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Review Article

Animal models of coronary heart disease

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Abstract

Cardiovascular disease, predominantly coronary heart disease and stroke, leads to high morbidity and mortality not only in developed worlds but also in underdeveloped regions. The dominant pathologic foundation for cardiovascular disease is atherosclerosis and, as to coronary heart disease, coronary atherosclerosis and resulting lumen stenosis, even total occlusions. In translational research, several animals, such as mice, rabbits and pigs, have been used as disease models of human atherosclerosis and related cardiovascular disorders. However, coronary lesions are either naturally rare or hard to be fast induced in these models, hence, coronary heart disease induction mostly relies on surgical or pharmaceutical interventions with no or limited primary coronary lesions, thus unrepresentative of human coronary heart disease progression and pathology. In this review, we describe the progress of animal models of coronary heart disease following either spontaneous or diet-accelerated coronary lesions.

Keywords: coronary heart disease, animal models, coronary atherosclerosis, coronary arteriosclerosis

Introduction

Cardiovascular disease (CVD), predominantly coronary heart disease (CHD) and stroke, has been a leading health killer in the developed world for more than half a century and for the recent decades has been soaring rapidly in many underdeveloped regions. According to WHO's report, it claimed 17.3 million deaths worldwide in 2008, accounting for 30% of the total deaths of that year. Among those died from CVD, 7.3 million people were victims of CHD[1]. The dominant pathologic foundation for CVD is atherosclerosis (AS) and, as to CHD, coronary AS and resulting lumen stenosis, even total occlusions. The high morbidity and mortality of CHD require appropriate animal models for translational research, not only to better understand the underlying mechanisms but also to explore corresponding targets and drugs for clinic treatment. To date, several animals, such as mice, rabbits and pigs, have been commonly used as disease models of human AS and related cardiovascular disorders. However, coronary lesions are either naturally rare or hard to be fast induced in these models, so CHD induction mostly relies on surgical or pharmaceutical interventions with no or limited primary coronary lesions. As a result, CHD progression and pathophysiological changes seen in these disease models are unrepresentative of those seen in humans. In this review, we are going to describe the progress of

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animal models of CHD following either spontaneous or diet-accelerated coronary lesions.

Small animal models of CHD

Murine models of CHD

Mice are naturally resistant to AS, probably because the pro-atherogenic low density lipoprotein cholesterol (LDL-C) can be fast degraded from plasma and the athero-protective high density lipoprotein cholesterol (HDL-C) is much higher than LDL-C. Ever since the creation of hypercholesterolemic apolipoprotein E (apoE) gene knockout (KO)[2-3] and LDL receptor (LDL-R) KO[4-5] mice with predicted spontaneous and diet-accelerated AS, mice have been established as the most widely used animal models in cardiovascular research. However, the atherosclerotic plaques in mice are usually restricted to the aorta and aortic sinus with their coronary arteries often lesion-free.

Murine models with SR-BI deficiency

Scavenger receptor class B type I (SR-BI) is an 85 KDa membrane glycoprotein that contains a large extracellular domain, two transmembrane domains, a short cytoplasmic N-terminal domain and a PDZK1-binding-motif containing C-terminal domain[6-8]. Mainly expressed in liver and steroidogenic glands, it can also be found in many other tissues, such as brain and intestine, and a wide range of cells including endothelial cells (ECs), macrophages and smooth muscle cells (SMCs)[8-9]. Known as the first and major HDL receptor with high binding affinity, SR-BI not only mediates the efflux of unesterified cholesterol (UC) from peripheral cells to the circulating HDLs but also promotes the selectively uptake of cholesterol esters (CE) from HDLs for biliary secretion or glucocorticoid synthesis[7,9-11]. Modulation of its expression by deficiency of the homonymic gene[12] or disruption of its adaptor protein PDZK1[13-14] exerts significant effects on lipid metabolism, especially HDL metabolism. For example, ablation of SR-BI expression by global knockout of *srb1* causes a nearly two-fold increase of HDL-C, mainly in the form of UC, and a causative two-fold increase of total cholesterol[15]. Partial ablation of SR-BI expression by knockout of *Pdzk1*, which preserves 5% and 50% of SR-BI expression in liver and intestine respectively with almost no change in other sites, generates similar but milder lipid disorders[13-14]. The accumulation of UC in HDLs from SR-BI deficient mice attenuates the normal anti-atherogenic functions of HDLs. In hypercholesterolemic conditions, more UC would accumulate, leading to the formation of pro-atherogenic HDLs (toxic HDLs). As such, SR-BI deficiency aggravated AS. Moreover, it even led to occlusive coronary AS followed by spontaneous myocardial infarction (MI) in apoE KO mice on rodent chow diet[16]. Yet, the CHD in SR-BI/apoE dKO mice progressed so rapidly that no dKO mice survived 8 weeks after birth[16]. Preserved expression of apoE, even only 2%-5% of its normal levels, either by targeted disruption of the apoE gene (Thr61→Arg61, designated as HypoE)[17-18] or received bone morrow transplant from non-apoE KO donors[19], prevented the development of hypercholesterolemia preconditioned to generate the toxic HDLs and causative lethal CHD on normal chow diet or mild atherogenic Western diet (0.15% cholesterol, 22% fat) but not on intense atherogenic Paigen diet (1.25% cholesterol, 15.8% fat, 0.5% sodium cholate). Preserved expression of SR-BI by knockout of *Pdzk1* also protected the mice from CHD progression on chow diet. Yet after initiation of Paigen diet for 3 months, PDZK1/apoE dKO mice developed coronary AS and MI, but no cardiac dysfunction and death, probably due to the residual SR-BI expression or insufficient Paigen diet feeding[20]. In another AS-prone model of LDL-R KO mice, we and another group recently demonstrated SR-BI deficiency also resulted in coronary AS and lethal CHD on various atherogenic diets, including modified Western diet (0.5% cholesterol, 20% fat) (unpublished data), high cholesterol diet (2% cholesterol)[21], standard Paigen diet[21] and modified Paigen diet (1.25% cholesterol, 15.8% fat without sodium cholate addition)[21]. The progression of CHD in SR-BI/LDL-R dKO mice, evaluated by the median time of survival, varied due to the specific atherogenic diet adopted, with the shortest 3.5 weeks on standard Paigen diet[21], 9.4 weeks on modified Paigen diet[21], 11.4 weeks on high cholesterol diet[21] and the longest 13.9 weeks on modified Western diet (unpublished data). Even with the same atherogenic diet feeding, a different feeding protocol also led to different outcome, as demonstrated in SR-BI KO/HypoE mice that a sustained Paigen diet feeding caused fast death in less than 1 month while a restricted Paigen diet for only 1 week slowed down the onset of heart failure and resulted in ischemic cardiomyopathy with multiple diffused coronary lesions[18].

Murine models with NOS deficiency

The endothelium is a multi-functional player in maintaining cardiovascular hemostasis and health. Its functions include regulation of vascular tone and growth, control of thrombosis and thrombolysis, inhibition of inflammation and SMC proliferation[22]. Many of these functions are mediated *via* nitric oxide (NO) synthesized and released by endogenous NO synthase

(NOS), which consists of three isoforms, namely neuronal, inducible, and endothelial NOS (nNOS, iNOS and eNOS respectively) with eNOS attracting the most attention, as endothelial dysfunction, due to disrupted eNOS activity and causative defect in NO production, is now widely accepted as the initiative step in the onset and progression of AS. In mice, knockout of *eNOS* resulted in elevated blood pressure variability, ejaculatory abnormalities, impaired wound healing and angiogenesis[23-25]. What's more, when eNOS KO mice were bred into apoE KO background, the generated eNOS/apoE dKO mice presented coronary arteriosclerosis, myocardial ischemia/infarction, heart failure and vascular complication of aortic aneurysm and dissection on Western diet feeding[26]. Yet deletion of eNOS resulted in up-regulation of other NOS isoforms as represented by preservation of both NOS activity and nitrite plus nitrate production[27-29], suggesting that there might be compensatory interactions among the NOS family. To observe the effect of the entire NOS system on the cardiovascular system, NOS tKO mice were generated[30]. These mice suffered severe spontaneous cardiovascular abnormalities, including hypertension, dysfunctional vascular relaxation and constriction, MI, left ventricular hypertrophy and subsequent death[30]. Although dyslipidemia could be observed, coronary arteriosclerosis rather than coronary AS, similar to those seen in eNOS/apoE dKO mice, illustrated the onset of MI. Besides, a significant mast cells infiltration was noted at the coronary artery adventitia, suggesting coronary spam, caused by mast cell-derived histamine release, might also be contributory[30].

Murine models with fibrillin deficiency

Elastic fibres, comprised by a cross-linked elastin core and fibrillin-rich microfibrils mantle, are key extracellular matrix that is critical to elasticity and resilience of the arterial walls. Disturbance of the elastic fibres, due to a series of physiological and pathological factors including aging, metabolic syndrome and genetic defects, can cause irreversible stiffness and/or weakness of the vessels and may result in multiple adverse consequence, such as hypertension and aneurysms[31-32]. Fibrilin-1, a member of the fibrillin superfamily, is the major structural component of microfibrils. Besides, it plays a major role in binding and sequestering various growth factors such as pro-inflammatory transforming growth factor-β, which also facilitates the release of proteases that degrade elastin fibres. Deficiency of *fibrilin-1* leads to Marfan syndrome featured by aneurysmal dilatation, ectopia lentis and skeletal defects[33]. In apoE KO mice fed Western diet, heterozygous mutation in *fibrilin-1* led to elastin fragmentation, which not only accelerated AS development but also induced intraplaque hemorrhage and neovascularization, resulting in spontaneous plaque rupture. With restricted blood flow to the heart and brain due to thrombosis formation and embolism post rupture, the mice presented myocardial and cerebral ischemia/infarction and finally died[34]. The combination of MI and stroke following plaque erosion and rupture suggested these mice were especially unique for studying the mechanisms of vulnerable plaques progression and therapeutics.

Other murine models

Apart from the above strains, three other models also exhibited CHD when fed atherogenic diets. These models were apoE/LDL-R dKO mice[35], apoE KO mice with macrophage-targeted overexpression of urokinase[36] and apoE KO mice with Akt1 deficiency[37-38]. Braun et al have already discussed these three models in 2008[39]. We sincerely recommend their review for more information. For quick reference, basic information about murine CHD models is summarized in ***Table 1***.

Rat models of CHD

Similar to mice, rats are also resistant to AS. However, gene-modified strains of rats were much less than those of mice that no AS-prone rat strains have been reported until the generation of LDL-R mutant strain recently[40]. Although the LDL-R mutant rats developed AS on atherogenic diet feeding, the plaques were only seen in the aorta but not in the coronary vasculature[40]. To date, only two rat strains were reported to develop coronary AS and heart diseases. One strain was the JCR: LA-cp rats which carried the corpulent (cp) gene mutation. Due to an absence of the leptin receptors caused by the mutation possibly, the JCR: LA-cp rats became obese, insulin resistant and hypertriglyceridemic and developed vasoculopathy and AS, possibly resulting from the disturbed functions of SMCs and ECs[41]. Male JCR: LA-cp rats even developed thrombotic occlusions in the coronary arteries and ischemic damages in the myocardium[41]. Although hyperlipidemia is an undeniable metabolic disorder present in these rats, insulin resistance and its related other factors played a dominant destructive effect, as both dietary and pharmacological interventions provided supporting evidence. Dietary supplement of fructose[42] or ethanol[43] and food restriction combined with[44] or without exercise[45] all led to a virtual reduction of plasma insulin levels and a following reduction of ischemic myocardial infarctions, yet lipid-lowering olive oil or redfish oil supplement[46] provided no cardiac protection. Drugs that could improve insulin and glucose metabolism,

Table 1 **Murine models of coronary heart disease.**

Strain	Induction	Diet	Cardiac phenotype		Survival
			Coronary	Myocardium	
apoE/LDL-R dKO	Stress-induced	Sustained WD feeding	Plaque stenosis/occlusion in the proximal segment	AMI, myocardial apoptosis, inflammation, cardiac fibrosis	Died after 6 months on this diet
SR-BI/apoE dKO	Spontaneous	NCD	Extensive lipid- and fibrin-rich occlusion	AMI, cardiac hypertrophy, fibrosis and lipids accumulation	50% mortality at 6 weeks old
SR-BI KO/HypoE	Diet-induced	PD for 4 weeks	Lipid-rich occlusion, intraplaque hemorrhage	Cardiac hypertrophy, infarction and fibrosis	50% mortality after 20 days on this diet
	Diet-induced	PD for 1 week	Multiple diffuse lipid-rich stenosis, occasional thrombus	Cardiac fibrosis, predominantly located near the endocardium	50% mortality after 36 days on this diet
SR-BI/LDL-R dKO	Diet-induced	PD for 12 weeks	Lipid-rich occlusion, platelet accumulation	Cardiac hypertrophy, infarction and fibrosis	50% mortality after 3.5 weeks on this diet
	Diet-induced	PD without sodium cholate for 12 weeks	Lipid-rich occlusion, platelet accumulation	Cardiac hypertrophy, infarction and fibrosis	50% mortality after 9.4 weeks on this diet
	Diet-induced	2% cholesterol diet for 12 weeks	Lipid-rich occlusion, platelet accumulation	Cardiac hypertrophy, infarction and fibrosis	50% mortality after 11.4 weeks on this diet
	Diet-induced	WD with 0.5% cholesterol for 20 weeks	Plaque stenosis/occlusion in the proximal segment	Cardiac hypertrophy and ischemia	50% mortality after 13.9 weeks on this diet
PDZK1/apoE dKO	Diet-induced	PD for 3 months	Lipid-rich occlusion, perivascular fibrosis	Cardiac fibrosis	No additional mortality
eNOS/apoE dKO	Diet-induced	WD for 16 weeks	Distal arteriosclerotic lesion with fatty streak, perivascular fibrosis	Cardiac ischemia, hypertrophy and fibrosis	No additional mortality
n/i/eNOS tKO	Spontaneous	NCD	Distal arteriosclerotic lesion, perivascular fibrosis and mast cell infiltration	Cardiac fibrosis and hypertrophy	50% mortality after 7.5 months on this diet
SR-uPA^{tg}/apoE KO	Diet-induced	sustained WD feeding	Ostial stenosis, proximal coronary occlusion	AMI, cardiac hypertrophy and fibrosis	50% mortality after 20 weeks on this diet
Akt1/apoE dKO	Diet-induced	PD for 12-14 weeks	Lipid- and fibrin-rich plaques in the proximal and distal segment	AMI	20% mortality
Fbn1$^{mut+/-}$/apoE KO	Diet-induced	WD for 35 weeks	Coronary occlusion, perivascular fibrosis	Cardiac hypertrophy, infarction, inflammation and fibrosis	50% mortality after 20 weeks on this diet

WD: western-type diet; NCD: normal chow diet; PD: paigen diet; AMI: acute myocardial infarction

such as the anorectic compound benfluorex[47] and D-fenfluramine[48] and the α-glucosidase inhibitor acarbose[42], also protected against ischemic damage to the myocardium. Another strain was the hypertensive Dahl salt-sensitive rats with human cholesteryl ester transfer protein (CETP) transgene (Tg[hCETP]^{DS} rats). The CETP is a key player in lipoprotein metabolism, which mediates the exchange of CE from HDL to apoB-containing lipoproteins such as intermediate density lipoproteins (IDL) and LDL for triglycerides (TG). CETP transgene resulted in a significant increase of pro-atherogenic IDL-C/LDL-C and TG and a significant decrease of anti-atherogenic HDL, leading the rats prone to AS development[49]. The additional hypertensive status then accelerated atherosclerotic lesion progression, which could be prevented by low-salt diet feeding[50]. However, hypertension itself did not induce coronary AS, as blood pressure in Tg[hCETP]^{DS} rats was even slightly lower than their hypertensive Dahl salt-sensitive but non-hCETP transgenic controls, which had no coronary AS[49]. Apparently, CETP transgene and hypertension alone could not explain the presence of CHD seen in Tg[hCETP]^{DS} rats. How these two factors combined modulated the susceptibility of coronary AS thus warrants further investigation.

Large animal models of CHD

Rabbit models of CHD

Rabbits are another animal model widely used for cardiovascular diseases[51-54]. Compared to rodents, rabbits are better representative of human lipoprotein metabolism. For examples, plasma cholesterol is distributed mainly in HDLs in rodents rather than in LDLs in both rabbits and humans. The aforementioned CETP is naturally inactive in rodents, yet plays its key role in lipoprotein metabolism as previously described in both rabbits and humans; Another key player, liver apoB-editing protein, which edits apoB100 into apoB48, is just the opposite of CETP[55]. Even so, rabbits are still resistant to AS. The Watanabe heritable hyperlipidemic rabbits (WHHL rabbits) are a very special strain found in Japan which are naturally deficient in LDL-R and have hypercholesterolemia on chow diet and develop spontaneous AS[56]. Selective breeding of WHHL rabbits obtains offsprings with higher plasma cholesterol and accelerated AS not only in aorta but also in coronary arteries (designated as WHHL-CA rabbits)[57]. However, the incidence of MI in WHHL-CA rabbits was rather low (only 23%). Following further selective breeding of WHHL-CA rabbits, the incidence of MI could reach 97% (designated as WHHL-MI rabbits)[58-59]. Study into coronary arteries of WHHL-MI rabbits revealed the occurrence of atheromatous plaque containing a large lipid core with a thin fibrous cap, accompanied by accumulation of macrophages and foam cells and expression of high levels of matrix metalloproteinase, strongly suggesting these plaques were unstable. Yet no signs of plaque ruptures and following thrombus formation could be detected[60].

Porcine models of CHD

Genetically closer to humans, large animals, represented by pigs and non-human primates, also share similar characteristics of lipoprotein metabolism including cholesterol distributions and enzymatic activities and vasculature anatomy including heart size and coronary circulation. Besides, their life styles are more comparative to humans as both pigs and non-human primates are omnivorous and diurnal. Elderly farm pigs[61] and non-human primates[62] even develop spontaneous AS. Yet for ethical issue, non-human primates are restricted in bio-medical research. Thus pigs are currently the most acceptable large animal models. Different from the situation in the above described animals, the coronary arteries of farm pigs are vulnerable to AS development, although the time cause for such lesions to reach severe occlusion (>50%) usually takes no less than half a year even on atherogenic diet feeding with coronary endothelium injury surgery and irradiation[61,63-65]. What's more, the large sizes of these animals place much burden on raising and handling. The last three decades have seen the rises of several modified miniature pigs that weigh no more than 80 kg, only one third of their original sizes. Recently, a strain of micro-minipigs have been developed in Japan which even only weigh 7 kg[66]. Besides the significant reduction in size, the time course for diet-accelerated coronary atherosclerotic occlusion drops to only three months. These modified strains include the LDL-R deficient Rapacz minipigs[67], the Ossabaw metabolic syndrome pigs[68], the proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutant minipigs[69] and the Japanese microminipigs[66], although balloon injury was applied in some, but not all, of these models. Although coronary atherosclerotic occlusions reached at least 50% and in some cases 90-95%, ischemic lesions in the myocardium were not reported, suggesting that these modified porcine strains are more appropriate as models of coronary artery disease (CAD) rather than CHD.

Conclusion

In this review, we described several animals including both small animals represented by mice and rats and large animals represented by rabbits and pigs, about their application as disease models of CHD. While small animals, especially mice, are now commonly

used in basic research for molecular mechanism of AS and related cardiovascular disorders, large animals were mostly applied in pre-clinic studies for evaluation of drug treatment and imaging techniques. The distinction of pigs as models of CAD rather than CHD suggests coronary arteries may have a powerful fractional flow reserve to support the myocardium. Although the establishment of diet-induced CHD/CAD models provided researchers with more options of which type of and how atherogenic diets were given to better manipulate the disease onset and progression, as compared to spontaneous CHD models, all these animal models were definitely invaluable tools for translational research.

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