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Mouse Models for Atherosclerosis Research—Which Is My Line?

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Atherosclerosis is one of the primary causes of cardiovascular disease and mortality. This chronic immunometabolic disease evolves during decades in humans and encompasses different organs and immune cell types, as well as local and systemic processes that promote the progression of the disease. The most frequently used animal model to study these atherogenic processes and inter-organ crosstalk in a short time frame are genetically modified mouse models. Some models have been used throughout the last decades, and some others been developed recently. These models have important differences in cholesterol and lipoprotein metabolism, reverse cholesterol transport pathway, obesity and diabetes as well as inflammatory processes. Therefore, the disease develops and progresses differently in the various mouse models. Since atherosclerosis is a multifaceted disease and many processes contribute to its progression, the choice of the right mouse model is important to study specific aspects of the disease. We will describe the different mouse models and provide a roadmap to facilitate current and future atherosclerosis researchers to choose the right model depending on their scientific question.

Keywords: atherosclerosis, cardiovascular disease (CV disease), mouse models, immunometabolic disease, lipoprotein metabolism, inflammatory signaling, PCSK9 (proprotein convertase subtilisin kexin type 9), Fibrillin 1

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BACKGROUND

Atherosclerosis is a chronic immunometabolic disease and remains asymptomatic until a plaque becomes large enough to obstruct the lumen to cause ischemic pain or ruptures and causes a myocardial infarction, stroke, or peripheral artery disease. At the early stage, the disease is driven by the retention of cholesterol-rich, apolipoprotein B-containing lipoproteins at specific predilection sites such as bifurcations. High level of plasma low-density lipoprotein (LDL)-cholesterol is the most important risk factor promoting the development and progression of atherosclerosis. Lipoproteins that accumulate in the arterial wall undergo various modifications, such as oxidation and carbamylation. These modified lipoproteins and other pro-inflammatory triggers mediate the activation of vascular endothelial cells (**Figure 1**). In turn, activated endothelial cells express adhesion molecules, which bind to and recruit circulating innate and adaptive immune cells, such as monocytes and T cells (**Figure 1**). Within the intima, monocytes differentiate into macrophages and ingest modified lipoproteins, becoming cholesterol-laden foam cells (1). Plaque macrophages express different scavenger receptors that recognize and mediate the uptake modified lipoprotein antigens, such as oxidized lipoproteins, hence promoting foam cell formation and a pro-inflammatory polarization (**Figure 1**) (2). The excessive storage of cholesterol esters leads to a defective esterification pathway, thus resulting in a consistent accumulation of free cholesterol

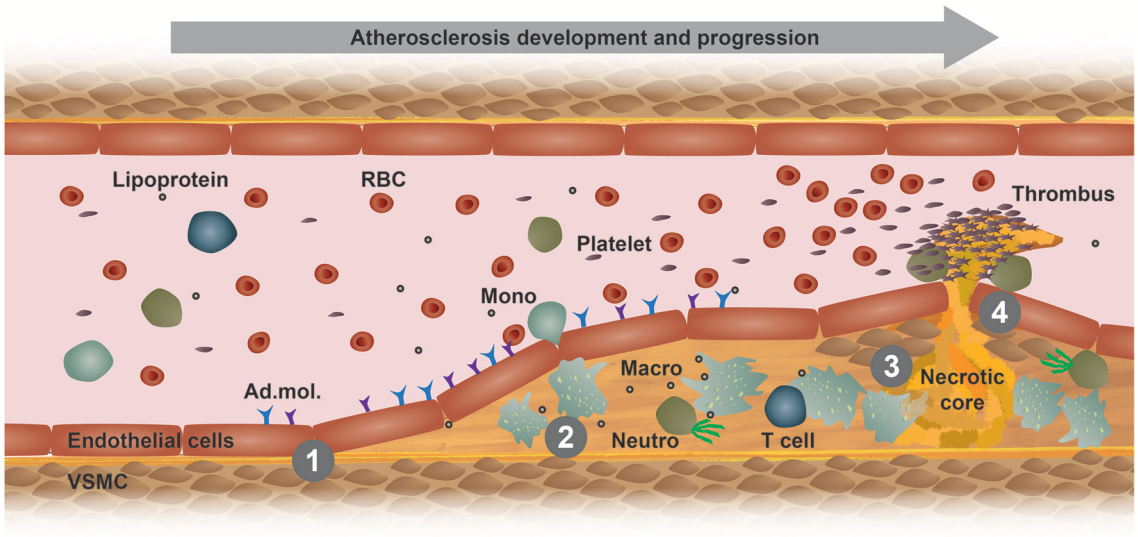

FIGURE 1 | Model of atherogenesis. This scheme illustrates the development of an atherosclerotic plaque from left to right in a longitudinal section of an arterial vessel. (**1**) Upon activation by metabolic or inflammatory triggers, endothelial cells express adhesion molecules (Ad. mol.) that promote the recruitment of immune cells, such as blood monocytes (Mono). These cells then infiltrate the arterial intima, where monocyte differentiate into macrophages (Macro) and interact with other immune cells, such as neutrophils (Neutro) and T cells. (**2**) Increased uptake of modified lipoproteins via scavenger receptors or decreased cholesterol efflux accelerates the accumulation of intracellular free cholesterol and cholesteryl ester-loaded lipid droplets that promote foam cell formation. (**3**) Macrophage foam cells eventually die and fall apart, thereby forming a necrotic core. (**4**) Advanced, vulnerable plaques can rupture and thereby form an arterial thrombus, which can lead to a myocardial infarction or stroke. RBC, red blood cell; VSMC, vascular smooth muscle cell.

that forms cholesterol crystals that damage the cells and activate apoptotic pathways. Efferocytosis, i.e., the phagocytosis of apoptotic and necrotic cells, gets impaired and promotes a further accumulation of foam cell debris and the release of inflammatory mediators that together potentiate the inflammation of the arterial wall (3). Additionally, foam cells release enzymes that degrade the extracellular matrix, thus increasing plaque vulnerability and the eventual risk of rupture, which would lead to platelet aggregation, blood coagulation and thrombus formation (**Figure 1**) (1). The development and stability of atherosclerotic plaques is also affected by inflammatory cytokines that are released by different immune cells, such as TNF-α and IFN-γ (4). These released cytokines induce an intra-plaque immune response and promote vascular smooth muscle cells (VSMCs) death, thus destabilizing the matrix of the plaques. Moreover, other cells and organs also contribute to the immunometabolic dysregulation happening during atherosclerosis development. Therefore, it is advisable to compare the different atherosclerosis mouse models and choose one that resembles the aspects of the human pathology as good as possible.

ANIMAL MODELS

The pathophysiology of atherosclerosis in humans is a complex process that is triggered by various risk factors, including aging, hyperlipidemia, hypertension and diabetes, which lead to an immunometabolic dysregulation. The study of the immunometabolic processes and molecular mechanisms driving the disease requires animal models that mimic the human pathophysiology. Notably, there is no perfect animal model that recapitulate all the features of the human disease. Several animal models have been studied for atherosclerosis research over the last decades, and all of them show advantages and disadvantages. Different animal models can be chosen depending on the focus of the research. In terms of human physiology similarities and clinical relevance, non-human primates are the best model for atherosclerosis investigation. However, non-human primates are expensive to maintain, they develop the disease over a long time, there is a high risk of infections, and they have high ethical hurdles (5, 6). Alternative animal models should be cheaper, easier to handle and reproduce the human disease as good as possible (7). Moreover, they should be appropriate to perform genetic, pharmacological and/or interventional studies.

OF MICE AND MEN

Mouse models meet these criteria at least in part and are thus are the most common animal model used for atherosclerosis studies. Nevertheless, mice also display major genetic and physiological differences compared to humans (8). One of the most evident difference between mice and humans resides in the lipoprotein metabolism. Mice are considered as a high-density lipoprotein (HDL) models since most of the cholesterol is transported in HDL particles, and not in LDL as in humans. Consequently, mice carry most plasma cholesterol in HDL particles and overall have massively lower cholesterol levels, which confers atherosclerosis protection due to an improved reverse cholesterol transport