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Genetically-engineered animals as research models for atherosclerosis : their use for the characterization of PPAR agonists in the treatment of cardiometabolic disorders

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1. ABSTRACT

Experimental approaches to understand the pathogenesis and to develop treatments of atherosclerosis involve studies in animal and cellular models. However, relevant animal models are rare since atherosclerosis is a disease that naturally affects only humans and one or two other species (pigs and certain primates). For a long time, atherosclerosis studies were carried out using diet-induced atherosclerosis models, even though the diets were unphysiological and the arterial lesions that developed were often limited in size, composition and location. During the last decade, with the advent of molecular genetics and genetic manipulation techniques, the development of genetically-engineered animals, mainly mice, allowed an explosion in the number of models resulting in a tremendous progress in atherosclerosis research and enhancement of our understanding of the disease. Atherosclerosis is a multifactorial disease which normally develops very slowly and asymptomatically during several decades, leading to atheromatous plaque formation. Once the plaque is weakened, its rupture or erosion induces severe clinical complications, such as myocardial infarction or cerebrovascular accidents. Several risk factors predispose to atherosclerosis including hypertension and abnormalities in lipoprotein metabolism and glucose homeostasis. The formation of the atherosclerotic lesion is a complex process, characterized by the presence of lipid-laden monocyte-derived macrophages (called foam cells), establishing therefore a status of chronic inflammation. The dysregulated expression of genes encoding proteins involved in the control of metabolic pathways contributes to vascular inflammation and the development of atherosclerosis. The expression of these genes is controlled by different transcription factors amongst which are the Peroxisome Proliferator-Activated Receptor (PPAR) family of nuclear receptors. This review focuses on the use of genetically-engineered animals as models for experimental atherosclerosis research, pointing out their contribution to investigate the implication of PPARs and their ligands in regulating metabolic and inflammatory abnormalities predisposing to atherosclerosis development.

2. INTRODUCTION

It has been almost 100 years that the first evidence of experimental atherosclerosis was revealed using rabbits fed a special diet rich in proteins (meat, milk, eggs) (1). Until 1992, atherosclerosis research was executed using animals fed a cholesterol-containing diet, including, over the years, models such as rabbits, pigeons, pigs, dogs, rats, primates and, eventually, mice. Indeed, for a long time, the mouse was not used as an experimental model for atherosclerosis research principally because of its natural high resistance to the disease. Studies in the late 60's and early 70's first demonstrated that only when fed diets high in cholesterol and fat, containing moreover cholic acid, certain strains of mice could develop atherosclerotic lesions (2, 3). These diets were very toxic and few mice survived. Moreover, when present, vascular lesions were not reproducible and their pathology differed from the human condition. Lower-fat and less toxic diets were then used, solving therefore the survival problem but most mice did not develop lesions. Next, the use of inbred rather than outbred strains improved the reproducibility problem (4). Finally, the knowledge that inbred mouse strains exhibit differences in susceptibility to atherosclerosis when fed an atherogenic diet, resulted in the most frequent use of those strains developing lesions (5). Although these mouse models of diet-induced atherosclerosis have provided considerable insight into mechanisms of atherogenesis, there were also many disadvantages in using them. The lesions are very small and largely limited to the aortic root. They consist almost entirely of macrophage foam cells with little evidence for smooth muscle cell involvement, limiting therefore the models to the early fatty streak stage without progression to complicated lesions. Therefore, the use of diet-induced atherosclerosis mouse models gradually diminished with the advent of genetically-engineered animals. This development has mainly been performed in the mouse system using transgenic and gene knock-out (KO) or knock-in (KI) technologies. Mice that displayed a higher susceptibility to the disease and exhibited larger atherosclerotic lesions were so created. Transgenic rats or rabbits have also been produced and used to study atherosclerotic mechanisms.

3. ATHEROSCLEROSIS AND PPARs

Atherosclerosis is a multifactorial process which may silently progress over decades but ultimately results in acute cardiovascular diseases (CVDs), principally ischemic events (e.g. myocardial infarction and stroke). Numerous factors, called risk factors, promote atherosclerosis and play significant roles in its development. Among them, some are genetic (sex, familial history), others are linked to environmental conditions (cigarette smoking, life-style and dietary habits) or metabolic perturbations (visceral obesity, hepatic steatosis, insulin resistance) resulting in clinical symptoms and pathologic systemic biological parameters like hypertension, obesity, dyslipidemia, hyperglycemia. These abnormalities are generally clustered and constitute the metabolic syndrome, yielding a prothrombotic and proinflammatory state. Atherosclerosis results from a cascade of events that involve interactions between the vessel wall and blood components (Figure 1). These interactions result in abnormal tissue growth and lipid deposition within the vessel wall. Development of the atherosclerotic lesion starts as a result of endothelial injury and dysfunction triggered by risk factors. In this phase that precedes lesion formation, endothelial permeability is increased to circulating low-density lipoprotein (LDL) particles which are trapped into the vessel wall and therefore have increased susceptibility to oxidation. Subsequently, upregulation of endothelial adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, or E-selectin, along with chemokine release from the endothelium and subendothelial cells, such as monocyte chemotactic protein (MCP)-1, facilitate the recruitment and migration into the vessel wall of peripheral blood cells, including lymphocytes and monocytes. Once migrated into the vessel wall, monocytes differentiate to macrophages and accumulate lipids from oxidized LDL via macrophage scavenger receptors (MSRs), especially MSR-A and CD36, leading to the generation of foam cells, a characteristic of the early atherosclerotic lesion. The foam cells, as well as endothelial cells (ECs), present in the atheroma, express inflammatory cytokines and a variety of growth factors (interleukin (IL)-1, angiotensin (Ang)-II, tumor necrosis factor (TNF)-alpha, vascular endothelial growth factor (VEGF), endothelin (ET)-1) that cause smooth muscle cells (SMCs) to migrate from the media to the intima, where they proliferate and participate in the formation of the neointima and fibro-proliferative lesions, characteristic of advanced stable atherosclerotic plaques containing large amounts of extracellular matrix. At the same time, apoptosis, necrosis and further lipid accumulation lead to the development of a necrotic lipid core in the center of the plaque. The extracellular matrix plays an important role in the stability of the plaque. Destabilization with breaks in the continuity of the endothelial lining, and generation of occlusive thrombus, involve multiple factors including matrix metalloproteinases (MMPs), such as MMP-9 from macrophages, generation of tissue factor (TF) and plasminogen activator inhibitor (PA)-1 which inhibits fibrinolysis.

The PPARs are members of the nuclear receptor superfamily that act as ligand-transcription factors. Three distinct PPARs termed alpha, beta/delta and gamma, each encoded by a separate gene, have been described. All PPARs are activated by endogenous and natural ligands consisting of low-affinity dietary lipids and their metabolites. In addition, there exist synthetic and specific ligands that are used as drugs in clinical applications or molecules that are currently in development.

The PPARs regulate gene expression by binding as heterodimers with the 9 cis retinoic acid receptor (RXR), an obligate partner, to specific DNA sequences known as peroxisome proliferator response elements (PPREs) located in the promoters of target genes. In the basal state and absence of activation, the PPAR/RXR heterodimer actively represses the transcription machinery through interactions with corepressor complexes. Binding of a ligand allows for

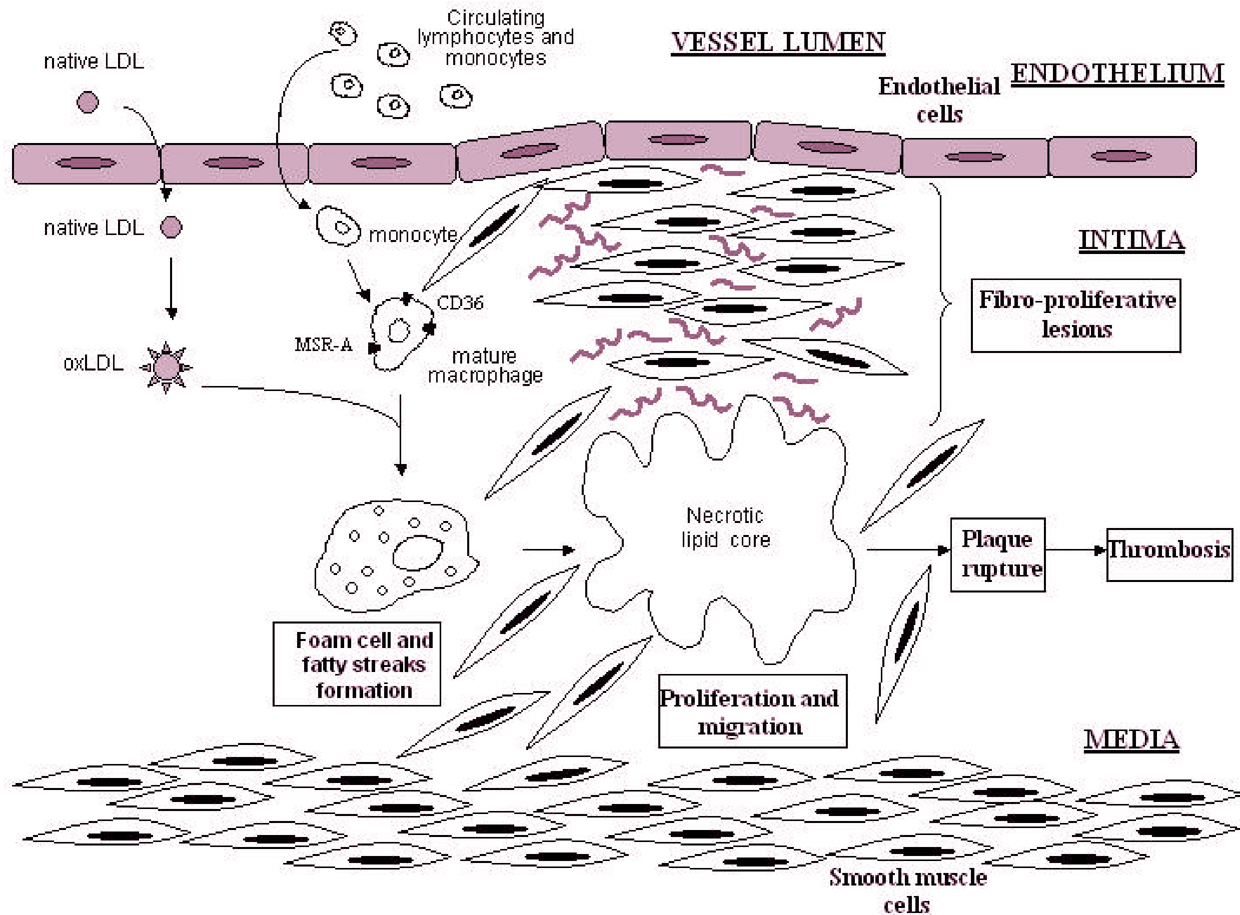

Figure 1. The atherosclerotic process. Atherosclerosis is a complex vascular disease initiated by oxidation of plasma low-density lipoprotein (LDL) and accumulation in the sub-endothelial space of the vessels, followed by endothelial cell dysfunction resulting in the recruitment of circulating lymphocytes and monocytes. Trapped monocytes differentiate into macrophages that take up oxidized LDL (OxLDL) through macrophage scavenger-receptors (MSRs) (MSR-A, CD36), thus forming foam cells. Activated smooth muscle cells proliferate and migrate from the media into the intima, thus leading to intimal hyperplasia and fibro-proliferative lesion formation. Activation of these cells leads to the release of pro-inflammatory cytokines, which combined with the secretion of metalloproteinases and expression of pro-coagulant factors, results in chronic inflammation and plaque instability. This can further evolve to plaque rupture and acute occlusion by thrombosis, resulting in myocardial infarction and stroke.

a conformational change in the protein, which results in the recruitment of coactivator proteins as well as the dissociation of corepressors and an increased transcription of the target gene (process called “activation”). In addition, PPARs can repress gene transcription in a DNA-binding-independent manner by antagonizing the activities of other classes of signal-dependent transcription factors (process called “repression”) (Figure 2). This repression function contributes to the anti-inflammatory actions of PPARs.

Although all three PPARs are widely expressed, their relative levels differ greatly between tissues in reflection of their distinct biological functions. PPARalpha is the primary PPAR subtype expressed in the liver where it plays a central role in the control of fatty acid (FA) and lipoprotein metabolism. Upon activation, PPARalpha stimulates intravascular lipoprotein lipolysis as a result of increased lipoprotein lipase (LPL) activity and reduced expression of apolipoprotein (apo) CIII, a natural LPL inhibitor. It also inhibits triglyceride (TG) synthesis and very-low density lipoprotein (VLDL) production by favouring FA uptake and retention, enhancing FA beta-oxidative catabolism and reducing FA synthesis in hepatocytes. Moreover, when activated, PPARalpha induces the expression of apoAV, an important determinant of plasma TG levels. Decreasing circulating TG levels lowers the TG content of LDL and, therefore converts the atherogenic small dense LDL into less atherogenic larger particles. Finally, PPARalpha activation enhances the production of apoAI and apoAII in humans, thus leading to increased high-density lipoprotein (HDL) production. Besides its action at the hepatic level, PPARalpha also stimulates FA oxidation in other tissues in which it is expressed, including the heart, skeletal muscle and kidney.

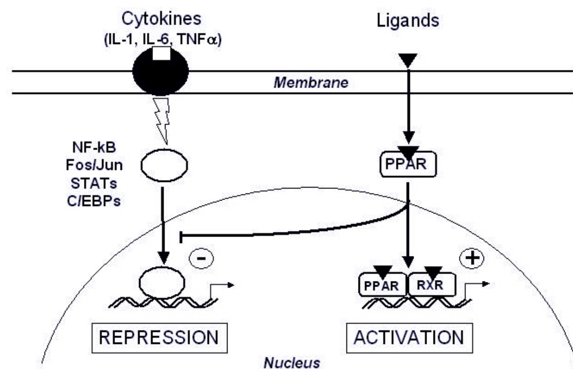

Figure 2. Mechanisms of transcriptional regulation by PPARs. Following activation, PPARs heterodimerize with retinoic X receptor and bind to response elements (PPREs) in the promoter region of target genes, thereby activating their transcription. PPARs also repress gene transcription in a DNA-binding independent fashion by interfering with other signalling pathways (e.g., nuclear factor kappaB (NF-kappaB), activating protein-1 (AP-1) (Fos/Jun), signal transducers and activators of transcription (STATs), CCAAT/enhancer-binding proteins (C/EBPs)) which transmit the interactions of cytokines (interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNF-alpha) with their cell surface receptors.

PPARgamma is predominantly detected in adipose tissue where it promotes adipocyte differentiation and mediates lipogenesis. Indeed, activation of PPARgamma induces the expression of the LPL gene, generating therefore FAs at the adipocyte surface, as well as the genes that encode FA transport proteins and acyl-CoA synthetase, favouring the uptake of FAs and storage of TGs in adipocytes. Consequently, lipid levels in adipose tissue rise whereas circulating FAs diminish, and it has been proposed that by repartitioning lipids away from liver and muscle, the two primary tissues that are responsible for insulin-mediated glucose disposal and metabolism, PPARgamma agonists ameliorate insulin sensitivity by reducing insulin resistance. PPARbeta/delta is ubiquitously expressed with relative highest levels in skeletal muscle. PPARbeta/delta activation influences lipoprotein metabolism, increasing the number of HDL particles, decreasing circulating TG concentrations and decreasing LDL-cholesterol levels. Also, recent data suggest that PPARbeta/delta activation reduces intestinal cholesterol absorption via downregulation of the Niemann-Pick C1 like 1 (NPC1L1) gene. Genetic models and ligand-treatment studies have also demonstrated powerful regulatory functions for PPARbeta/delta in adipose tissue metabolism and weight control, by increasing FA transport and oxidation as well as thermogenesis through uncoupling protein (UCP)-1 and 3 gene regulation, thereby retarding weight gain and preventing obesity. In skeletal muscle, PPARbeta/delta regulates FA transport and oxidation, thermogenesis, and the formation of slow-twitch fibers, resulting in increased endurance capacity. Moreover, a recent study shows that PPARbeta/delta activation decreases glucose output in liver, contributing to improved glucose homeostasis. Finally, by increasing FA transport and oxidation in the heart, PPARbeta/delta enhances contractile function and may improve cardiomyopathy.

With regard to their critical role in metabolism, PPARs have emerged as interesting molecular targets for the treatment of metabolic disorders that predispose to atherosclerosis and CVDs. Moreover, further data have established a function for PPARs in other settings, including involvement in vascular responses and inflammation. Indeed, expression of all PPARs has been identified in the major cellular constituents of the arterial wall, including ECs, T lymphocytes, monocytes/macrophages and vascular SMCs, where PPARalpha and PPARgamma influence several steps of atherogenesis, including cell recruitment and activation, and the local inflammatory response, by regulating the expression of adhesion molecules, chemokines and cytokines, and by limiting the oxidative stress pathways therefore leading possibly to less oxidized LDL. PPARalpha and PPARgamma activation have been shown to modulate lipid accumulation within the plaque by regulating the expression of genes involved in cholesterol uptake by macrophages (MSR-A and CD36 genes), and cholesterol removal through regulation of transporters like ATP-binding cassette transporter A1 (ABCA1), scavenger receptor (SR)-B1, NPC proteins 1 and 2. Moreover, both PPARs may control cell proliferation and migration by decreasing growth factors and MMPs expression as well as by blocking G1/S SMC cycle transition. Finally, PPARalpha and PPARgamma can ensure the stability of the atherosclerotic plaque and prevent thrombosis by inhibiting the expression of MMP-9, by controlling platelet aggregation through regulation of TF and platelet aggregation inducers or their receptors, and possibly by limiting fibrinolysis through PA-1 regulation.

Although most evidence attributes anti-atherogenic and anti-inflammatory effects to PPARalpha and PPARgamma, PPARs may also exert some deleterious effects on atherosclerosis progression. Indeed, activation of both PPARs can induce macrophage apoptosis in vitro (6), and despite the fact that this effect can impede the development of atherosclerosis via reduction of the production of growth factors and inflammatory cytokines, it may also contribute to the development of the necrotic lipid core, thus potentially contributing to the destabilization of the plaque. Moreover, loss of macrophages may promote a proatherogenic environment, due to, for example, decreased production of apoE and reduced scavenging of toxic substances (oxidized LDL). Another surprising effect of PPARalpha, which is not exhibited by PPARgamma, is the stimulation by activated macrophages of hydrogen peroxide production, a marker of reactive oxygen species that induces the oxidative modification of LDL and activate the inflammatory pathways (7). Finally, in contrast to the unquestionable large literature identifying anti-inflammatory effects of PPARalpha, some reports also suggest a role for the receptor in promoting or potentiating the expression of inflammatory responses in endothelial or mesangial cells (8, 9).

In contrast to PPARalpha and PPARgamma, the role for PPARbeta/delta in vascular biology and atherosclerosis development remains relatively controversial. Taken together, data suggest that, in the mouse, PPARbeta/delta does not significantly affect macrophage cholesterol metabolism but does ameliorate inflammation through the regulation of inflammatory mediators.

The role of PPARs in metabolic control and the mechanisms that participate in the development of atherosclerosis has been extensively reviewed (10-16).

4. GENETICALLY-ENGINEERED ANIMALS: STRATEGIES FOR THEIR GENERATION AND USE AS ATHEROSCLEROSIS RESEARCH MODELS

The development of genetically-modified animals has substantially enhanced our understanding of the atherogenic mechanisms, making it possible to study in vivo functions, expression and regulatory mechanisms of genes implicated in atherosclerosis. They can also be used to develop experimental models which resemble as close as possible the human disease to test pharmacological molecules or evaluate protocols for gene therapy. Apart from being the easiest and cheapest laboratory mammal to maintain, the availability of genetic information and the ability to genetically manipulate the genome have contributed to making the mouse the most widely used laboratory animal. There are however some drawbacks to using mice for atherosclerosis research. First, lipid and lipoprotein metabolism is distinct between mice and humans. In the mouse, most cholesterol is carried by HDL instead of by LDL (which is the major carrier of cholesterol in humans). This is partly due to the absence, in mice, of cholesterol ester transfer protein (CETP), a key enzyme involved in cholesterol transport. Second, the regulation of genes encoding proteins that are involved in lipid and lipoprotein metabolism are not identical between humans and mice and thus data obtained in the mouse are not always directly relevant to humans (17). Third, the mouse is highly resistant to atherosclerosis and does not develop atherosclerotic lesions spontaneously. Indeed, this is why most current mouse models for atherosclerosis research are based on genetic manipulations that result in susceptibility to atherosclerosis in the animals.

4.1. Animal models with gene overexpression

Transgenesis is the most common used method to induce overexpression of a gene in animals. It consists in pro-nuclear DNA micro-injection into fertilized ovocytes which are then reimplanted in a surrogate mother. This technique was applied for homologous or human gene overexpression. Although it is a well established and highly efficient technique which allows the generation of a large number of founder animals within a relatively short period of time, it is hampered by several major drawbacks. In particular, vector integration occurs randomly in the genome and sequences neighbouring the integration sites may strongly influence transgene expression. As a consequence, the expression of the transgene occurs randomly and may influence the expression of other neighbouring genes. Also, the copy number of integrated transgenes is highly variable, despite the fact that the integration generally does occur at one unique site. All these limitations can lead to unpredictable patterns and levels of transgene expression. Ideally, the injected DNA should contain all regulatory elements, and the transgenic construct should contain a specific tissue enhancer in order to reliably reproduce endogenous gene expression. In some studies, the production of animals with large transgenes was achieved by microinjection of bacterial artificial chromosomes (BAC) or yeast artificial chromosomes (YAC) (18). These transgene constructs often contain the natural promoter with all cis regulatory elements for gene expression, therefore allowing normal temporal, tissue-, and cell-specific expression of the transgene. However, inclusion of specific endogenous promoter sequences may be selected, allowing dissection of the contribution of different sequences to the normal regulation of the transgene. Somatic adenovirus-mediated gene transfer is another possible way to investigate the impact of a transgene and therefore to study its in vivo function (19).

Although there is substantial interest in this strategy, due to its relative facility and rapidity, its use is limited by the short duration of transgene expression. Moreover, due to its hepatic tropism, the efficiency of intravascular gene delivery to atherosclerotic lesions may be low because lesions that are frequently rich in connective tissue contain limited numbers of transfectable cells (20). Finally, there are important reservations about applicability for gene therapy in humans, particularly due to the use of an adenovirus as vector which can induce an immune response.

By using these diverse techniques, numerous transgenic mouse models that overexpress an endogenous (Table 1) or more interestingly a human gene (named throughout the text as human transgenic mice) have been created. The pioneer was the human apoAI transgenic mouse strain described in 1989 (21). It was followed by numerous other transgenic models for human apolipoproteins, enzymes, receptors or transport proteins (Table 2). Since variant forms of apolipoproteins have been identified in humans that are associated with the severity of dyslipoproteinemia and predisposition to atherosclerosis, transgenic mouse lines carrying some of these gene variants, such as apoE2 (22, 23), apoE3 Leiden (24, 25) or apoAI Milano (26, 27) have been created to determine the implication of these variants in the development of the disease. Besides these models used to study the relationships between dyslipoproteinemia and atherosclerosis, other transgenic mice that express proteins with other biological functions were developed and shown to impact on atherogenesis, such as, for example, globular adiponectin (28), demonstrating in vivo the anti-diabetic and anti-atherogenic effects of this adipokine, or paraoxonase, demonstrating that this enzyme is necessary for HDL integrity and function during oxidative stress (29).

Rabbits display several characteristics making it an excellent model for the study of mechanisms involved in the development of atherosclerosis. New Zealand White

Table 1. Deletion or overexpression of endogenous genes: selected mouse models for lipoprotein metabolism and atherosclerosis research

Gene	Deletion	Overexpression
Apolipoproteins		
AI	137	
AII	138	148
AIV		149
AV	139	150
B100, B48	140-144	
CI	145	
CII		
CIII	146	
E	46-48	
Cluster AI/CIII/AIV	147	
Enzymes		
LPL	151-153	
HL	154, 155	166
HSL	156	
LCAT	157, 158	
PLTP	159	
Cholesterol 7alpha-OH	160	
ACAT-2	161	
ACAT-1	162-164	
Sterol 27-OH	165	
Receptors		
LDLR	49	
LRP	167-169	
VLDLR	170	174
LDL/LRP/VLDLR	171	
CD36	172	175
MSR-A	67, 173	
Transport proteins		
ABCA1	155, 176-179	182
SRB1	180, 181	183-186
MTP	144	

Abbreviations: LPL, lipoprotein lipase; HL, hepatic lipase; HSL, hormone-sensitive lipase; LCAT, lecithine:cholesterol acyltransferase; PLTP, phospholipid transfer protein; ACAT, acyl CoA:cholesterol acyltransferase; LDLR, low-density lipoprotein receptor; LRP, low-density lipoprotein receptor-related protein; VLDLR, very low-density lipoprotein receptor; MSR-A, macrophage scavenger receptor A; ABCA1, ATP-binding cassette transporter A1; SRB1, scavenger receptor class B type 1; MTP, microsomal transfer protein

(NZW) rabbits have lipoprotein profiles more similar to humans than mice, and present a high susceptibility to atherosclerosis as do humans. However, rabbit strains have a more diverse genetic background than mouse strains, and this may hamper its use. Despite this limitation, NZW transgenic rabbits were developed, expressing rabbit, and more frequently human transgenes (Table 3). In addition, human transgenes have been introduced into Watanabe heritable hyperlipidemic (WHHL) rabbits, which carry a LDL receptor (LDLR) mutation and are a model of familial hypercholesterolemia (Table 3).

Compared to the mouse and rabbit, genetically-modified rat models are rare (30, 31). Notably, a transgenic Dahl salt-sensitive hypertensive rat strain that expresses moderate levels of human CETP is among the rare transgenic animal models of coronary artery disease (30, 32). This model has been particularly useful to investigate the role of hypertension in the aggravation of coronary atherosclerosis, the implication of infectious agents such as Chlamydia pneumonia (a common human respiratory pathogen) in coronary plaque progression, and the differential regulation of functional gene clusters in overt coronary artery disease characterized by atherosclerotic plaque destabilization and resultant myocardial injury.

Employing all these transgenic models, the identification of genes affecting atherosclerosis susceptibility, as well as the study of environmental factors affecting atherosclerosis (such as diet) and the assessment of therapies that might block atherogenesis or lesion progression have become able to be studied. Moreover, overexpression of human proteins in animals naturally lacking them, is another advantage of transgenic manipulation. Overexpression of apo(a), CETP (Table 2) or C-reactive protein (CRP) (33) in mice, and human hepatic lipase (HL) or apo(a) in rabbits (Table 3) are excellent examples.

4.2. Mouse models with gene deletion or targeted recombination

Highly elegant are the relatively recent homologous recombination methodologies in embryonic stem (ES) cells, presently feasible only in the mouse (34-36). In these technologies (37), an engineered construct (such as a reporter gene), is inserted into the chromosome in place of the targeted mouse gene of interest, without affecting any other locus in the genome. The mouse gene will be no longer expressed, and the gene is “knocked-out” (KO). Numerous mouse models were so generated (Table 1). Conversely, when a transgene is introduced in replacement at the locus of interest, in such a way that its transcription is driven by the promoter of the mouse gene, the transgene is expressed with the same pattern of expression as the mouse gene. This strategy is called “knock-in”, and the resulting mice are referred to as KI mice. If the transgene is the human counterpart of the mouse gene, then this strategy is called humanization and the mouse is a “humanized” mouse. The main advantage of the KI technology is that both copy number and the genetic environment of the transgene is controlled. Conventional gene targeting leads to inactivation of a gene in all tissues of the body from the onset of development throughout the whole lifespan (38). More recently, methods have been developed that aimed at controlling gene targeting in a tissue-or cell type-dependent manner. These conditional gene targeting approaches use the Cre-Lox system (38-40) and are particularly useful in cases where complete gene inactivation leads to a lethal or otherwise adverse phenotype that prevents a more detailed in vivo analysis. Moreover, if a given gene has a widespread pattern of expression, tissue-specific gene inactivation may define physiological roles of the gene product in a certain tissue, without compromising other functions in the organism. For completeness on the diverse genetic manipulation technologies that result in tissue-specific gene inactivation in mice, we have to mention new technologies in which selective gene silencing is induced in a specific tissue of mice through RNA degradation by adenoviral delivery of small interfering RNA (siRNA) or short hairpin RNA (shRNA) (41, 42). These approaches are principally developed in in vitro experiments, and only few studies have been described that used them in vivo to assess the role of susceptible genes for atherosclerosis (43).

Table 2. Human transgenic mouse models for lipoprotein metabolism and atherosclerosis research

Transgene	Expression site (non induced state)	References
Apolipoproteins		
AI	liver	187-192
	liver, intestine	193
	macrophages	63
AII	liver	194-196
	liver, kidney	197
AIV	liver	198, 199
	intestine	200
AV	liver	139
B	liver	201, 202
	liver, intestine	203, 204
	liver, kidney, brain	205
CI	skin, liver[1], lung, testis, stomach	206
	liver	207
	liver, skin, AT	208
CII	liver, brain	209
CIII	liver>intestine[1]	210, 211
E	kidney	212
	kidney, liver[1]	213
Apo(a)	liver	214, 215
Cluster AI/CIII/AIV	liver, intestine	216
Cluster AI/CIII/AIV/AV	liver, intestine (AI CIII, AIV), liver (AV)	217
Enzymes		
LPL	heart, skeletal muscle, AT	218
	heart, skeletal, …, liver	219
	AT, muscle, heart, kidney, stomach	220
	skeletal muscle	221-223
	liver	224, 225
	cardiac muscle	226
HL	liver, heart, kidney	227
	liver, adrenal cortex	228
HSL	macrophage	229
LCAT	liver	230-234
PLTP	liver	235
	AT, lung, heart, spleen	236
	liver>kidney>brain>small intestine> lung>spleen>heart> AT	237
	adrenal testis>lung>liver, kidney, intestine, brain, spleen	238
Sterol 27-OH	ubiquitors	239
Cholesterol 7alpha-OH	liver	240, 241
Receptors		
LDLR	liver	49, 242
VLDLR	liver	174
	testis>heart>kidney, liver, aorta	243
Transport proteins		
CETP	heart, AT, brain>liver, small intestine, muscle	244
	liver spleen, small intestine, kidney, heart, brain[1]	245
	not indicated	246
ABCA1	liver, macrophages	247
	liver>spleen, testis, lung, small intestine	248
	liver>small intestine, brain, lung, testis, stomach, macrophage	249
	liver	250

[1] Depending on the construct or the lines. Abbreviations: AT, adipose tissue; CETP, cholesteryl ester transfer protein.

Mouse models with a gene deletion are very important tools for bone marrow experiments. Upon bone marrow injection into non-mutated recipient mice that have been depleted of white blood cells by irradiation (44), or upon bone marrow transplantation from mice with the normal gene (45), it is possible to study the contribution of macrophage (and other hematopoietic cell) gene expression to atherogenesis.

The advent of gene targeting to modify the expression of genes involved in atherosclerosis was an improvement, and the creation of targeted mouse models, particularly those resulting from the deletion of the apoE (46-48) and LDLR (49) genes, has greatly facilitated the research on genetic and environmental determinants of the disease. Both strains are widely used as models for dyslipoproteinemia and atherosclerosis, and also as sensitized strains to investigate the role of additional modifier genes of atherosclerosis. By interbreeding them with another deficient or transgenic murine strain, either double knockout mice or deficient mice expressing a transgene can be created. Using these models, the role of genes encoding proteins implicated in lipoprotein metabolism has been substantiated. Genes involved in inflammation, cell cycle control, hypertension**,** and coagulation have been also identified as key modulators of plaque progression (50-54). Also, by interbreeding apoE or LDLR gene-targeted deficient mice with other murine

Table 3. Human transgenic rabbit models for lipoprotein metabolism and atherosclerosis research

Rabbit strain	Transgene	References
New Zealand White	apoAI	251
	apoB100	252, 253
	apoE2	254
	apoE3	255, 256
	apo(a)	253, 257, 258
	cluster AI/CIII/AIV	259
	HL	256, 260
	LCAT	261, 262
	LPL	263-265
	SRB1	266
Watanabe	apoAI	267, 268
	LCAT	269, 270
	apo(a)	271
	LPL	272

models that are genetically predisposed to atherosclerosis or to diet-induced metabolic abnormalities, it is possible to study the relative contributions of such perturbations in atherosclerosis development. For example, when interbreeding LDLR-deficient mice with leptin-deficient (ob/ob) mice (55) or viral glycoprotein (GP)-transgenic mice (56), it is possible to study the relationship between dyslipidemia, insulin resistance and atherosclerosis. Finally, apoE- and LDLR-deficient mice are used in numerous nutritional and pharmacological studies, for example, to assess the effects of agents that act on cardiovascular risk factors (discussed in the following sections), antioxidant therapy (57), steroid hormone replacement therapy (58), or the inhibition of the renin angiotensin system (59, 60) on atherosclerosis. A specific and interesting utility of LDLR-deficient mice is for bone marrow experiments (61-64), serving as a better host model for transplantation as compared to apoE-deficient mice which, due to the synthesis of apoE by macrophages, are rescued for apoE deficiency upon transplantation.

If arguably the advent of homologous recombination techniques deleting a specific gene has become central for research programmes on atherosclerosis, there are some drawbacks to these models. First, the functionality of all metabolic pathways is not necessarily maintained in the modified mice, and thus the model only provides information about whether a mechanism or a pharmacological compound requires the presence of the deleted gene. Second, a genetic deletion may lead to a compensatory adaptation that in turn would affect metabolic pathways or lesion development in unexpected ways. The conflicting results on the physiopathological role of MSR-A, a scavenger-receptor which mediates cholesterol uptake into the vessel wall might be an example. Although recent work reassessed the role of the receptor as pro-atherosclerotic mediator (65), it was previously reported that deleting the MSR-A gene in apoE3 Leiden-transgenic mice induced an increase in atherosclerotic lesion size (66) while inhibiting the same gene in apoE-deficient mice led to decreased lesion size (67). A possible explanation for this difference relates to the role of apoE in the vessel wall which is to mediate efflux of cholesterol from macrophages. Therefore, deficiency in apoE probably predisposes to foam cell formation, a process which in turn could be limited by deletion of MSR-A. On the contrary, macrophages from mice carrying the apoE3 Leiden gene show normal apoE-mediated cholesterol efflux, and MSR-A-mediated cholesterol uptake does not lead to enhanced foam cell formation.

Interestingly, homologous recombination also permits the replacement of a specific gene, without altering the genome organization. This strategy allows the creation of KI mouse models which certainly are the most powerful experimental models since the replaced gene is expressed according to normal physiological regulation. Examples are KI mice for the human LDLR minigene (68), or the different human apoE isoforms E2, E3, E4 (69-71). The apoE2 KI mice exhibit plasma lipoprotein characteristics that are equivalent to those of type III hyperlipidemic patients. These mice spontaneously develop atherosclerotic lesions composed predominantly of macrophage foam cells and they are responsive to a Western diet, enhancing the dyslipidemia and increasing atherosclerosis development. Lesions formed during the feeding of modified diets are also predominantly composed of macrophage foam cells (69). Using this model, it is possible to determine which conditions predispose to the development of dyslipoproteinemia in humans, as for example a reduced expression of the LDLR (68). Another advantage of apoE2 KI mice is their responsiveness to pharmacological agents that act on lipid metabolism and atherosclerosis, indicating suitability of the model for drug-testing (72). In apoE isoform KI mice, aortic root atherosclerosis increases in the following order: murine apoE<apoE3<apoE4<apoE2 (70). In a recent study, it has been demonstrated that overexpression of human LDLR in apoE4, but not in apoE3, KI mice, causes severe atherosclerosis with marked hypercholesterolemia when the animals are fed an atherogenic diet (73). This result was totally unexpected and contrary to the current hypothesis that downregulation of LDLR in individuals with an apoE4 allele is the cause of their dyslipoproteinemia and increased risk of atherosclerosis. Thus, using these KI mice expressing human apoE isoforms, the occurrence of important interactions between the apoE genotype, LDLR expression and diet is demonstrated.

Although all these gene targeting approaches have become essential in the study of atherosclerosis-related genes, complex and time-consuming preparative molecular biology work is still required. Moreover, an important issue that should be considered before starting a lengthy targeting experiment is the genetic background on which the mutation will be studied. Indeed, mice containing exactly the same genetic manipulation can exhibit profoundly different phenotypes due to the diverse genetic backgrounds (74, 75), making it imperative to take the genetic background into account when interpreting experimental results. The majority of available ES cell lines are derived from the SV-129 strain which unfortunately presents a low susceptibility to atherosclerosis. It is therefore necessary to develop a congenic strain by transferring the mutation to a more appropriate genetic background. The C57BL/6 strain is the most frequently used atherosclerosis-prone background. The easiest but most time-consuming approach to generate a congenic

strain is via traditional backcrossing, a process which involves sequential breeding of mutated offspring to a pure genetic background strain. Ten generations (commitment of 2-3 years) of successive backcrossing are theoretically required to assure that less than 0.1% of the genetic material from the original background strain remains. However, even after that long time, due to the reliance on statistical probabilities to achieve congenesis (the percent of residual donor background contamination is never quantified), all experiments using these mice should preferentially be performed with wild-type littermates as controls. The goal of developing a congenic strain in much less time can be accomplished by another process referred to as "speed congenesis" (76). This technique uses marker-assisted selection of breeders and identifies "best" founders at each generation. However, while reducing by half the time to obtain a congenic strain, its development is expensive.

In conclusion, using genetic manipulation techniques, many animal models have been developed for research on atherosclerosis. However, despite that they represent invaluable tools, and except very few reports (32, 77-79), nearly all these models suffer the disadvantage that they do not progress to plaque rupture and occlusive thrombosis that occur in humans, limiting therefore their utility to study genetic factors contributing to the pathogenesis and potential treatment of the disease.

5. GENETICALLY-ENGINEERED ANIMALS : RESEARCH MODELS TO STUDY THE ROLE OF PPARs IN ATHEROSCLEROSIS

Two different strategies can be applied to investigate in vivo the pathophysiological role of PPARs in atherosclerosis. The first is based on mice, virtually the sole animal species that has been subjected to genetic manipulation of the different PPAR genes, whereas the second employs pharmacological treatment with a specific PPAR ligand. Despite the fact that both approaches have elucidated many important functions of PPARs in atherogenesis, it has to be kept in mind that these findings are obtained in experimental animal models displaying species differences that might limit the extrapolation of the results to humans. Lipid and lipoprotein metabolism pathways, particularly between rodents and rabbits or humans, present important differences. Moreover, PPAR ligand affinity may differ between species. Also, some target genes are expressed differentially (tissue localization and level of expression) across species. Lastly, because the promoter regions of genes are less well-conserved across species**,** the regulatory sequences of some genes are different between species. The nuclear receptors that control certain gene expression in one species may therefore not be crucial regulators in another (80-82), or the regulation pathways that are activated by certain nuclear receptors can lead to opposite results depending on the species (17).

All the genetic manipulations described above with the goal of creating animal models for atherosclerosis research have been applied to the PPARs, including conventional or conditional tissue or cell-specific PPAR gene deletion, targeted transgenesis of PPAR subtypes, bone marrow transplantation from PPAR subtype-deficient mice to mice predisposed to atherosclerosis, and overexpression of PPAR subtypes by adenoviral gene transfer (Table 4). The technique of conventional gene targeting deletion was particularly successful for PPARalpha, resulting in the first viable homozygous PPARalpha deficient mouse model described in 1995 (83). Recently, the same laboratory reports the KI of human PPARalpha gene under the control of natural promoter and regulatory elements, on a background of PPARalpha deficient mice. In these mice, the transgene is expressed specifically in the liver (84). This model is particularly pertinent to examine the mechanisms determining species differences in the peroxisome proliferator response between mice and humans. Conditional gene targeting deletion approaches using the Cre-Lox system are determinant to study the role of the other PPAR isoforms gamma or beta/delta, for which complete deletion results in embryonic lethality, as well as for the analysis of tissue-specific activities of the different PPAR isoforms. The main characteristics and informations provided on the role of PPARs through these various models are detailed in Table 4.

By analysing the phenotype or response to different situations (nutritional or hormonal stress, ligand activation) of PPAR subtype-deficient mice, it has been possible to identify target genes and evaluate the adaptive capacity of the mice, yielding therefore insight about the function of the PPAR subtype or identify the requirement of PPAR for activity of a ligand (analysis of on versus off target effects). For example, when compared to wild-type mice, the characterization of PPARalpha-deficient mice maintained in basal state, or submitted to a high fat diet or fasting, or stimulated by beta1 adrenergic receptor agonists, demonstrates the pivotal role for PPARalpha in controlling lipid and glucose homeostasis, as well as maintaining cardiac functions (85-89). Also, the targeted disruption of PPARgamma in beta cells or liver of mice that are further treated by a specific agonist, revealed that PPARgamma is not required for the pharmacological actions of the ligand in the beta cells and that adipose tissue is the major site of ligand action (90, 91). The administration of an atherogenic or diabetogenic diet to PPAR subtype-deficient mice (high fat diet to PPARalpha- or PPARbeta/delta-deficient mice), or by interbreeding them with other strains susceptible to metabolic abnormalities predisposing to atherosclerosis (PPARalpha-deficient mice crossed with apoE-deficient mice or leptin-deficient mice), allows the investigation on the role of the receptor in the pathophysiology of the disease, demonstrating therefore the role of the PPAR subtype on obesity and its associated disorders like insulin resistance, or atherosclerosis susceptibility (92-95).

Paralleling these genetic strategies, pharmacological approaches consisting in the administration of a specific PPAR ligand to animals are more widely applied because of their relative ease. Among these ligands, some are used clinically in humans while other molecules that are more active and more specific are

Table 4. Genetically-modified mouse models as useful tools for the analysis of PPAR subtype function on metabolic disorders predisposing to atherosclerosis

PPAR subtype	Model	Methodology	Characteristics	Ref.
PPARalpha	KO	Targeted disruption gene	- no induction of hepatomegaly, peroxisome proliferation and transcriptional activation of target genes upon treatment with specific ligands	83
			- abnormalities in pancreatic response of beta-cells on ob/ob background or palmitate-induced lipotoxicity in islets	94
			- reduced atherosclerosis and improved insulin resistance in apo E KO background	131
			- decreased glucocorticoid-induced insulino resistance in LDLR KO background	273
			- no regulation of HDL by specific ligands in human apoA-I transgenic background	92
	KI	Transgenesis of human PPARalpha in liver of PPARalpha KO mice	no hepatocellular proliferation upon treatment with specific ligands	84, 274
	Human expressor in liver	Adenoviral gene transfer	restored pleiotropic responses, including peroxisome proliferation and expression of target genes upon mouse PPARalpha KO background	275
PPARgamma	KO (homozygous)	Targeted disruption gene	lethality due to abnormalities in placental, cardiac and adipose tissue development (embryonic or perinatal phases)	276
	KO (heterozygous)	Targeted disruption gene	- survival and protection from the development of insulin resistance	277,278
			- little or no contribution of null cells to adipose tissue development	279
	Over expressor in liver (gamma 1)	Adenoviral gene transfer	hepatic steatosis	280
	KO in macrophages	Conditional specific gene disruption	- impaired cholesterol efflux from primary peritoneal macrophages and cholesterol transport in plasma	281
			- increased atherosclerosis and high number of macrophages in atherosclerotic lesions	44
		Bone marrow transplantation	increased atherosclerosis (lipid-rich and macrophages-containing aortic lesions) in LDLR KO background	282
	KO in liver	Conditional specific gene disruption	- decreased hepatic steatosis but aggravation of the diabetic phenotype on ob/ob background	283
			- decreased hepatic steatosis but aggravation of the insulin resistance in muscle and adipose tissue	91
	KO in adipose tissue	Conditional specific gene disruption	- insulin resistance in adipose tissue and liver, but not in muscle, unless on a high fat diet	284
			- reduced fat formation, protection, from the development of high fat-induced obesity and insulin resistance increased hepatic PPARgamma mRNA	285
	KO for PPARgamma 2		- lipid and glucose homeostasis relatively well maintained, compensation by muscle	286
			- reduced adipose tissue, lowered lipid accumulation in fat, increased whole body insulin resistance	287
	KO in muscle	Conditional specific gene disruption	- glucose intolerance, progressive insulin resistance	288
			- excess adiposity, whole body insulin resistance, impaired hepatic insulin action	289
	KO in pancreas	Conditional specific gene disruption	islet hyperplasia, no change in glucose homeostasis	90
PPARbeta/delta	KO (homozygous)	Targeted disruption gene	- frequent (>90%) embryonic lethality	290
			- impaired development (foetuses and newborns), altered myelinisation in the central nervous system, accentuated epidermal cell proliferation	291
			- glucose intolerance and decreased insulin sensitivity	125
	KO in adipose tissue	Conditional specific gene disruption	reduced adiposity of PPARdelta null mice not reproduced	290
	KO in cardiomyocyte	Conditional specific gene disruption	lipotoxic cardiomyopathy	292
	KO in macrophages	Bone marrow transplantation	attenuated inflammation, reduced atherosclerotic lesion area on LDLR KO background	293
	Overexpressor in adipose tissue	targeted transgenesis	resistance to both high-fat diet-induced and genetically predisposed (db/db) mice	95
	Overexpressor in muscle	Targeted transgenesis	resistance to high-fat diet-induced obesity	294

Abbreviations: KO, knock-out; KI, knock-in.

in development or still in experimental stages. These last compounds are indicated by numbers preceded by the initials of the pharmaceutical company (i.e GW 7647 for Glaxo Wellcome compound number 7647). PPARalpha ligands (fibrates, such as fenofibrate, ciprofibrate, clofibrate, gemfibrozil) were developed as hypolipidemic agents and PPARgamma ligands (thiazolidinediones (TZDs), such as rosiglitazone, pioglitazone or troglitazone) are used to improve insulin resistance in patients suffering from type 2 diabetes. Even though this review focuses on the use of genetically-engineered animal models, it should be mentionned that wild-type or lean animals fed a standard or atherogenic/diabetogenic diet (mice (96-102), rabbits (103-105), rats (106-114), hamsters (115, 116), guinea pigs (117), monkeys (118), pigs (119), or dogs (120, 121) have been widely used to study the effects of PPAR activation on molecular, metabolic, vascular or clinical markers and do provide information on the function of these PPARs.

Indeed, using these various models, mounting evidence demonstrates beneficial effects of PPARalpha activators on energy, lipid and carbohydrate metabolism. For example, in wild-type mice or golden Syrian hamsters fed a high fat diet, PPARalpha activation results in an improved lipid and lipoprotein phenotype, corrects insulin resistance and reduces adiposity (102, 116). Also, in rabbits, the administration of gemfibrozil enhances TG-rich lipoprotein catabolism in peripheral tissues such as adipose tissue and muscle by increasing the expression of VLDL-receptor in these tissues (104). Concerning atherogenesis, fenofibrate induces plaque regression in hypercholesterolemic rabbits (105), and reduces the tissue necrosis in an experimental rat model of myocardial infarction (122). Finally, in mice experiencing experimental cerebral injury, fenofibrate reduces the deleterious neurological consequences of stroke (101). Numerous experimental animal studies showed that PPARgamma activators reduce the development of atherosclerosis and limit its complications. Indeed, in the intimal hyperplasia rat model, treatment with TZDs prevents restenosis (110, 113) and, similar as for PPARalpha activators, the administration of troglitazone or pioglitazone to rats reduces infarction volume and improves neurological function following middle cerebral artery occlusion (109). Moreover, it has been shown that pioglitazone administration decreases platelet aggregation and delays intra-arterial thrombus formation in rats (111). Finally, chronic administration of rosiglitazone to dogs with mitral regurgitation results in an improved ventricular function (120). As for PPARalpha and gamma, the administration of PPARbeta/delta activators to animal models contributed to the demonstration that this PPAR subtype is a promising target for drugs aimed to treat or prevent atherosclerosis. Indeed, upon PPARbeta/delta activation with GW610742, wild-type mice show increased plasma HDL concentrations and reduced intestinal cholesterol absorption (96). Also, when dosed to insulin resistant obese rhesus monkeys, GW501516 causes dose-dependent rise in serum HDL cholesterol while lowering the levels of small-dense atherogenic LDL, fasting TGs and fasting insulin (118), therefore improving metabolic parameters associated with the metabolic syndrome and atherosclerosis risk. Human transgenic animal models are useful tools to test compounds which exhibit species-dependent regulation of a given gene, as is the case for human apoAI transgenic mice given that PPARalpha differentially regulate the human and mouse apoAI gene (17), or in demonstrating that the beneficial effects of such agonists on lipoprotein metabolism occur dissociated from effects on peroxisome proliferation. For instance, using the human apoAI transgenic rabbit, an animal species that, contrary to mice and similar to humans, is less sensitive to peroxisome proliferators, it was shown that fenofibrate treatment increased serum human apoAI concentrations via an increased expression of the human apoAI gene in liver without changing liver weight or expression and activity of fatty acyl-CoA oxidase, a rate-limiting and marker enzyme of peroxisomal beta-oxidation (123). Finally, the administration of PPAR ligands to animals that present risk factors for atherosclerosis (dyslipidemia, type 2 diabetes, insulin resistance) not only allows assessment of the role of PPARs in the development of the disease, including effects on metabolic and vascular parameters, but also establishes the preclinical efficacy and interest of PPAR ligands in managing the disease. These animals often suffer a constitutive genetic defect such as the diabetic and insulin-resistant db/db or ob/ob mice (95, 124, 125), fatty Zucker or OLETF (Otsuka Long-Evans Tokushima Fatty) rats (102, 126, 127), the stroke-prone spontaneously hypertensive (SHRSP) rat (128), the WHHL hyperlipemic rabbit (129). For example, treatment of OLETF rats with fenofibrate lowers fat of skeletal muscle and adipose tissue and improves insulin sensitivity in these animals, thus providing further knowledge on the metabolic effects of PPARalpha in tissues other than liver (126). In SHRSP rats, PPARgamma activation by pioglitazone attenuates cardiac inflammation which may participate in the prevention of cardiac hypertrophy (128). Moreover, oral administration of troglitazone to WHHL rabbits after balloon injury suppresses acute recruitment of monocytes/macrophages and accelerates re-endothelialization, suggesting that TZDs have additional therapeutic potential for the treatment of diabetic vascular complications (129). Very recently, the role of PPARbeta/delta in regulating glucose metabolism and insulin sensitivity has been demonstrated by testing its agonist, GW501516, in db/db mice, pointing out potential contributions of both hepatic and peripheral actions of this receptor (125). Moreover, acute treatment of db/db mice with the same activator depletes lipid accumulation in liver and fat, identifying PPARbeta/delta as a potential target in the treatment of obesity (95). Among mouse models that are generated by genetic manipulation (gene targeted deletion or replacement), LDLR- or apoE-deficient mice are the most widely used models to test the activity of PPAR agonists on atherosclerosis. Table 5 summarizes the use of both models and the consequences of the activation of the different PPAR subtypes on metabolic abnormalities predisposing to atherosclerosis or CVDs.

Although both genetic modification of a PPAR-subtype or the pharmacological activity of PPAR ligands unquestionably provide data supporting the pathophysiological functions of PPARs in atherosclerosis, apparently conflicting data can be observed depending on the experimental approach that is employed. For instance, while an atheroprotective effect of PPARalpha activation by fenofibrate was reported in apoE-deficient mice (130), PPARalpha deficiency in the same mouse model confers protection against atherosclerosis (131). This discordance may be explained by the fact that both approaches are not totally comparable and that PPARalpha deficiency does not necessarily lead to the opposite phenotype as that resulting from PPARalpha activation by its ligand.

6. CONCLUSION AND PERSPECTIVES

Over the past decade, gene technology has been used to create experimental animal models which have remarkably increased our understanding of the interaction between genetic and environmental factors in the development, prevention and treatment of atherosclerosis. How accurately these models mimic the process in humans is difficult to ascertain considering relevant species differences, including dissimilarities in metabolic pathways

that are involved in the pathogenesis of the disease, in cardiovascular physiology, and in plaque morphology, particularly the relative lack of lesion progression leading to thrombotic occlusion or plaque rupture in the mouse. Finally, it is important to emphasize that the experiments using targeted deficient mice are the genetic equivalent of recessively inherited conditions in humans due to the loss of gene function, a condition only representing a small proportion of the atherosclerosis cases. As a consequence, studying mice in the heterozygous state may be more appropriate with respect to the relevance for atherosclerosis susceptibility in humans. The ideal model could be defined as an animal that displays metabolic abnormalities predisposing to atherosclerosis, that spontaneously develops atherosclerotic lesions, that is not a homozygous deficient model, that develops similar responses to environmental factors and that is humanized through gene replacement technology.

It is now clear that acting on metabolic perturbations predisposing to atherosclerosis is a crucial step to limit its development and associated cardiovascular diseases. Important research programs have been undertaken to identify novel therapeutic pathways involving the modulation of the expression of target genes following the activation of nuclear receptors using specific activators. Preclinical development of these activators included the analysis of their effects in animal models, and this review attempted to highlight the importance of genetically-engineered mouse models for that purpose. Among these activators, some are used clinically in humans. They concern PPARalpha and PPARgamma activators, indicated respectively for treating dyslipidemia (fibrates) and diabetes (TZDs) in patients which have an extremely high risk of developing CVDs. Results of angiographic studies and CVD prevention trials in diabetic patients indicate that fibrate treatment decreases the risk of CVD in patients with type 2 diabetes without pre-existing CVD or metabolic syndrome (132, 133), and TZDs improve cardiovascular outcomes in secondary prevention (134). Unarguably these results demonstrate that PPARalpha and PPARgamma activators are interesting therapeutic targets for CVDs, despite the fact that some of them may present side effects (such as weight gain, oedema and fluid retention for PPARgamma). At present, research on other PPAR activators, including PPARbeta/delta activators, are in development, aiming to identify more specific and active molecules with high safety margins. Moreover, current strategies concern the development of dual PPARalpha/gamma activators, pan-activators or even more promising, based on the selective modulator concept, compounds that would be devoid of adverse effects while maintaining the desirable biological efficacy (135, 136).

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Abbreviations: FF, fenofibrate; CiF, ciprofibrate; CloF, clofibrate; Rosi, rosiglitazone; Tro, troglitazone; Pio, pioglitazone; TC, total cholesterol; TG, triglycerides; non HDL-C: non high-density lipoprotein-cholesterol; glc, glucose; ins, insulin; IS, insulin sensitivity; KI, knock-in; ↑, increased following treatment; ↓, decreased following treatment; =, unchanged; STZ, streptozotocin.

Key Words: Animal Models, Genetic Modifications, Transgenesis, Targeted Gene Deletion, Conditional Gene Knock-Out, Targeted Gene Replacement, Adenoviral Transfer, Atherosclerosis, Risk Factors, Peroxisome Proliferator-Activated Receptors, Ligand Activation, Review

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