Transgenic laboratory animal models in atherosclerosis research.

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Introduction

Atherosclerosis and its clinical sequela coronary heart disease (CHD) is a major cause of death in the modern word. This disease of the arterial intima and media due to dynamic interaction between plasma lipoproteins and cells of the arterial wall is influenced by genetical and environmental factors.

During the last nine decades several animal models have been used to study atherosclerosis. The most popular has been the cholesterol-fed rabbit and lately the Watanabe heritable hyperlipidemic (WHHL) rabbit (Mortensen et al. 1994). However, none of the models can fulfil the criteria for an ideal animal model of human atherosclerosis and the search for better models still continues.

Over the last decade the development of transgenic techniques and the isolation of human genes coding for proteins that directly interact with plasma lipids made it possible to create new transgenic animal models in atherosclerosis research. These models are mainly based on mice.

The laboratory mouse as an animal model of human atherosclerosis

The suitability of an animal species in atherosclerosis research is estimated by three criteria: 1) the nature of atherosclerosis, 2) biology of the chosen species, and 3) the practical aspects of the species selection in relation to the experimental procedure (Mortensen et al. 1994).

The laboratory mouse would be a good model organism based on the practical aspects. It is easy to handle and house, especially when a large number of animals is needed. The small size of the animal, earlier regarded as disadvantage, is no longer an obstacle for measurement of blood lipids, and for evaluation of aortic atherosclerosis. Paigen et al. (1985) described the method for quantification of experimental atherosclerosis in the mouse.

When the biology of the species is considered the laboratory mouse would be a favourable model, especially for studying the genetic contributions to the development of atherosclerosis. This is because the mouse has been widely used in other fields of biological research, and therefore it has a well characterized anatomy, physiology, pathology, and genetic background. Several inbred strains are available. Recombinant inbred strains are regarded as a powerful tool for genetic analysis of a complex trait such as atherosclerosis (Hegele 1992). Furthermore, the mouse is easy to breed, and has a short generation time. In addition, the susceptibility of different strains to experimental atherosclerosis (Paigen 1985), the type of experimental lesions (Thompson 1976, Paigen 1985), and blood lipids have been characterized (Jiao et al. 1990, Camus et al. 1983).

However, when the nature of atherosclerosis is considered the laboratory mouse does not appear an acceptable model organism. Firstly, the mouse is highly resistant to atherosclerosis. The development of aortic lesions demands extreme atherogenic diets (Vesselinovitch et al. 1968, Thompson 1976, Paigen 1985), which have been shown to cause adverse effects such as body weight loss and high mortality. Furthermore, the development of experimental atherosclerosis has been inconsistent even among the animals in the same treatment group (Vesselinovitch et

al. 1968). Secondly, the mouse has physiologically a low plasma cholesterol compared to man (Jiao et al. 1990). Thirdly, the lipoprotein systems of the mouse and man are different. The major carrier of the plasma cholesterol in mouse is high density lipoprotein(HDL) (Jiao et al. 1990, Camus et al. 1983), while in man it is low density lipoprotein (LDL). In contrast to man the mouse lacks apolipoprotein(a) and cholesteryl ester transfer protein (Rubin & Smith 1994). All this has discouraged the use of the laboratory mouse in atherosclerosis research. Only later, when the problems with adverse effects of atherogenic diets were solved (Roberts & Thompson 1977, Paigen 1985), the induction of lesions has been shown to be reproducible (Paigen 1985), and the morphology of the lesions has been found similar to those of other species a new interest in using the laboratory mouse in atherosclerosis research has arrised. However, the real turning-point in using the mouse in atherosclerosis research has come with development of molecular biology and transgenic technology.

Transgenic techniques for creation of genetically engineered mice for atherosclerosis research

Transgenic mice for atherosclerosis research are produced by two methods: 1) direct introduction of foreign genes into the germ cell line or 2) targeted modification of genes in mouse embryonic stem cells (ES cells).

Direct introduction of foreign gene into the germ cell line. Shortly after the fertilization egg cells from pregnant mice are isolated and several thousand copies of a linear DNA molecule including the sequence of interest are injected into the pronucleus. Then the eggs are surgically implanted into oviduct of a pseudopregnant foster mother. The incorporation of the transgene is usually analyzed from DNA in the tail of the offspring. The transgenic animals created by this method add extra copies of genes to the genome and therefore allow to study the effect of gene overexpression in vivo.

Targeted modification of genes in mouse ES cells. ES cells are derived from the inner cell mass of mouse blastocysts and can be maintained in culture. Using homologous recombination a normal gene is replaced by a gene with a specifically designed mutant sequence in ES cells in culture. Subsequently these ES cells are injected into the host blastocyst. There they resume a normal development, giving rise to all tissues of the adult mouse, called ES chimera, including germ cells. If the chimera has got ES cells progeny in the germ line, then any genetic alteration introduced into ES cells is present in the functional gametes and can be bred from the chimera. The replacement of active genes with nonfunctional counterparts in ES cells by homologous recombination is the simplest form of gene targeting and is called gene »knock out«. The knock out transgenic animals allow to study the consequences of a decreased amount or total lack of the expression of a gene in vivo.

Lipoprotein transport proteins

Atherosclerosis develops as deposition of cholesterol and fat in the arterial wall due to disturbances in lipid transport and clearance from the blood into cells and from the cells to blood and the liver. These processes are mediated by approximately 17 proteins, the so-called lipoprotein transport proteins. These can be divided in three groups: 1) apolipoproteins which coat lipoprotein particles – A-I, A-II, A-IV, B, CI, CII, CIII, D, E, apo(a), 2) lipoprotein processing proteins – lipoprotein lipase, hepatic lipase, lecithin cholesterol acyltransferase and cholesterol ester transfer protein, and 3) lipoprotein receptors – the low density lipoprotein (LDL) receptor, chylomicron-remnant receptor (the socalled LDL receptor like protein or LDL receptor related protein – LRP), and the scavenger receptor. From 1982 to 1990 the genes that code for lipoprotein transport proteins were isolated (Breslow 1993). These genes have been used to make transgenic mice to study the lipid metabolism and atherogenesis.

Transgenic mouse models in atherosclerosis research

Apolipoprotein A (apo A-I, A-I) is the major protein in HDL. It is also present in chylomicrons. Apo A-I activates lecithin cholesterol acyl transferase and plays role in tissue cholesterol efflux. It is the primary determinant of HDL concentration, which inversely correlates with the risk of CHD.

Human A-I transgenic mouse (HuAITg). Mice with human apo A-I have 1) elevated HDL cholesterol (HDL-C) (Walsh et al. 1989, Chayek-Shaul et al. 1991), 2) decreased levels of mouse A-I (Chayek-Shaul et al. 1991, Rubin et al. 1991 A), and 3) three types of HDL corresponding to human HDL_1, HDL_2 and HDL_3 in contrast to normal mice which have only one type of HDL (Chayek-Shaul et al. 1991, Rubin et al.1991 A). HuAITg mice have been shown to be resistant to atherosclerosis in dietary studies (Rubin et al. 1991 B). This provides experimental evidence for a direct anti-atherogenic role of apo A-I and HDL. HuAITg mice can be used to examine effects of diet (Hayek et al. 1993 B) or drugs on HDL-C and A-I levels.

Apo A-I gene knock out mouse. The homozygous mice lacking apo A-I have levels of total cholesterol and HDL-C that are approximately one-third and one-fifth of the normal levels (Wiliamson et al. 1992). The levels of total cholesterol and HDL-C in heterozygous mice are a half that of normal levels (Maeda 1993). When fed an atherogenic diet the mice lacking apo A-I do not show increased susceptibility to atherosclerosis (Li et al. 1993). This finding have been surprising, because humans deficient in apo A-I appear to show premature CHD. On the other hand this finding is in accordance with results of human studies which indicate that not all cases of HDL deficiency in humans are associated with premature CHD (Maeda 1993).

Apolipoprotein A-II (apo A-II, A-II) constitutes about 20% of all proteins in the HDL particle. It is also present in chylomicrons.

Human apo A-II transgenic mouse (HuAIITg). Human A-II expression in the mouse has no effect on HDL-C levels when compared to normal mice but alters the size of the HDL particles (Breslow 1993). HuAIITg mice have two types of HDL: smaller HDL consisting almost entirely of A-II and larger consisting of mouse A-I and human A-II. The lack of effect of human A-II expression on the HDL-C levels in the mouse is in accordance with the lack of correlation between plasma A-II and HDL-C levels in clinical studies, and with the reported relatively normal HDL-C levels in patients with A-II deficiency.

Mouse apo A-II transgenic mouse (MuAIITg). Due to overexpression of mouse apo A- II these mice exhibit an increase in 1) total cholesterol, 2) HDL-C, 3) HDL diameter (Hendrick et al. 1993, Warden et al. 1993), and 4) develop atherosclerotic lesions on a low-fat diet in contrast to normal mice (Hendrick et al. 1993, Warden et al. 1993).

Human apo A-I and human apo A-II transgenic mouse (HuAIAIITg). These mice are produced by breeding HuAIITg mice with a high-expressing human A-I transgenic mouse line (Schultz et al. 1992, 1993). HuAIAIITg mice 1) express a decrease in murine A-I levels as the HuAITg mice, 2) have the same levels of plasma cholesterol and HDL-C as HuAITg mice both on standard and atherogenic diets, 3) have an extension of atherosclerotic lesions significantly greater than the HuAITg mice (Schultz et al. 1993). The latter provides the experimental evidence for the less anti-atherogenic effect of HDL particles containing both A-I and A-II than the HDL containing A-I alone. The HuAIAIITg mouse has been proposed as an animal model for studying the specific in vivo mechanisms responsible for the protective role of HDL against atherogenesis and for explaining the metabolic role of A-II (Schultz et al. 1993).

Apolipoproteins B (apo-B48 and apo-B100) are major structural components of very low density lipoprotein (VLDL), intermediate

density lipoprotein (IDL), LDL, chylomicrons, chylomicron remnants and lipoprotein (a), the classes of lipoproteins that are considered atherogenic. High levels of apo B-containing lipoproteins are associated with increased risk of CHD.

Human apo-B100 transgenic mouse (HuB100Tg). In these mice the human apo-B100 is found in low concentration in the plasma. These mice have the same total cholesterol and triglyceride levels as their normal litter mates (Chiesa et al. 1993).

Human apo-B48 and apo-B100 transgenic mouse. These mice express high levels of human apo-B48 and apo-B100. They have higher plasma cholesterol and triglyceride levels than non-transgenic control mice (Linton et al. 1993).

Apo B knock out mouse. In homozygous mice the total plasma cholesterol is about half normal and in heterozygous mice the level is about 80% of normal. These mice are expected to be a useful model for investigating the effect of reduced plasma apo B levels on the development of atherosclerosis (Maeda 1993, Homanics et al. 1993).

Apolipoprotein CI (apo CI, CI) is present in chylomicrons, VLDL and HDL. It modulates the binding of triglyceride-rich particles to LRP and LDL receptors.

Human CI transgenic mouse (HuCITg). These mice have mild triglyceridemia (Simonet et al. 1991, Breslow 1993).

Apolipoprotein CIII (apo CIII, CIII) is present in chylomicrons, VLDL and HDL. It modulates the uptake of triglyceride-rich lipoproteins.

Human CIII transgenic mouse (HuCIIITg). Several transgenic mouse lines have been made with the human CIII gene. These mice have elevated triglyceride levels primarily because of decreased tissue uptake of VLDL. HuCIIITg mice appear a suitable animal model for primary familial hypertriglyceridemia, a common lipoprotein disorder (Ito et al. 1990, Aalto-Setälä et al. 1992).

Apolipoprotein E (apo E, E) is present in chylomicrons, chylomicron remnants, VLDL, and HDL. It serves as a ligand for the LDL and LRP receptors.

Human apo E transgenic mouse (HuETg). These mice have relatively low levels of apo E expression with no significant effect of transgene expression on lipoprotein levels (Breslow 1993). Their serum lipid levels are normal (Smith et al. 1990).

Rat apo E transgenic mouse (RatETg). Compared to normal mice the RatETg mice have decreased plasma levels of triglycerides and cholesterol due to an increased clearance of VLDL and LDL from the circulation, and they are resistant to diet-induced hypercholesterolemia (Shimano et al. 1992 A, B).

Apo E3-Leiden transgenic mouse. Apo E3-Leiden is associated with a dominantly inherited form for familial dysbetalipoproteinemia. The mice carrying the apo E3-Leiden gene have elevated total plasma cholesterol and triglycerides when fed standard diet. Atherogenic diet causes dramatic increase in total plasma cholesterol and triglycerides. These mice have been proposed as a model for studying the metabolism of apo E-containing remnant lipoproteins and the etiology of familial dysbetalipoproteinemia (Maagdenberg et al. 1993).

Apo E gene knock out mouse. Homozygous E knock out mice exhibit strong hypercholesterolemia primarily due to elevated levels of VLDL and IDL as a consequence of a severe defect in the lipoprotein clearance from plasma. These mice develop atherosclerotic lesions which progress with age and resemble human lesions (Zhang et al. 1992, Plump et al. 1992, Nakashima et al. 1994, Reddick et al. 1994). These mice seem to be a promising model for studying the effect of diet and drugs on atherosclerosis.

Apolipoprotein (a) (apo(a)) is a large glycoprotein in lipoprotein (a) (Lp(a)). Elevated levels of apo(a) are associated with increased risk of atherosclerosis. Lp(a) resembles LDL except for the presence of apo(a) which in

Lp(a) is linked to apolipoprotein B100 at a single point (Lawn 1992).

Human apo(a) transgenic mouse (Huapo(a)Tg). These mice 1) have plasma apo(a) concentrations comparable to the level in humans but only 5% of the apo(a) is bound to LDL, 2) their HDL-C levels are similar to the level in non-transgenic littermates, when both types of mice are fed high-fat diet, 3) are more susceptible to diet induced atherosclerosis than control mice (Lawn et al. 1992, Rubin & Smith 1994).

Human apo-B and Lp(a) transgenic mouse (HuBLp(a)Tg). These double transgenic mice have been created by crossing animals that are singly transgenic for each. Coexpression of human apo-B and apo(a) in transgenic mice resulted in the production of an Lp(a) particle indistinguishable from human Lp(a) (Linton et al. 1993). Further studies are necessary to characterize the lipid profile, the development of lesions and the susceptibility to atherosclerosis in these mice. However, already now these mice seem a unique model for studying the role of apo-B and Lp(a) in atherosclerosis, and the pathogenic factors that cause Lp(a) to be atherogenic.

Lipoprotein lipase (LPL) is a key enzyme in the hydrolysis of triglyceride-rich lipoproteins.

Human LPL transgenic mouse (HuLPLTg). These mice have 1) significantly decreased triglyceride levels, 2) enhanced clearance of VLDL and conversion to LDL, and 3) suppressed hypercholesterolemic response to high-cholesterol diet compared to non-transgenic controls (Shimada et al. 1993).

Cholesteryl ester transfer protein (CETP) is a plasma protein that mediates the exchange of neutral lipids between HDL, VLDL and LDL.

Simian CETP transgenic mouse (SiCETPTg). These mice express the cynomolgus monkey CETP gene. They have 1) decreased HDL-C levels and concominant increase in VLDL-C and LDL-C levels without altered (Marotti et al. 1993) or decreased (Marotti et al. 1992) total cholesterol, and 2) develop more severe atherosclerosis on an atherogenic diet than nontransgenic controls (Marotti et al. 1993). The last finding is the experimental evidence for the pro-atherogenic role of CETP, which has been indicated by positive correlation between the level of CETP activity in various animal species and the species tendency to develop atherosclerosis.

Human CETP transgenic mouse (HuCETPTg). Zinc induction of human CETP transgene expression causes depression of total cholesterol due to significant reduction in HDL (Agellon et al. 1991, Hayek et al. 1992). These mice have been used to study the effect of CETP on apo-B-containing lipoproteins (Jiang et al. 1993), and may provide a model system for development of CETP inhibitors.

Human apo A-I CETP transgenic mouse (HuAICETPTg). These double transgenic mice have been generated by crossing HuAITg with HuCETP mice. Compared to non-transgenic controls they have lower HDL-C before and after Zinc induction (Hayek et al. 1992).

Human apo CIII CETP transgenic mouse (HuCIIICETPTg). These mice have been generated by crossing HuCIIITg with HuCETPTg mice. Compared to HuCIIITg mice they have significantly reduced HDL-C (Hayek et al. 1993 A).

Human apo A-I apo CIII and CETP transgenic mouse (HuAICIIICETPTg). These mice have been generated by crossing HuAICIIITg with HuCETP mice (Hayek et al. 1993 A). Introduction of human apo A-I, apo CIII and CETP genes into transgenic mice produces a high-triglyceride low HDL-C lipoprotein phenotype. These mice can be an animal model for high-triglyceride low HDL-C phenotype in humans, which is the most common disorder associated with susceptibility to CHD. Thus these mice may be helpful for studying genes and metabolic mechanisms involved in this phenotype in

humans and its consequences on atherosclerosis susceptibility.

Low density lipoprotein receptor (LDLR) mediates lipoprotein clearance from plasma through recognitions of apo B and apo E on the surface of lipoprotein particles. Humans, who lack or have a decreased number of the LDL receptor have familial hypercholesterolemia and develop CHD at early age.
Human LDL receptor transgenic mouse (HuLDLRTg). These were the first mice expressing the human gene involved in lipid metabolism (Hofmann et al. 1988). In these mice the human LDL receptor gene has been under control of the mouse metallothionine-I promoter that is not tissue specific. These mice have an increased LDL clearance from the blood. Later on the HuLDLRTg mice expressing the human LDL receptor gene in the liver under control of the transferrin promoter were produced (Yokode et al. 1990). These mice have a decreased hypercholesterolemic response to high-fat diet compared to non-transgenic controls.
LDL knockout mouse. The homozygous mice lacking LDLR have elevated levels of plasma cholesterol IDL and LDL without a significant change in HDL compared to wild type mice. Unlike the wild type they respond to moderate amounts of dietary cholesterol with major increase in cholesterol content in IDL and LDL particles (Ishibashi et al. 1993). These mice may provide a good rodent model for familial hypercholesterolemia.

Transgenic models in atherosclerotic research based on other species
Human apo A-I transgenic rats have been produced (Swanson et al. 1992). These rats have significantly higher levels of HDL-C and total cholesterol compared to non-transgenic littermates. The increase in blood lipids has been found proportional to total level of apo A-I. These rats have been proposed as a model for studying the effect of human apo A-I gene expression on lipid metabolism with regard to pharmacological, hormonal and nutritional modulation of HDL.
An attempt to generate rabbits transgenic for human apo A-I gene has been reported. The two transgenic rabbits obtained had paralysis of the limbs. It was proposed to view this transgenosis as modeling of the neurological syndrom of human Tangier disease (Perevozchikov et al. 1993), an autosomal co-dominant disorder in which homozygotes have a marked deficiency of HDL-C and apo A-I levels, decreased LDL-C and mild hypertriglyceridemia (Serfaty-Lacrosniere et al. 1994).

Mouse as a key species for transgenic models
Transgenic animal models in atherosclerosis research are mainly based on mice because the mouse has been the mammalian system of choise for gene engineering. Easy breeding and short generation time of the laboratory mouse permit to evaluate the results of the specific gene modification within a relatively short time, and if of interest, to generate several individuals with this particular modification, or to obtain individuals expressing several modifications by cross-breeding of singly or doubly transgenic, or knock out animals.

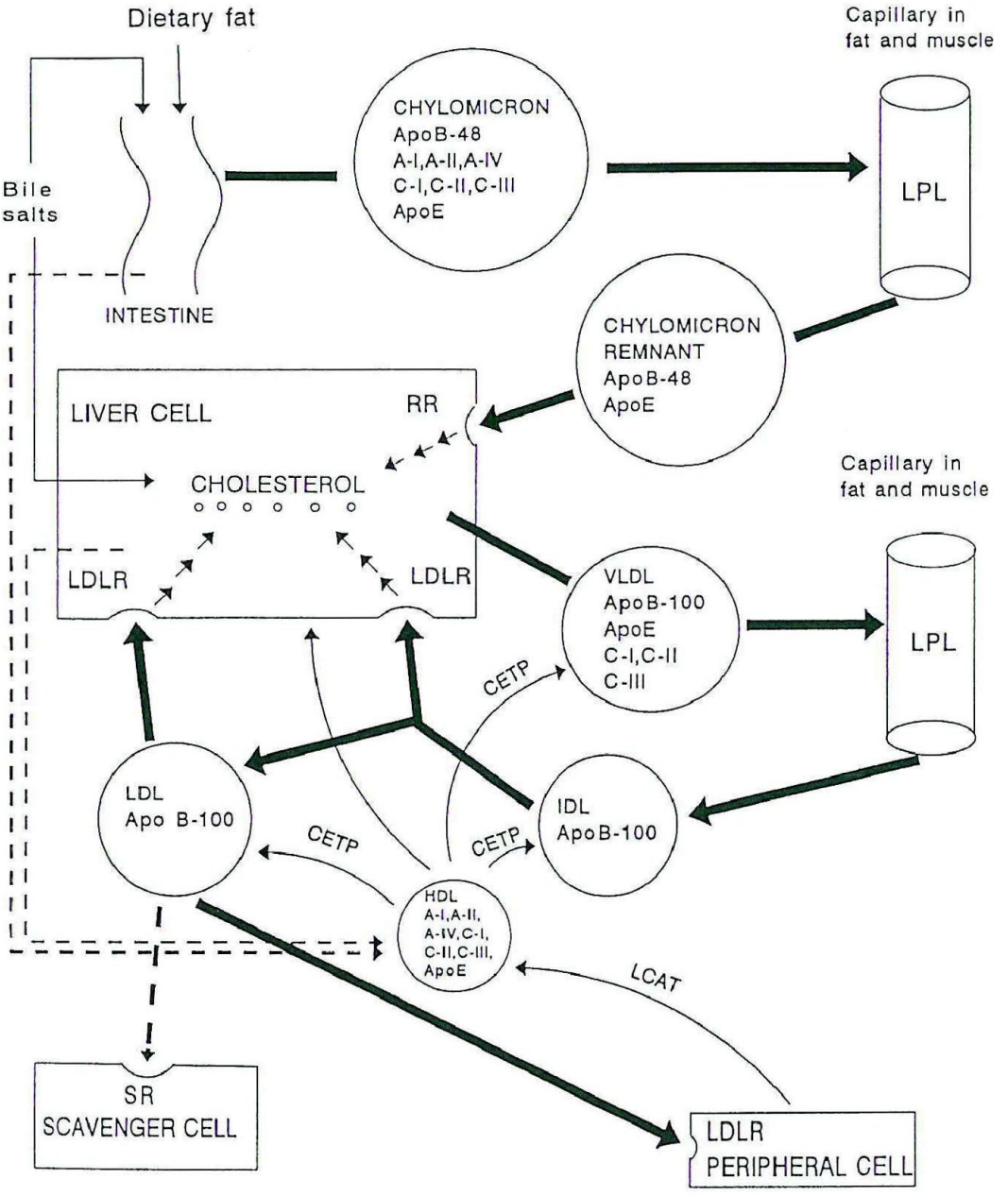
Relevance of mouse transgenic models in atherosclerosis research
The studies of human atherosclerosis in transgenic mice are at an early stage. Until now the experimental efforts have been directed at constructing specific transgenic models expressing human genes or being deficient in chosen genes important for the lipoprotein metabolism. It appears that the experimental results in these models are consistent with our knowledge about the atherogenic properties of various lipoprotein transport proteins (Rubin & Smith 1994). This support the relevancy of mouse transgenic models in atherosclerosis research.

Possible application of transgenic animal models in atherosclerosis research
Transgenic animals with a controlled genetic

TABLE. Various transgenic mouse models in atherosclerosis research

Lipoprotein transport protein	Transgenic model	Phenotype of transgennic model
A-I	HuAITg	Chol↑ HDL↑
	A-I gene knock out	Chol↓ HDL↓
A-II	HuAIITg	HDL→
	MuAIITg	Chol↑ HDL↑
	HuAIAIITG	Chol↑ HDL↑
B	HuB100Tg	Chol→ TG→
	HuB48B100Tg	Chol↑ TG↑
	B gene knock out	Chol↓ HDL↓ TG↓
CI	HuCITg	Tg↑
CIII	HuCIIITg	Tg↑
E	RatETg	Chol↓ TG↓
	HuETg	Chol→ TG→
	E3-Leiden Tg	Chol↑ Tg↑
	Apo E knock out	Chol↑
Apo(a)	Huapo(a)Tg	HDL→
LPL	HuLPLTg	TG↓
CETP	SiCETPTg	HDL↓
	HuCETPTg	HDL↓ VLDL+LDL↑
	HuAICETPTg	HDL↓ Chol↓
	HuCIIICETPTg	HDL↓
	HuAICIIICETPTg	HDL↓ TG↑ HDL↓
LDLR	HuLDLRTg	LDL↓ Chol↓
	LDLR knock out	Chol↑ LDL↑ IDL↑

Upward arrow: increase. Downward arrow: decrease.



A schematic presentation of the lipoprotein metabolism. In the intestine the dietary cholesterol together with triglycerides is built into chylomicrons which are then transported by lymph into the bloodstream. In the capillary vessels the chylomicrons are hydrolysed to chylomicron remnants by lipoprotein lipase (LPL)and hepatic lipase (HL). Chylomicron remnants are taken up by remnant receptors (RR) in the liver. Cholesterol from the chylomicron remnants is 1) secreted in the bile (as cholesterol or bile salts) into the intestines and 2) is used in the synthesis of very low density lipoproteins (VLDL), which are secreted into the blood. In the circulation VLDLs are hydrolysed to intermediate density lipoproteins (IDL) by LPL and HL. IDLs 1) bind to the low density lipoprotein receptor (LDLR) and are transported into the liver cells, and 2) are catabolised to low density lipoprotein (LDL) in the blood stream. LDLs are 1) taken up by LDLR in liver cells and peripheral cells, and 2) some of them undergo modification in the circulation and then bind to the scavenger receptor (SR) and are transported into scavenger cells. HDLs are directly produced both in the liver and intestine. HDL constituent are also derived from chylomicron and VLDL catabolism. There are two main types of HDLs: HDL2 and HDL3. HDLs serve as acceptors of lipids especially free cholesterol from varying tissues. Free cholesterol is then estrified due to reaction mediated by lecithin cholesteryl acyltransferase (LCAT). Cholesterol esters are then transferred from HDLs to other lipoproteins nonspecifically, as well as by cholesteryl ester transferred protein (CETP). HDLs contribute in the transport of cholesterol from periphery to the liver.

background allow in vivo investigation of over- or underexpression or total lack of different lipoprotein transport genes on the development of atherosclerosis under controlled environmental conditions. They provide unique animal models for studying cause and effect relationships between genetic variations and complex phenotypes in human atherosclerosis, and the interaction between the genetic and environmental factors. Additionally, the use of these models overcomes some of the limitations of human studies such as long life span and small family size, and lack of possibilities to conduct detailed biochemical studies on human subjects. Furthermore, the defined laboratory environment facilitates interpretation of the results by minimalizing the number of environmental factors which can interfere with the study outcome. They are promissing tool for dietary studies, development of new drugs, and the search for new therapies based on gene targeting.

Conclusion

Consistency of results in transgenic mouse models with the results of studies in man supports the relevancy of these models in atherosclerosis research. These models are promising tools for studing the effect of genetic background, diet, environment and drugs on atherosclerosis and will alongside other animal models facilitate the understanding of this disease. With progress in transgenic technology and a growing availability of genetically modified mouse lines transgenic mice may even become the leading animal models in this field of research.

Abstract:
Atherosclerosis and its clinical sequela coronary heart disease is a major cause of death in the modern world. It is caused by a complex interaction between genetical and environmental factors. Over the last decade the development of transgenic techniques and the isolation of human genes coding for proteins that directly interact with plasma lipids made it possible to create new transgenic animal models in atherosclerosis research. Several transgenic mouse lines have now been established that overexpress many of the lipoprotein transport genes. Additionally, the technique of homologous recombination in embryonic stem cells has been used to knock out lipoprotein transport genes. The new models allow in vivo investigation of over- or underexpression or total lack of different lipoprotein transport genes on development of atherosclerosis under controlled conditions. The models are a promising tool for studying the effect of drugs, diet and chosen environmental factors on atherosclerosis, and will facilitate the understanding of the pathophysiology of atherosclerotic lesions.

Resumé;
Atherosklerose og dens kliniske følgesygdom iskæmisk hjertesygdom, er en af de største dødsårsager i den moderne verden. Sygdommen forårsages af en kompleks interaktion mellem genetiske- og miljøfaktorer. I det sidste tiår har udvikling af transgene teknikker og isolering af humane gener, der koder for proteiner, som direkte går i interaktion med lipider i plasma, muliggjort nye transgene dyremodeller for atheroskleroseforskningen. Flere linjer af transgene mus med overekspression af nogle gener for lipoproteintransport er blevet skabt. Yderligere, er homologisk rekombination i embryonale stamceller anvendt til at inaktivere gener for lipoproteintransport. De nye modeller muliggør undersøgelser af over- eller underekspression af eller total mangel på diverse gener i tranporten af lipoproteiner under kontrollerede forhold. Modellerne er lovende værktøjer i undersøgelser af effekten af lægemidler samt effekten af kost- og miljøfaktorer på udvikling af atherosklerose, og de forventes at hjælpe til at forstå patofysiologien af atherosklerotiske læsioner.

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