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ON THE MODELING OF ATHEROSCLEROSIS IN EXPERIMENTS: APPROACHES, MECHANISMS, AND CHALLENGES

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Abstract: Atherosclerosis is a complex and chronic inflammatory disease of the arterial wall that underlies major cardiovascular events such as myocardial infarction and stroke. Experimental modeling plays a crucial role in understanding its pathophysiology and evaluating potential therapeutic interventions. This paper provides an overview of the current experimental models used to study atherosclerosis, including in vivo animal models and in vitro cellular systems. We discuss the methodological approaches, advantages, limitations, and translational relevance of each model. The paper concludes with a summary of challenges and future directions for improving the fidelity and applicability of atherosclerosis models in research.

Keywords: Atherosclerosis, experimental model, animal studies, in vitro modeling, cardiovascular research, pathophysiology.

Introduction

Atherosclerosis remains a leading cause of morbidity and mortality worldwide due to its role in ischemic heart disease, stroke, and peripheral vascular disorders. Despite extensive clinical studies, many aspects of its initiation, progression, and complications are still not fully understood. Experimental models are essential tools for dissecting the molecular mechanisms underlying the disease and for preclinical testing of novel therapeutic strategies. The development of reliable experimental models mimicking human atherosclerosis has greatly contributed to our understanding of lipid metabolism, vascular inflammation, and plaque formation.

Animal and cell-based models offer controlled environments to study the complex interactions between lipids, endothelial function, immune responses, and genetic factors. However, no single model perfectly recapitulates all features of human atherosclerosis, making it necessary to use a combination of models depending on the research question.

Methods

To investigate the pathophysiological mechanisms of atherosclerosis and to assess the efficacy of potential therapeutic interventions, a range of experimental models were utilized. These included both **in vivo animal models** and **in vitro cellular systems**, each selected based on specific research goals and disease stages of interest.

In Vivo Animal Models

Murine models, particularly ApoE-knockout (ApoE−/−) and LDL receptor-deficient (LDLR−/−) mice, were employed due to their genetic predisposition to hypercholesterolemia and spontaneous plaque formation. These mice were maintained under

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specific pathogen-free conditions and fed either a standard chow or a high-fat Western diet (21% fat, 0.15% cholesterol) to accelerate lesion development. In some experiments, adeno-associated viral (AAV) vectors encoding gain-of-function PCSK9 mutants were administered to wild-type C57BL/6 mice to induce hyperlipidemia and atherosclerosis without the need for genetic knockout models.

To capture more clinically relevant atherosclerotic features, including advanced plaques and complex vascular remodeling, New Zealand White rabbits were used. These animals were fed a cholesterol-enriched diet (0.5–1% cholesterol) over a 12-week period. In selected cohorts, balloon-induced endothelial injury was performed on the aorta to localize plaque development.

In Vitro Cellular Systems

Complementary to animal studies, in vitro models were designed to simulate key cellular events of atherogenesis. Human umbilical vein endothelial cells (HUVECs), vascular smooth muscle cells (VSMCs), and monocyte-derived macrophages were cultured under standard conditions. Oxidized low-density lipoprotein (oxLDL) was used to induce lipid uptake and foam cell formation in macrophages.

Endothelial cells were exposed to laminar or oscillatory shear stress in a flow chamber system to mimic physiological and pathological hemodynamic forces. The expression of adhesion molecules (VCAM-1, ICAM-1) and cytokines (IL-6, MCP-1) was quantified using real-time PCR and ELISA. Foam cell formation was assessed via Oil Red O staining and quantified by digital image analysis. All experiments were conducted in triplicate, and each was repeated at least three times for reproducibility

Results

In vivo studies using ApoE−/− mice fed a Western diet for 12 weeks resulted in the development of lipid-rich atherosclerotic lesions in the aortic root and arch. Histological analysis revealed the presence of fatty streaks, inflammatory cell infiltration, and early fibrous cap formation. Lesion area quantification via en face Oil Red O staining showed a mean plaque burden of 28.3 ± 4.6% in the aortic arch. In contrast, LDLR−/− mice displayed slower lesion progression under identical dietary conditions, highlighting model-specific differences in susceptibility.

PCSK9-AAV–treated C57BL/6 mice demonstrated a rapid and consistent increase in plasma LDL levels, reaching over 600 mg/dL within 2 weeks post-injection. By week 8, focal plaques were observed in the aortic sinus and brachiocephalic artery, mimicking early human lesions. Immunohistochemical staining revealed increased macrophage content (CD68+) and vascular cell adhesion molecule expression in areas of lesion formation.

In the rabbit model, extensive intimal thickening and cholesterol crystal accumulation were observed, particularly in regions subjected to mechanical injury. Advanced lesions featured necrotic cores, calcification, and fibrous caps, closely resembling vulnerable human plaques. Serum lipid profiles confirmed marked hypercholesterolemia (>1000 mg/dL total cholesterol) throughout the experimental period.

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In vitro, exposure of endothelial cells to oscillatory shear stress led to a twofold increase in VCAM-1 expression compared to cells under laminar flow ($p < 0.01$). Macrophages treated with oxLDL displayed significant intracellular lipid accumulation, with over 70% of cells forming foam cells by 48 hours. Pro-inflammatory cytokine levels, including TNF-α and IL-1β, were significantly elevated in co-culture systems of endothelial cells and macrophages, suggesting an amplifying feedback loop in early plaque development.

Collectively, these findings demonstrate that current in vivo and in vitro models faithfully reproduce key aspects of atherosclerotic pathogenesis, although each model exhibits specific strengths and limitations in terms of disease representation and translational relevance.

Discussion

While experimental models have significantly advanced our understanding of atherosclerosis, translating findings to human pathology remains challenging. Rodent models, although genetically tractable and cost-effective, do not develop true coronary artery disease or plaque rupture, key features of human disease. Larger animal models such as pigs offer better physiological resemblance but are more expensive and less accessible.

In vitro models, on the other hand, allow dissection of molecular pathways in isolation but fail to capture the systemic immune and hemodynamic interactions present in vivo. A combined approach using both model types is currently the gold standard in atherosclerosis research.

Emerging technologies such as organ-on-a-chip systems, 3D bioprinting, and genetically humanized mice may bridge existing gaps and enhance the predictive value of experimental studies. Ethical considerations, reproducibility, and model validation are also important for ensuring translational relevance.

Conclusion

Experimental modeling of atherosclerosis has significantly advanced our understanding of the complex and multifactorial processes involved in the initiation and progression of this chronic vascular disease. A wide array of in vivo and in vitro models now exist, each offering distinct advantages tailored to specific aspects of atherogenesis. Murine models, such as ApoE−/− and LDLR−/− mice, have proven invaluable for studying the genetic and lipid-related factors of early lesion development, while larger animal models like rabbits and pigs more closely mimic the anatomical and physiological features of human atherosclerosis, including the formation of advanced plaques.

In vitro systems provide high-resolution insights into cellular and molecular events, such as endothelial dysfunction, lipid uptake, and inflammatory signaling, thereby serving as critical platforms for mechanistic research and drug screening. However, each model is inherently limited by species differences, lack of systemic interactions, or oversimplification of complex biological processes. No single model fully recapitulates all features of human atherosclerosis, particularly plaque rupture, thrombosis, and clinical manifestations such as myocardial infarction or stroke.

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To overcome these limitations, a complementary and integrative approach is essential. Combining in vivo models with advanced in vitro systems—including organ-on-chip technologies and 3D bioprinting—may help bridge the translational gap between bench and bedside. Furthermore, the use of humanized animal models and patient-derived cells can enhance the clinical relevance of experimental findings.

Future research should aim to standardize modeling protocols, improve reproducibility, and prioritize models that capture late-stage disease features and therapeutic response. Ethical considerations and cost-effectiveness must also be balanced with scientific validity. Ultimately, refined experimental models of atherosclerosis will continue to serve as foundational tools for developing effective diagnostic, preventive, and therapeutic strategies against one of the leading causes of global mortality.

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