The study illuminated the mechanism by which anti-PD-1 monoclonal antibodies exerted their effects. When captured by Fc gamma receptors (FcγRs) on myeloid cells, these antibodies mimicked natural PD-1 ligands, inhibiting T-cell activity within the atypical PD-1 ligand-deficient milieu of atherosclerosis plaques.

CyTOF analysis and subsequent functional assays validated that the PD-1+ T-cells in atherosclerosis plaques were functionally active and not terminally exhausted. This was critical as it demonstrated the potential for these cells to be reactivated and hence, susceptible to immunotherapy.

A further prospective cohort study underlined the importance of Fc-binding capabilities. Anti-PD-1 monoclonal antibodies with the ability to engage Fc receptors were effective in reducing atherosclerosis plaque size, whereas those without this ability showed no significant effect. This finding not only confirmed the results of the retrospective study but also pointed towards the necessity of Fc receptor engagement for therapeutic efficacy.

The study's implications for clinical application are profound. By demonstrating the feasibility of reducing atherosclerosis plaque size through a targeted immunotherapeutic strategy, the researchers have opened up potential new avenues for the treatment of atherosclerosis. Their work suggests a future where cardiovascular inflammation can be resolved through the strategic modulation of immune responses, shifting the paradigm from lipid-centric to immune-centric therapy.

The findings of this research stand as a testament to the power of immune system modulation in treating diseases traditionally managed by non-immunological means. By repurposing anti-PD-1 monoclonal antibodies, originally designed for oncological purposes, the study highlights the intersectionality of disease processes and the benefits of a cross-disciplinary approach in medical science.

Furthermore, the research implicates the potential of precision medicine. The heterogeneous nature of atherosclerosis plaques, as revealed by the various T-cell subsets and their states of activation, suggests that tailored immunotherapy could be more effective than the one-size-fits-all strategies currently in place. It also raises important questions about the balance between inflammatory suppression and immune competence, considering the broader implications for host defense mechanisms.

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Looking ahead, the prospective cohort study provides a roadmap for larger-scale clinical trials. The safety and efficacy of Fc-binding anti-PD-1 monoclonal antibodies must be rigorously tested in diverse populations over more extended periods. Such studies will need to carefully consider the risk-benefit profile, given the complexity of immune-modulating therapies and their potential for adverse effects. Anti-PD-1 antibodies are known to trigger serious autoimmune side effects including myocarditis.[9]

In conclusion, the study marks a significant advance in our understanding of atherosclerosis and its potential treatment. Interestingly, the effect is not through inhibition of PD-1, but rather through FcγR binding. This suggests that it may be possible to target PD-1 in atherosclerosis without triggering autoimmune side effects. By identifying the key role of pro-inflammatory PD-1$^+$ T-cells in atherosclerosis plaque formation and progression, and revealing a novel approach to modulate these cells, this research lays the groundwork for potential future therapeutic strategies that could revolutionize the management of atherosclerosis.

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