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Animal models of atherosclerosis

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Abstract

In this mini-review several commonly used animal models of atherosclerosis have been discussed. Among them, emphasis has been made on mice, rabbits, pigs and non-human primates. Although these animal models have played a significant role in our understanding of induction of atherosclerotic lesions, we still lack a reliable animal model for regression of the disease. Researchers have reported several genetically modified and transgenic animal models that replicate human atherosclerosis, however each of current animal models have some limitations. Among these animal models, the apolipoprotein (apo) E-knockout (KO) mice have been used extensively because they develop spontaneous atherosclerosis. Furthermore, atherosclerotic lesions developed in this model depending on experimental design may resemble humans' stable and unstable atherosclerotic lesions. This mouse model of hypercholesterolemia and atherosclerosis has been also used to investigate the impact of oxidative stress and inflammation on atherogenesis. Low density lipoprotein (LDL)-r-KO mice are a model of human familial hypercholesterolemia. However, unlike apo E-KO mice, the LDL-r-KO mice do not develop spontaneous atherosclerosis. Both apo E-KO and LDL-r-KO mice have been employed to generate other relevant mouse models of cardiovascular disease through breeding strategies. In addition to mice, rabbits have been used extensively particularly to understand the mechanisms of cholesterol-induced atherosclerosis. The present review paper details the characteristics of animal models that are used in atherosclerosis research.

Key words: Atherosclerosis; Dyslipidemia; Disease; Animal models

Core tip: This mini-review provides the essential information obtained from a number of animal models in the field of cardiovascular research. Such information can help researchers design their studies for understanding the pathophysiology of atherosclerosis.

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INTRODUCTION

Atherosclerosis is still a leading cause of mortality and

morbidity worldwide[1]. Several modifiable and non-modifiable risk factors have been identified for the disease. Many clinical and experimental attempts have been made to understand the pathophysiology of the disease. Among them, a number of animal models have been used for understanding the mechanisms involved in both induction and regression of atherosclerotic lesions. It was first in 1908 that Ignatowski reported atherogenesis in a rabbit model[2]. Subsequent studies documented a significant relationship between elevated levels of serum cholesterol and development of atherosclerotic lesions in experimental animals[3-6]. That was the basis of cholesterol-feeding trials in experimental models of atherosclerosis. However, later a naturally defective rabbit model namely Watanabe Heritable Hyperlipidemic (WHHL) rabbits was discovered and used in most of experimental settings[7-13]. Recent technology has allowed generation of a number of genetically-modified animal models in this field of research.

Overall, one may think that an ideal animal model for studying human disease should possess several features including availability, affordability and close resemblance to human conditions. In particular, an optimal animal model of atherosclerosis should develop various stages of the disease including fatty streaks, accumulation of foam cells, vulnerable and stable plaques as well as relevant complications such as calcification, ulceration, hemorrhage, plaque rapture, thrombosis and stenosis and the formation of aneurysms. Efforts are being made to develop animal models that replicate human atherosclerosis, however each of current animal models have some limitations. In this paper, attempts have been made to summarize the important features of the common animal models of atherosclerosis.

MICE

The mouse has been used in medical research for decades. Well-known genetic background, easy to breed and low cost of maintenance are among advantages of this model. However, small size and some physiological characteristics may be considered as limiting factors. For example, the plasma lipoprotein profile in mice is very different from that in humans. The circulating cholesterol is mainly in high density lipoprotein (HDL) particles in the mouse, while it is in low density lipoprotein (LDL) particles in humans. This is probably the main reason that wild-type mice do not develop atherosclerosis, but humans do. One reason for this lipoprotein profile differences is the absence of cholesterol-ester transfer protein (CETP) in the mouse[14]. Another difference between the mouse and the man is their response to dietary cholesterol. The mouse does not absorb dietary cholesterol significantly[15], while the man absorbs approximately 50% of dietary cholesterol. This may also be seen as a limiting factor for cholesterol-induced atherogensis in wild-type mice (C57BL/6J).

To overcome these limitations, researchers have used DNA technology to generate a number of genetically modified mouse models. It was in 1992 that the very first line of such genetically modified mouse model was introduced to our research community. Zhang *et al*[3] reported a successful deletion of mouse apolipoprotein (apo) *E* gene. Further research led to generation of other genetically modified mouse models suitable for studying human dyslipidemia and atherosclerosis. Among them, LDL receptor-knockout (KO)[16], hepatic lipase-KO[17], human apo B_{100} expression[18] and human CETP expression[19] can be named.

Of these genetically modified mouse models, apo E-KO mice develop spontaneous atherosclerosis. This is associated with elevated levels of circulating cholesterol-rich very LDL (VLDL) particles. This feature makes this animal model to be very robust for both induction and prevention of the disease. Several studies have reported that hypercholesterolemia and atherosclerosis can be prevented by dietary plant sterols in this animal model[20-22]. Unlike apo E-KO mice, LDL-r-KO mice need dietary cholesterol to develop hypercholesterolemia and atherosclerosis[16,23]. Morphological features of atherosclerotic lesions in apo E-KO and LDLr-KO mice are illustrated on Figure 1. Another mouse model which develops hypercholesterolemia and atherosclerosis on high fat/high cholesterol diets is apo E*3-Leiden transgenic mice[24-26]. Furthermore, a number of breeding experiments have been carried out to generate additional mouse models of human dyslipidemia and atherosclerosis. For example, cross breeding of human apo B_{100} transgenic mice with LDL receptor deficient mice produced a highly susceptible strain ($HuBTg^{+/+}Ldlr^{-/-}$) with severe hypercholesterolemia and atherosclerosis[16]. Furthermore, Föger *et al*[19] reported that when human lecithin cholesterol acyl transferase (LCAT) transgenic mice were cross-bred with CETP transgenic mice they produce offspring with low total cholesterol levels and reduced atherosclerosis burden. Similarly, Lweis *et al*[27] generated apoE/GPx1 double KO ($ApoE^{-/-}$ $GPx1^{-/-}$), by cross breeding GPx1-deficient mice with apo E-deficient mice. This model features combined hyperlipidemia and hyperglycemia with increased oxidative stress. Chen *et al*[28] reported a mouse model that develops unstable/ruptured atherosclerotic plaques. They used surgical procedures to introduce a tandem stenosis in the carotid artery of apo $E^{-/-}$ mice fed a high fat diet, in order to develop unstable plaques in these mice. Atherosclerosis is known to be an inflammatory disease. We know that there are major differences in immune system between mice and humans[29]. This is another reason for questioning the mouse model for studying human atherosclerosis. Several inflammatory markers have been detected in both atherosclerotic plaques and in circulation of subjects or animals with atherosclerosis. Several strategies have been implemented to understand the role of inflammatory pathways in the progression of the disease and its complications. One of such experimental strategies was application of bone marrow transplant. Ishibashi and colleagues used bone marrow

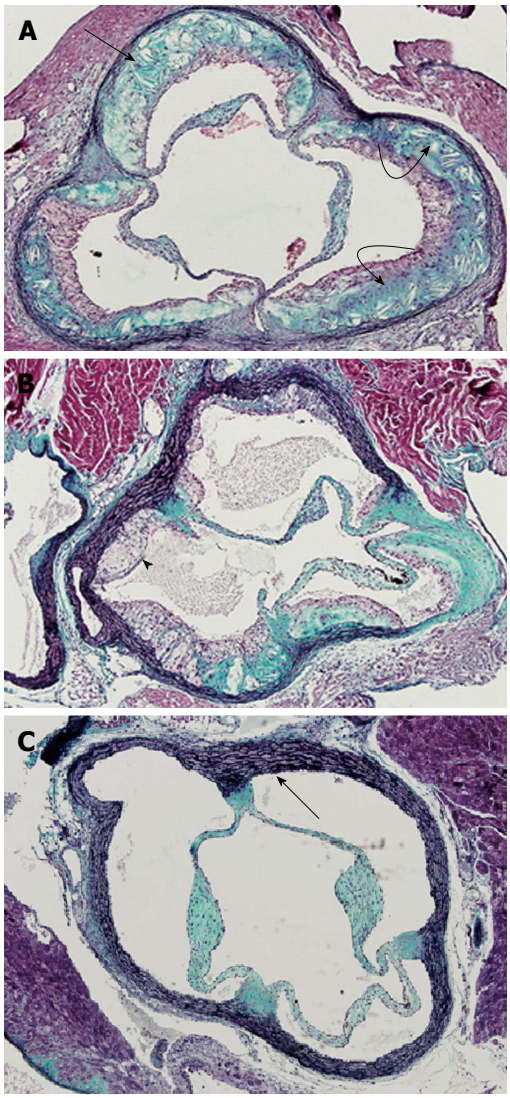

Figure 1 Representative photomicrographs taken at aortic root from apolipoprotein E-knockout (A), low density lipoprotein-r-knockout (B) and their wild-type background C57BL/6J (C) mice. A: Advanced atherosclerosis lesions in all 3 valves of the aortic root (arrow); these lesions are composed of numerous cholesterol clefts (curved arrows); B: Illustrating lipid-rich atherosclerotic lesions in the aortic root; the arrow head points to an atherosclerotic plaque primarily composed of apparent foam cells. No cholesterol cleft is visible in B; C: Demonstrating an atherosclerotic-lesion-free aortic root with normal-looking vascular wall (arrow) with apparent intact elastic lamina and endothelium. Trichrome staining; × 40.

transplant procedures to produce apo E-KO mice with and without deficiency of chemoattractant protein-1 receptor, CCR2[30]. Results from their studies suggest that CCR2 plays a crucial role in vascular inflammation and atherosclerosis. In another study, bone marrow transplant procedures were used to investigate the effects of macrophage-derived apo E on atherogenesis in apo E-KO mice[31]. Transplantation of bone marrow from wild-type mice to apo E-KO mice resulted in significant reductions in the formation of atherosclerotic lesions in apo E-KO mice.

Although we have significantly advanced our knowledge in understanding the process of induction of atherosclerotic lesions using various mouse model, our knowledge on regression of these lesions is still very limited. In an attempt to regress atherosclerotic lesions we used apo E-Ko mice. Over a 42-wk of low-fat diet and diets enriched phytosterols, we were unable to regress atherosclerotic lesions in this animal model[32]. Similarly, literature search did not show any significant evidence for a successful regression of advanced atherosclerotic lesions.

RABBITS

The rabbit has been used in many research facilities as an animal model of diet induced atherosclerosis. This species shares several aspects of lipoprotein metabolism with humans. These include composition of apo B containing lipoproteins[33], production of apo B_{100} containing VLDL by the liver[34] plasma CETP activity[35], and high absorption rate of dietary cholesterol[35]. However, the lack of hepatic lipase makes the rabbit to be different from man[36]. Dietary approach is a common method to induce atherogenesis in rabbits. Under these conditions, the animals develop atherosclerotic lesions in the aortic arch and thoracic aorta rather than abdominal aorta which is almost always affected in humans[36].

Two strains of rabbits, namely WHHL and St. Thomas' Hospital (STH) rabbits are naturally defective and relevant models for human hyperlipidemia[7-13,37-39]. The WHHL rabbits are deficient in LDL receptors and therefore resemble human familial hypercholesterolemia[7-13,37], while STH rabbits are used as a model for human hypertriglyceridemia and combined hyperlipidemia[38,39]. Recent advances in gene technology have allowed generation of transgenic rabbits. For example, New Zealand White rabbits have been used to produce human apo B_{100} transgenic rabbits; these animals manifest combined hyperlipidemia with reduced HDL-cholesterol concentrations[33]. On the other hand, over expression of human apo AI or human LCAT in rabbits was associated with elevated HDL-cholesterol levels and reduced atherosclerosis[34,35].

PIGS

Pigs have been used for induction of coronary atherosclerosis by several different laboratories[40-42]. However, induction of advanced atherosclerotic lesions required high levels of dietary cholesterol (up to 4% w/w)[41,43,44]. A strain of pigs has been discovered with three lipoprotein-associated mutations (designated Lpb5, Lpr1, and Lpu1) developing hypercholesterolemia and atherosclerosis without dietary cholesterol[43,44]. In addition to coronary arteries, iliac and femoral arties also develop atherosclerotic lesions which become complicated by 2 years of age[44].

NON-HUMAN PRIMATES

Spontaneous atherosclerosis has been reported in squirrel monkeys, baboons, wooly and spider monkeys[45]. Similar to humans, monkeys can be divided into "hyper-

Table 1 Animal models and their features

Model	Features	Ref.
Mice		
Apo $E^{-/-}$ mice	Develops spontaneous atherosclerosis, associated with elevated levels of circulating cholesterol-rich VLDL particles	Zhang *et al*[3]
LDL receptor deficient KO mice	This model needs dietary cholesterol to develop hypercholesterolemia and atherosclerosis- associated with elevated levels of circulating cholesterol-rich LDL and VLDL particles	Sanan *et al*[16]
Apo E*3-Leiden transgenic mice	This model needs dietary cholesterol to develop hypercholesterolemia and atherosclerosis-associated with elevated levels of circulating cholesterol	Groot *et al*[24] van Vlijmen *et al*[25]
Hepatic lipase-KO mice	This model lacks hepatic lipase and develops elevated levels of plasma cholesterol, phospholipids, and HDL cholesterol and can be used for the study of HDL metabolism.	Homanics *et al*[17]
Human apo B_{100} transgenic mice	This mouse model, associated with substantial increased level of LDL cholesterol level and useful for studying various aspects of lipoprotein metabolism and for further delineating the role of LDL in atherogenesis.	Greeve *et al*[18]
Human CETP transgenic mice	This model has reported to have decreased HDL cholesterol levels with variable degree of atherosclerosis	Föger *et al*[19]
Cross breeding of human apo B_{100} transgenic mice with LDL receptor deficient mice	This model develops severe hypercholesterolemia and atherosclerosis	Sanan *et al*[16]
Cross breeding of human LCAT transgenic mice with CETP transgenic mice.	A mouse model with low total cholesterol levels and reduced atherosclerosis burden.	Föger *et al*[19]
Apo E/GPx1 double knockout (apo $E^{-/-}$ $GPx1^{-/-}$)	This model features combined hyperlipidemia and hyperglycemia with increased oxidative stress	Lewis *et al*[27]
Surgical model of apo $E^{-/-}$ mice	A mouse model for studying unstable/ruptured atherosclerotic plaques	Chen *et al*[28]
Animal model developed using bone marrow technique	Apo E-KO mice model with and without deficiency of CCR2	Ishibashi *et al*[30]
Rabbits		
WHHL	Naturally deficient in LDL receptors resembling human familial hypercholesterolemia	Watanabe[10]
STH	Rabbit model for human hypertriglyceridemia and combined hyperlipidemia	Beaty *et al*[38]
NZW-human apo B_{100} transgenic rabbits	Transgenic animal model manifesting combined hyperlipidemia with reduced HDL-cholesterol concentrations	Fan *et al*[33]
NZW-human apo AI or human LCAT transgenic rabbits	Rabbit model with elevated HDL-cholesterol levels and reduced atherosclerosis	Duverger *et al*[34]
Pigs		
Lipoprotein-associated mutations (designated Lpb5, Lpr1, and Lpu1)	This pig model develops hypercholesterolemia and atherosclerosis without dietary cholesterol. In addition to coronary arteries, iliac and femoral arties also develop atherosclerotic lesions which become complicated by 2 year of age.	Prescott *et al*[44]
Non-human primates		
Rhesus monkeys	Develops spontaneous atherosclerosis. This animal model develops majority of atherosclerotic lesions in the anterior descending and circumflex branches of the left coronary artery	Carey[45]
Cebus monkeys	Develops spontaneous atherosclerosis. This animal model develops atherosclerotic lesions in their carotid bifurcation and coronary arteries	Carey[45]
Cynomolgus monkeys and African green monkeys	These monkeys develop spontaneous atherosclerosis. Atherosclerotic lesions being developed in coronary arteries and abdominal aorta, respectively	Hollander *et al*[49]
Others		
Dogs	These animal models have significant amount of limitations that have not extensively used	Geer *et al*[50]
Hamsters		Nistor *et al*[52]
Guinea pigs		Fernandez *et al*[54]
Birds		Wagner *et al*[56]

Apo $E^{-/-}$: Apolipoprotein E deficient; KO: Knockout; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein; HDL: High density lipoprotein; CETP: Cholesterol-ester transfer protein; LCAT: Lecithin cholesterol acyl transferase; CCR2: Chemoattractant protein-1 receptor, CCR2; WHHL: Watanabe Heritable Hyperlipidemic; STH: St. Thomas' Hospital; NZW: New Zealand White.

responders" and "hypo-responders"[46,47]. Anatomical locations of atherosclerotic lesions vary among different strains of monkeys. For example, majority of atherosclerotic lesions are found in the anterior descending and circumflex branches of the left coronary artery in rhesus monkeys, while cebus monkeys develop such lesions in their carotid bifurcation and coronary arteries[45,48]. The cynomolgus monkeys and African green monkeys also vary from each other in the location of atherosclerotic lesions being developed in coronary arteries and abdominal aorta, respectively[49].

OTHER ANIMAL MODELS

Dogs[50,51], hamsters[52,53], guinea pigs[54], and birds[55,56] have been also used in experimental atherosclerosis. However,

these animals have shown a significant amount of limitations that has not allowed popularity for the use of such animals extensively.

CONCLUSION

This mini-review aims to summarize the features of the most commonly used animal models of atherosclerosis. Despite many advances in medical research, we still do not have specific animal models for specific human conditions. Every animal model has its own advantages and disadvantages. For example, while non-human-primates are the closest animals to humans, variability in lesion development, high cost, availability, possible hazard, ethical issues and handling matters are among major limitations in the use of these animals. Mice and rabbits also vary from humans in regard to lipoprotein metabolism and development of atherosclerotic lesions. However, these species have been the most common animal models used so far. Among these species, either naturally defective animals such as WHHL and STH rabbits[7-13,37-39,57-59], or genetically modified mice have been used extensively in atherosclerosis research. In particular, LDL-r-KO mice[23,60], apo E-KO mice[61-63], Cystathionine γ-lyase-KO mice[64] have contributed to our understanding of the disease pathophysiology. Furthermore, surgical procedures and infectious agents have been also used in a number of animal models to study the postoperative injuries such as neointimal hyperplasia[65], atherosclerotic plaque instability[28] or the role of Chlamydophila pneumoniae[66,67] in disease development. The use of these animal models has certainly advanced our knowledge of the induction of atherosclerotic lesions. However, there is no reliable animal model for regression of atherosclerotic lesions. Further research and development is needed to generate such animal models. The list of animal model and their characteristic are summarized in Table 1.

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