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EDITORIAL

Targeted immune cells: A fresh approach to treating atherosclerosis

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Since atherosclerosis is now recognized as a chronic inflammatory disease mediated by the immune system, treatment approaches that increase immunomodulation based on lipid reduction have been developed. According to bioinformatic research, active mast cells, T cells, resting natural killer cells, and macrophages are important players in plaque inflammation.[1] In addition to interacting with a range of altered endogenous antigens, innate immunity has a quick but comparatively slow inflammatory and toxic response.[2] Although it may take days or even weeks for adaptive immunity to fully mobilize, it is more specific than innate immunity. The adaptive immune response is typically the focus of immunomodulatory treatments. Targeting elements of innate immunity, however, can also modify how immunity affects the adaptive immune response.[3]

The intricate function of several immune cells is intimately linked to the development of AS. While Th17 cells that produce IL-17 speed up the formation and growth of plaque, pro-inflammatory T cells, like CD8+ T cells, promote inflammatory responses and worsen plaque instability by secreting pro-inflammatory substances and exerting cytotoxicity.[4-6] Conversely, regulatory T cells (Tregs) have the ability to control vascular endothelial function, directly suppress inflammatory cells, and affect antigen-presenting cells to reduce inflammation and stabilize plaques. The balance between Tregs and pro-inflammatory T-cell subsets is vital for preserving vascular immune homeostasis because pro-inflammatory immune responses will predominate if Treg numbers decline or their function is compromised, increasing plaque vulnerability.[4] Macrophages are also the primary regulators of AS; once they enter the atherosclerotic environment, they will absorb oxidized low-density lipoprotein (ox-LDL) and change into foam cells, which will increase inflammation and the formation of plaque. Targeting the formation of foam cells is important in preventing the instability and rupture of plaque. Lipid metabolism disorders will cause macrophages to polarize toward the M1-type, which intensifies the inflammatory response, and the lesion's susceptibility is directly determined by its activation status. The lesion's local inflammatory microenvironment's properties are directly determined by the activation state,[2] and ox-LDL also influences macrophage activity through a number of different methods. The antigenic specificity of B cells is the primary determinant of their specific impact, and B cell receptor (BCR) sequencing is essential for assessing said impact. B cells exhibit significant heterogeneity in atherosclerosis, with B1 cells being atheroprotective and the majority of B2 cells pro-atherogenic. BCR sequencing technology can assist in identifying autoreactive

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antibodies and distinct B cell subpopulations to enable accurate research. A number of obstacles still need to be addressed, even though recent research has opened up new avenues for the treatment of atherosclerosis: the precise function of Th17 cells in various disease processes needs to be clarified,[5,6] the safety and accuracy of current therapies need to be improved, and the dynamic balance between Tregs and pro-inflammatory T-cell subsets needs to be further elucidated. Further integration of single-cell transcriptomics and other technologies is required in the future to realize the precise regulation of T-cell immune responses through multitargeted synergistic interventions and to investigate the potential of peripheral blood as a window for lesion monitoring.[7] Immune cell-targeting therapies, particularly those that target the balance of T-cell subpopulations, have advanced from fundamental research to clinical translation and have demonstrated significant promise in reducing inflammation in atherosclerosis and stabilizing plaques. A more complete approach to treating atherosclerosis will be offered by fostering the natural fusion of immunomodulatory therapies and conventional treatments, as well as by deepen relevant research on the functional heterogeneity of T cell subtypes and their interactions.

Immunotherapy for atherosclerosis covers both intrinsic and adaptive immune mechanisms. Through the intrinsic immunity mechanism, pro-inflammatory cytokines can be inhibited by interleukin (IL)-1 receptor antagonist anakinra and IL-6 inhibitor tocilizumab to improve the profile of inflammatory markers.[8] Meanwhile, complement activation is a key link, and oxidized lipids can initiate complement activation, leading to endothelial dysfunction and inflammatory cell recruitment. Clinical data show that complement inhibitors may be effective therapeutic targets, and through the pathway of targeting specific complement systems, it can reduce plaque damage and inflammatory response can attenuate plaque damage and inflammatory responses.[9] Adaptive immunomodulation focuses on antigen-specific responses, with ox-LDL antibodies showing cardioprotective effects in animal models, and targeting specific BCR or T cell receptor clonotypes may be a new approach for future,[7] with drugs targeting PD1 or CTLA4 being more commonly used to stabilize plaques and reduce the risk of cardiovascular events, and activation of T-cell pathways with agonistic antibodies may prevent T-cell damage and inflammatory responses. The use of agonistic antibodies to activate co-inhibitory pathways to prevent T-cell over-activation and reduce inflammation, as well as the development of vaccines against atherosclerosis-specific antigens, such as apolipoprotein B, provides new avenues for atherosclerosis treatment. In addition, atherosclerosis is closely related to the metabolic reprogramming of immune cells, which tend to favor aerobic glycolysis over oxidative phosphorylation. Altering the metabolic pathway can reduce inflammatory response and slow down the progression of atherosclerosis, e.g., using drugs that block glycolytic enzymes, breaking the glycolytic switch reduces T cell activation and inflammatory macrophage function, and the exploitation of metabolic weaknesses identified in cancer treatment is expected to lead to the development of new therapeutic approaches for atherosclerosis. However, related therapeutic techniques face problems such as uncertainty of efficacy and side effects in clinical application, and further studies are needed to improve therapeutic regimens and to determine their role in atherosclerosis treatment.[8]

Enhancing the specificity and effectiveness of therapeutic medicines against immune cells has been the main focus of developments in drug delivery technology. Targeting atherosclerosis lesions, raising local medication concentrations, and lowering systemic adverse effects are all possible with novel precision delivery systems.[10] Red blood cell or platelet cell membranes are used by bionic drug delivery systems to increase targeting capacity and circulation duration. In a mouse model of atherosclerosis, liposomal nanoparticles are also utilized to deliver the *IL10* gene, which results in a 40% increase in collagen content within plaques.[11] Granulocyte activity at the site of vascular damage may also be decreased using polymer particles to prevent platelet-leukocyte aggregates from adhering to endothelial cells. This strategy lowers the risk of acute cardiovascular events by limiting the inflammatory response and possibly minimizing the impact of neutrophils on plaque instability and rupture.[12] Previous animal models for the study of atherosclerosis have limitations because they cannot fully replicate human pathological features, such as the mouse model's lack of the complex cellular composition found in human plaques.[13,14] Current *in vitro* models are also limited because they lack microenvironmental cells and 3D vascular structures. Organoid microarray technology can simulate the humanized plaque microenvironment and offer a more accurate platform for drug screening.[15] The basis for accurate typing therapy can be laid using single-cell sequencing for immunophenotyping, which can reveal variations in the distribution of immune cells in various plaques.[16] Immunotherapy was more beneficial for patients with elevated C-reactive protein, according to a subgroup analysis of the CIRT study.[17] While butyrate improves Treg activity through histone deacetylase inhibition, trimethylamine N-oxide, a product of intestinal flora, exacerbates atherosclerosis by activating NLRP3 inflammatory vesicles, indicating that the "intestinal-vascular axis" may be a novel therapeutic target.[18] A

paradigm shift in controlling the autoimmune response in atherosclerotic plaques is represented by gene editing and cell therapy. By precisely changing immune cell function, technologies like CRISPR/Cas9 can produce specialized T cells or Tregs that regulate the plaque's inflammatory response. CAR-T cell therapy is a new field that may help stabilize plaques and reverse atherosclerosis by designing Tregs to target atherosclerosis-associated antigens.

The main obstacle in the investigation of immunotherapy for atherosclerosis is striking a balance between effectiveness and negative effects. The roles of the new generation of immune checkpoint medications programmed cell death protein 1 (PD-1), PD ligand 1 in atherosclerosis are complicated and dual-sided; while they can stimulate anti-tumor T cells, they may also cause autoimmune disorders or worsen inflammation.[19] To improve the treatment plan, more research on the precise mechanisms of immune cells in atherosclerosis is required in the future. The advantages of individual treatments are constrained by the variety of immune resistance mechanisms. Multiple cell types are involved in the mechanisms of immunological resistance, which differ from patient to patient. Consequently, in aneurysm immunotherapy, it is essential to utilize the component set of immune resistance prototypes. Clinical research has demonstrated that the risk of cardiovascular events is correlated with circulating leukocyte counts and that cardiovascular risk factors influence extramedullary hematopoiesis and the ecological niche of bone marrow stem cells, which in turn increase leukocytosis. Thorough research into the processes by which risk factors such as smoking, arterial hypertension, high cholesterol, and high blood sugar encourage leukocyte growth could yield new targets for atherosclerosis therapy.[2] The successful expansion and maintenance of Treg cell activity, as well as the avoidance of immunosuppressive side effects, are concerns for Treg cell augmentation therapy, an emerging immunotherapy technique.[20] To portray a varied environment, future research must examine the distinct traits of atherosclerosis-infiltrating immune cell subsets and examine the connection between immune cell ratios and types of atherosclerosis.[21]

Immune cell-targeted therapy has brought the treatment of atherosclerosis into the era of "precision immune intervention." In the future, synergistic breakthroughs can be made in the following three dimensions: first, establishing a spatio-temporal-specific drug delivery system to precisely regulate the inflammatory cascade response; second, utilizing multi-omics technology to analyze the "intestinal-vascular axis" and other novel microenvironmental networks to reveal the mysteries of regulating the activity of Treg cells; and third, constructing an efficacy prediction model based on the immune characteristics of single cells to realize the design of truly individualized treatment programs. Third, we will construct an efficacy prediction model based on single-cell immune characteristics to realize the design of truly individualized therapeutic regimens. Although the safety of long-term immunomodulation still needs to be deeply explored through combining bioengineering innovations with cutting-edge advances in systemic immunology, atherosclerosis is expected to be devolved from an irreversible chronic disease to a dynamic and controllable process that can be precisely intervened and treated. In summary, we call for enhanced interdisciplinary collaboration to accelerate the translation from laboratory discovery to clinical application to embrace this major change in the field of medicine.

Conflict of interest

Xianbin Kong is an Editorial Board Member of this journal. All authors declare no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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