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Atherosclerosis and Animal Models

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Abstract: Cardiovascular disease is currently the major cause of mortality and morbidity in developing and developed countries. Atherosclerosis is the core of cardiovascular disease and is complex inflammatory process. Many animal species have been used to investigate the pathogenesis of atherosclerosis. However, the most useful animal models have been restricted to genetically modified mice or larger animal models including rabbits, pig and non-human primates. Mouse models are widely used for atherosclerosis research due to genetic manipulation. Murine atherosclerosis are different from that of human. Thus, the models are used for investigation of biological processes of atherosclerosis. Rabbits do not develop spontaneous atherosclerosis but they are highly responsive to cholesterol diet and develop plaque in a short time. Pig and monkey are better suitable models because their plasma levels and atherosclerotic plaque are similar to that of human. However, these models are not widely used. Relatively high cost and ethical concern may be major causes.

Key words: Atherosclerosis, animal model, mouse, rabbits, cardiovascular disease

INTRODUCTION

Cardiovascular disease is currently the major cause of mortality and morbidity in developing and developed countries. Its incidence is expected to increase in the future (Bentzon and Falk, 2010). Cardiovascular disease is complex multifactor pathologies which including genetic and environmental factors. Atherosclerosis is the core of cardiovascular disease leading to myocardial infarctions, stroke and peripheral vascular disease encountered in most human populations. Atherosclerosis is complex inflammatory process (Zadelaar *et al*., 2007). So, yet its mechanism is not clear. However, development of animal modes provide us platform for studying pathophysiology and molecular mechanism of atherosclerosis. Additionally, animal models are also essential tools to evaluate effectiveness of preventative and therapeutic strategies. Researchers will summarize the common models of atherosclerosis in this review. It will be useful to further understand development of the models of atherosclerosis.

MICE MODEL

Wild-type mice are resistant to atherosclerosis due to high levels of HDL and low levels of LDL and VLDL. Mice need to been genetically modified to study atherosclerosis. Some of the most widely used strains are Apolipoprotein E (ApoE)-deficient mice, LDL receptor-deficient mice and ApoE*3-Leiden (E3L).

ApoE as a constituent of plasma lipoprotein is synthesized in the liver and macrophages and serves as a ligand for LDL receptor and LDL Receptor-related Proteins (LRP). Deletion of the ApoE in mice increase levels of plasma LDL and VLDL due to the failure of LDL receptor and LRP-mediated clearance of these lipoprotein. On a chow diet, mice exhibit marked hypercholesterolemia (a total cholesterol level >400 mg dL^{-1}) and they develop extensive atherosclerotic lesion widely distributed throughout the aorta. Western diet could accelerate formation of atherosclerotic lesion via rapidly elevating cholesterol level (>1000 mg dL^{-1}) (Nakashima *et al*., 1994). The ApoE-/-mice contains the entire spectrum of lesions observed during atherogenesis. The sequential events involved in lesion formation which is similar to those in human. Fatty streaks were observed in 3 months old mice ApoE-/-fed with chow diet. While fed chow, foam cell lesions first appear at 8-10 weeks of age. After 15 weeks, intermediate lesions are present, containing spindle shaped cells (mostly smooth muscle cells) and beyond 20 weeks, fibrous plaques are evident containing smooth muscle cells, extracellular matrix and an overlying fibrous cap. Predilection sites for atherosclerotic lesion are the aortic root followed by the aortic arch, the brachiocephalic trunk, left carotid and subclavian and

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coronary arteries (Hu *et al*., 2005; Bentzon and Falk, 2010). In older ApoE-/-mice, hemorrhage has been observed in lesions suggesting some degree of lesion instability (Rosenfeld *et al*., 2000). However, high levels of plasma cholesterol is major characters in the mice (Scalia *et al*., 2001). Furthermore, the most plasma cholesterol is confined to VLDL and not to LDL particles as in human. In addition, ApoE exerts antiatherogenic properties via antioxidant, antiflammatory, antiplatlet and up-regulation of NO (Grainger *et al*., 2004; Ali *et al*., 2005; Davignon, 2005; Raffai *et al*., 2005). The immunomodulatory effects of ApoE is important in development of atherosclerosis. It inhibits T-cell proliferation (Davignon, 2005). Macrophage derived ApoE has an independent role in lesion development, perhaps related to the promotion of reverse cholesterol transport (Mazzone and Reardon, 1994). However, the transfer of bone marrow from a mouse expressing ApoE into ApoE-/-recipient reduced atherosclerosis but also reduced plasma lipid level (Linton and Fazio, 1999).

In human, mutations in the gene for the LDL receptor cause familial hypercholesterolemia. The absence of the LDL receptor influences lipoprotein uptake and clearance, resulting in high levels of plasma VLDL and LDL in mice (Teupser *et al*., 2003; Barcat *et al*., 2006; Bentzon and Falk, 2010). LDL receptor-/-mice displays a moderate increase of plasma cholesterol level and develop atherosclerosis slowly on chow diet (Bentzon and Falk, 2010). On chow, limited lesion only develop in older LDL receptor-/-mice (Teupser *et al*., 2003; Barcat *et al*., 2006). However, the severity of hypercholesterolemia and atherosclerotic lesions requires the feeding of a high-fat, high-cholesterol diet (Knowles and Maeda, 2000). High-fat diet could induce accumulation of larger VLDL/remnant lipoproteins in addition, plasma cholesterol levels are much higher than in chow-fed ApoE-/-mice (Hartvigsen *et al*., 2007). Lesions in the LDL receptor-/-mice have a greater preponderance of foam cells than in chow-fed ApoE-/-mice. The systematic pathological analysis of lesion development were not reported in LDL receptor-/-mice (Linton *et al*., 1999). The advantage of this model is that LDL receptor dose not have the multitude of functions of ApoE.

The ApoE*3-Leiden mutation is a rare dominant negative mutation in the human *ApoE3* gene. ApoE*3-Leide transgenic mice have been generated by introducing a human ApoE*3-Leiden gene construct into C57B1/6 mice. ApoE*3-Leide mice are very useful to explored the mechanisms by which the ApoE isoforms influence lipid metabolism and atherosclerosis (Hofker *et al*., 1998; Pendse *et al*., 2009). ApoE*3-Leide mice show elevations of plasma cholesterol and triglycerides on chow diet. High-fat, high-sugar and high-cholesterol could accelerate this process (Van Vlijmen *et al*., 1994). In addition, ApoE*3-Leide mice also represent Dysbetalipoproteinemia Model in which plasma cholesterol and triglycerides are mainly VLDL and LDL-sized lipoprotein fraction (Hofker *et al*., 1998). This model develop atherosclerotic lesion with all the characteristics of human pathology, varying from fatty streak to mild, moderate and severe plaques (Leppanen *et al*., 1998; Lutgens *et al*., 1999).

Three mouse models have been used extensively as a springboard for study of other genes affecting atherogenesis. The murine products take the form of either double knockout mice or overexpression a gene. LDL receptor-/-mice coupled with an ApoB-editing deficiency or combined with human ApoB 100 transgenic mice show a larger increase in plasma LDL cholesterol and develop atherosclerosis on a low-fat diet (Powell-Braxton *et al*., 1998; Sanan *et al*., 1998). ApoE*3-Leide mice crossbred with human Cholesteryl Ester Transfer Protein (CETP)-expressing mice display an elevated basal cholesterol level and an even more human-like lipoprotein profile. CETP expression can shift the distribution of cholesterol from HDL toward VLDL/LDL (Rensen and Havekes, 2006; Westerterp *et al*., 2006). ApoE-/-mice overexpressing human ABCA1 do not protect against plaque development (Singaraja *et al*., 2002). Complete absence of ABCA1 in the setting of ApoE deficiency resulted in plasma lipid reduction and tissue foam cell accumulation but no increase in atherosclerosis. However, selective absence of ABCA1 in macrophages resulted in markedly increased atherosclerosis with no effect on plasma lipids (Aiello *et al*., 2002). ApoE-/-mice over-expressing ApoA-I show decreased lesion size with increased HDL formation (Paszty *et al*., 1994; Benoit *et al*., 1999). SR-A deletion in the ApoE-/-mice reduced atherosclerosis despite increased serum cholesterol (Suzuki *et al*., 1997). Its overexpression reduced serum cholesterol but did not promote atherosclerosis (Van Eck *et al*., 2000). SR-BI deletion in the ApoE-/-mice increased atherosclerosis compared with its overexpression (Zhang *et al*., 2003). The double knockout ApoE-/-RAG-/-dose not prevent atherosclerosis (Daugherty *et al*., 1997). The ApoE-/-mice overexpressing human C-reactive protein further promotes atherosclerosis development (Paul *et al*., 2004) P-selectin-/-ApoE-/-double knockout mice also reduced size of aortic sinus lesion (Dong *et al*., 2000) gene transfer of P53 to ApoE-/-mice did not alter plaque size but it cause a shift toward vulnerable plaque with a decrease in cap-to-intima area ratio, cap breaks and intrplaque hemorrhages (Von der Thusen *et al*., 2002).

RABBIT MODEL

The rabbit is sensitive to dietary cholesterol (Dornas *et al*., 2010). It as atherosclerosis model can supply useful information which is the progression and regression of atherosclerosis in human. Although, the rabbit express CETP not similar to mice is have low plasma levels of hepatic lipase and lack ApoA-II. Lipoprotein and atherosclerosis response were modulated by feeding cholesterol diets. On chow, the rabbit is not inherently prone to atherosclerosis due to low levels of plasma cholesterol (Finking and Hanke, 1997). High-cholesterol diet (0.5-4%) rapidly increases plasma cholesterol levels (>1000 mg dL^{-1}) and leads to the formation of lesion-enriched foam cell. This contributed to the mechanisms the lipid induce macrophage accumulation and other aspects of atheroma inflammation (Bustos *et al*., 1998; Aikawa *et al*., 2002). The development of advanced and complex atherosclerotic plaque requires long periods of cholesterol feeding. However, long term cholesterol feeding increases hepatic toxicity and induces a massive inflammatory response that does not resemble the chronic low-grade inflammatory response associated to human atherosclerosis. In addition, the formation of advanced lesion in rabbit depends on the age. Aged rabbits with 3-4.5 years old, frequently develop fibrous plaques whereas young animal (4 months of age) do not show advanced lesion (Dornas *et al*., 2010). Rupture of the atherosclerotic plaque is known to be the major cause of thrombosis and subsequent clinical manifestations of atherosclerosis (Libby, 1995; Lee and Libby, 1997; Shiomi *et al*., 2004). Models of plaque rapture in rabbit was been developed via the combination of aggressive vascular injury associated to a cholesterol diet. The aortic plaque had the three features of vulnerable plaque: lipid-rich core, accumulation of macrophages and a thin fibrous cap (Shimizu *et al*., 2009). In addition, the lesion is commonly induced using an intravenously injected ballon containing Russel's viper venom and histamine a procedure that will result in plaque rupture and thrombosis (Johnstone *et al*., 2001). The implantation of balloon catheter in the thoracic aorta also lead to lesion rupture (Rekhter *et al*., 1998).

Some rabbits carry genetic mutation that lead to hyperlipidemia and atherosclerosis. The most widely used hyperlipidemic rabbit in atherosclerosis research is the Watanabe Heritable Hyperlipidemic (WHHL) rabbit. WHHL rabbit carry an inactivating mutation in the gene encoding the LDL receptor and exhibit hypercholesterolemia with increased plasma levels of LDL and VLDL reduced plasma levels of HDL. The WHHL rabbit develop aortic atherosclerotic plaque ranging from fatty streaks to advanced lesion and exihibit severe coronary atherosclerosis (Shiomi *et al*., 1992). Transgenic rabbits provide a important pathway for researching atherosclerosis development. Rabbits with liver-specific expression of human apolipoprotein A-I exhibit smaller atherosclerosis lesions than nontransgenic rabbit (Rekhter *et al*., 2000; Broeders *et al*., 2002). Rabbits that overexpress human lecithin-cholesterol acyltransferase have reduced atherosclerosis compared to rabbits-fed a cholesterol diet (Aikawa *et al*., 1998). Furthermore, WHHL rabbits that express human apolipoprotein, exhibit accelerated atherosclerosis development and more complex lesions than nontransgenic rabbits. Additionally, human lipoprotein lipase overexpression in WHHL rabbit leads to enhanced aortic atherosclerosis (Abela *et al*., 1995; Corseaux *et al*., 2000).

PIG MODEL

Although, rodents and rabbits have been used extensively for atherosclerosis research these animal model limits the quantities of new agents required for *in vivo* screening due to different lipid physiology from that in humans and small size. Thus, lager Animal Models were pay attention for atherosclerosis research.

Pig is suitable atherosclerosis model. Many characteristics of pig resemble that of human such as development, morphology and function of the cardiovascular system, lipoprotein profiles and metabolism. Additionally, it develops spontaneous atherosclerotic lesions and may develop sudden death when under stress. Currently there is no single and golgen standard animal models of vulnerable plaque but pig model are probably the best way to recreate human plaque instability. It is worth mentioning that pig can offer the ability to evaluate coronary arteries rather than central aortic in smaller animals (Badimon *et al*., 1985; Fuster *et al*., 1985; Palazon *et al*., 1998; Royo *et al*., 2000).

Atherosclerosis can be generally quite slow and spontaneously occurs by regular chow or high cholesterol diet induction in most arterial beds of pigs (Skold *et al*., 1966; Fuster *et al*., 1991; Casani *et al*., 2005). Furthermore, the atherosclerotic plaque distribution and composition is similar to that in human (White *et al*., 1992; White and Bloor, 1992; Gal *et al*., 1992). This phenomenon may attribute to human like lipoprotein metabolism of pigs (Marzetta and Rudel, 1986). Additionally, atherosclerotic plaque first happen in coronary arteries of pigs. After gradually occlusion of coronary arteries, pigs may develop the coronary restenosis syndrome as human (Swindle, 1998).

Like in other animal models, atherosclerotic plaque development in pigs can be accelerated by high cholesterol diet. The high cholesterol diet firstly, induce hypercholesterolemia in pigs. Almost all pigs can develop fatty streaks localized in abdominal aorta and a lesser extent in the coronary arteries after 50 days with high cholesterol diet induction. Moreover, lesion composition was similar to early stage human atherosclerosis (Casani *et al*., 2005). After 100-150 days by the diet induction, lesion severity was higher degree than that of induction for 50 days. Pigs employed tend to be within the prepuberty period in long period study. However, their lesions are not as severe as those developed in adult human. Although, older pigs can be used to obtain relative severity plaque as adult human, management becomes more difficult due to their considerable weight (Jorgensen, 2006). Thus, miniature pigs are preferable to atherosclerotic animal models because of their small size and growth rate.

Both diabetes and hypercholesterolemia are major risk factors for atherosclerosis. Moreover, these disease frequently co-exist in patients with metabolic syndrome. However, the animal models which investigate mechanism underlying diabetes accelerated atherosclerosis are scare. People have found that pig are suitable model for atherosclerosis accompanying with diabetes. The combination of hypercholesterolemia and diabetes accelerates atherosclerotic lesion and makes animal handling easier and leads to the formation of advanced human like atherosclerotic lesion in pigs (Gerrity *et al*., 2001; Mohler III *et al*., 2008; Wilensky *et al*., 2008).

The angioplasty and stenting have become established treatments for coronary artery disease. The part stent implantation (20-30%) initially appeared promising in so-called ideal lesion. However, there is still a high rate of vessel resclosure resulting in the need for repeat procedure (Edelman *et al*., 1998). Compared to other animal models, pig coronary stenting is a suitable model because injury response is similar to human vessels with an adaptive response (Rodgers *et al*., 1990). Moreover, size and anatomic distribution of pigs coronary arteries are similar to those of human. Furthermore, angiography, intravascular ultrasound, instrumentation and stent deployment in the pig are all similar to the clinical situation (Gershlick and Baron, 1998).

NON-HUMAN PRIMATES

Non-human primates models for atherosclerosis reseach include Cebus, Woolly, squirrel, African Greeen, Rhesus and Cynomolgus monkey. Although, these models lipoprotein metabolism is similar to human, atherosclerosis susceptibility are different among them (Vesselinovitch *et al*., 1974; Davis *et al*., 1984; Mott *et al*., 1992; Wolfe *et al*., 1994). Rhesus, Cynomolgus, Cebus monkey are extensively researched because of distinct advantages. These models can develop spontaneous atherosclerosis in some arteries including the coronary arteries. High cholesterol diet greatly accelerates atherosclerosis development. Moreover, low fat diet can regress coronary atherosclerosis. The regression was associated with a reduction in cholesterol content of the lesion, consistent with a reduction in the number of foam cells (Mann *et al*., 1953; Taylor *et al*., 1954; Taylor *et al*., 1962; Bullock *et al*., 1969; Clarkson *et al*., 1979; Clarkson *et al*., 1984; Beere *et al*., 1992). Additionally, male were more affected than female in non human primates (Bullock *et al*., 1969). Older animals are more susceptible to atherosclerosis but young animals are resistant to atherosclerosis (Clarkson, 1998). Ethical concern limited utility for research of non human primates.

CONCLUSION

A variety of small and large animal models have been used to study the atherogenic process. No model is ideal. Each model has its own advantages and limitations with respect to manipulation of the atherogenic process and modeling human atherosclerosis or lipoprotein profile. The choice of the suitable animal model depends on the nature of the research that is to be performed.

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