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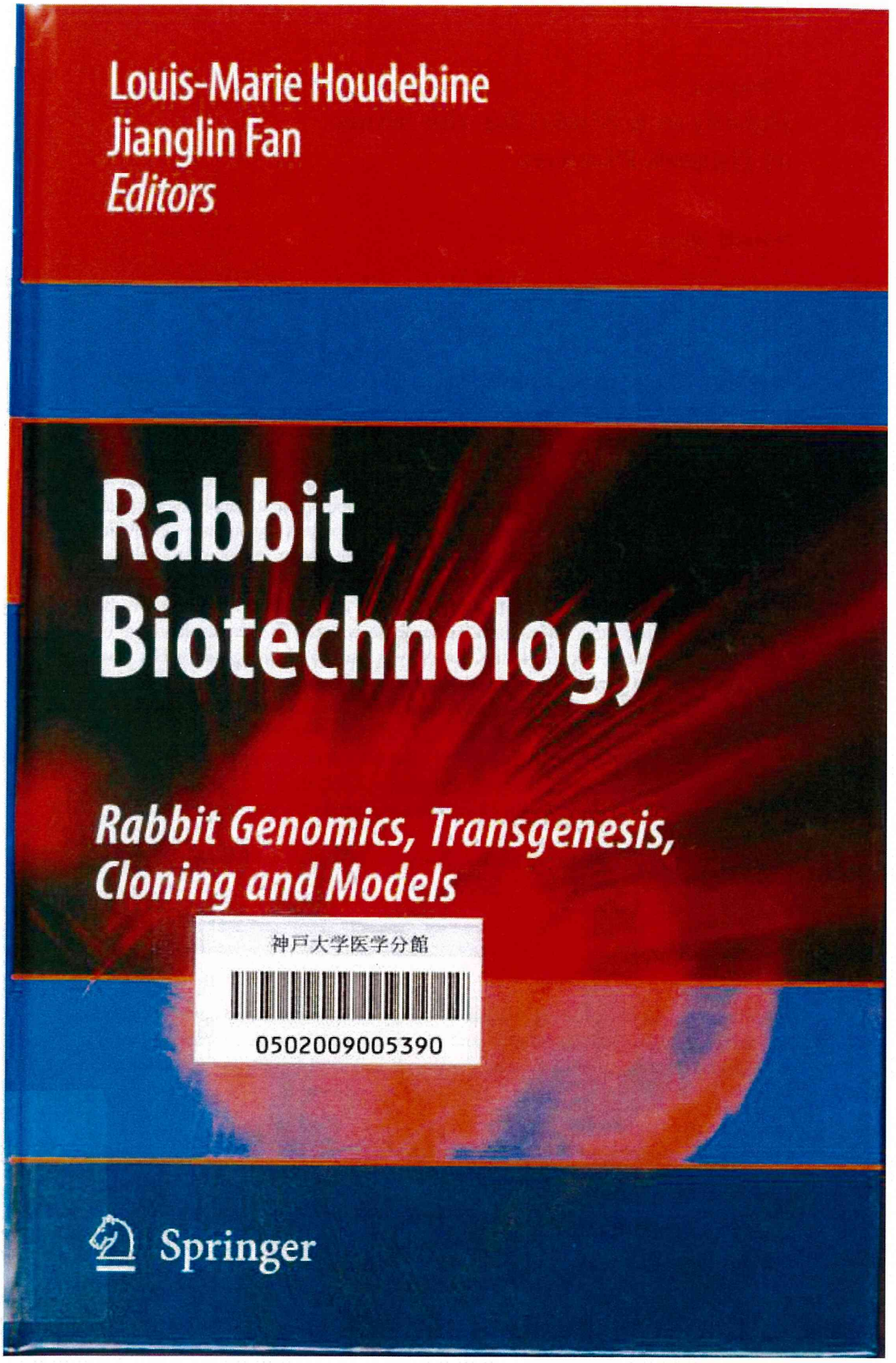
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Chapter 7
Rabbit as a Model for the Study of Human Diseases

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Abstract Although genetically modified mice are playing an essential role in the study of the expression and functions of individual genes, rabbits are useful animal models to extrapolate animal studies to humans. It is necessary that key gene expression and function are equivalent and close to human rather than the outward features or phenotype. For example, to study human hypercholesterolemia, the only hypercholesterolemia is insufficient, the lipoprotein profiles and enzymes in the lipoprotein metabolism of animal models are important for translational medicine. Lipoprotein metabolism of rabbits resembles humans closely. In addition, histopathological and/or immunohistochemical features of the tissues of disease similar to humans are important. In this field, spontaneous hypercholesterolemic rabbits (WHHL and WHHLMI rabbits) have contributed to the elucidation of lipoprotein metabolism, atherogenesis, and to the development of therapeutic compounds, such as statins. Recently, a number of transgenic rabbits have been developed and they also contribute to the study of cardiac function and infectious diseases. Furthermore, rabbits are useful for studies of orthopedic surgery, cardiovascular surgery, and neoplastic diseases. Rabbit models have contributed not only to the mechanistic studies of human diseases but also to the development of therapeutic compounds, devices, or techniques for therapeutics. Applying these animal models in translational researches promotes the elucidations of human diseases.

Keywords animal models for human diseases, translational research, transgenic rabbits, WHHL/WHHLMI rabbits

7.1 Introduction

After the genomes of human and mouse were fully deciphered, it has been recognized that the analyses of gene expression and functions are important to understand the pathogenesis and the mechanisms of diseases. It is critical for researchers to choose

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defect in LDL receptors which is characterized by the deletion of 12 base pairs of nucleotide in the LDL receptor gene (Yamamoto et al. 1986), which explained why there was marked accumulation of LDL in the plasma of WHHL rabbits (Tanzawa et al. 1980; Kita et al. 1981). In addition, WHHL rabbits, had tenfold higher levels of plasma triglycerides than normal rabbits. The CETP activity was high in the plasma (Son and Zilversmit 1986) and expression of apoB-editing enzyme was not detected in liver (Kozarsky et al. 1996). Therefore, lipoprotein metabolism of WHHL rabbits resembles that of human familial hypercholesterolemia patients. Because of these features, WHHL rabbits contributed to studies aiming at elucidating human lipoprotein metabolism, especially the LDL receptor pathway (Goldstein et al. 1983). In addition, WHHL rabbits have been used to screen the lipid-lowering effects of many compounds (Table 7.2). The best example of these studies examined in WHHL rabbits is statin (Watanabe et al. 1981; Tsujita 1986; Watanabe et al. 1988; Shiomi et al. 1995, 2005; Shiomi and Ito 1999a), which is one of the most effective hypocholesterolemic drugs prescribed right now for more than 30 million patients in the world each year.

WHHL rabbits have also contributed to studies of atherosclerosis and examination of anti-atherosclerotic effects of several compounds (Table 7.2). Due to the LDL receptor deficiency and hypercholesterolemia, atherosclerotic lesions developed spontaneously in WHHL rabbits under a normal standard chow. Therefore, WHHL rabbits can be used for the study of atherosclerosis initiation and the characterization of atherosclerotic pathology (Shiomi 2008). Atherosclerotic lesions of the aorta of WHHL rabbits were fatty streak at weaning, became macrophage-rich lesions at young age, established lesion (fibro-atheroma) at mature age, and complicated lesions (accumulation extracellular lipids, thin fibrous cap, calcification, and intra-

Table 7.2 Hypolipidemic and anti-atherosclerotic studies using WHHL or WHHLMI rabbits

Compounds	Hyperlipidemia	Aortic lesion	Coronary lesion
Statin	○	×, ○	○
Resin	○	○	n.d.
Statin + Resin	○	○	○
Squalene synthase inhibitor	○	○	○
MTP inhibitor	○	n.d.	n.d.
ACAT inhibitor	×, ○	×, ○	×, ○
Probucol	○	○	n.d.
M-CSF or GM-CSF	○	○	n.d.
ApoE	○	○	n.d.
Fibrate	×	n.d.	n.d.
Fish oil	×, ○	×, ○	n.d.
Thiazolidinedione	×	Δ	Δ
Ca^{2+} antagonist	×	×	×
β-blocker	×	×	×
ACE inhibitor	×	○	n.d.
A-II receptor antagonist	×	○	n.d.
Gene therapy	○	n.d.	n.d.

○, effective; ×, not effective; n.d., not determined

plaque hemorrhage) at old age. These histological features resemble many respects of human atherosclerotic lesions. Using WHHL rabbits, Watanabe et al. demonstrated that plasma cholesterol reduction by pravastatin, an inhibitor of cholesterol synthesis, can delay development of atherosclerosis (Watanabe et al. 1988).

7.3.2 WHHLMI Rabbits

Although atherosclerotic lesions developed in aorta of every WHHL rabbit, the incidence of coronary atherosclerosis was very low and myocardial infarction did not occur. To develop coronary atherosclerosis in WHHL rabbits, Watanabe et al. (Watanabe et al. 1985) started to develop coronary atherosclerosis-prone WHHL rabbits by selective breeding in 1995. Studies using the coronary atherosclerosis-prone WHHL rabbits demonstrated that reduction of plasma cholesterol levels by statins improved composition of coronary plaques from unstable lesions to stable lesions (Shiomi et al. 1995, 2005; Shiomi and Ito 1999a). However, the incidence of myocardial infarction was still very low due to macrophage-poor lesions. In quantitative analyses of atherosclerotic lesions using imaging techniques (Shiomi et al. 1994), the composition of coronary atherosclerosis differed from the aortic ones. Thereafter, Shiomi et al. (Shiomi et al. 2003) started selective breeding from 1993 using indices of macrophage-rich coronary lesions, severe coronary stenosis, higher plasma cholesterol levels, and development of myocardial infarction. Seven years after, the incidence and severity of coronary lesions increased. The cumulated incidence of myocardial infarction in 30 months old animals was increased from 23% of the original WHHL rabbits to 97% in WHHLMI rabbits by the selective breeding (Shiomi et al. 2003). The degree of coronary stenosis (cross-sectional narrowing) at the age of 10–14 months also increased from 38% in the original WHHL rabbits to 82% in the WHHLMI rabbits (Ito et al. 2004). Myocardial infarction of WHHLMI rabbits is classified into four types: subendocardial infarction, intramural infarction, transmural infarction, and subepicardial infarction. In WHHLMI rabbits, fresh myocardial lesions consisted of hyperemia, eosinophilic degeneration of myocardial cells and infiltration of inflammatory cells was observed in the vicinity of old myocardial lesions consisting of myocardial fibrosis, scar, and dissolution of myocardial cells. The electrocardiograms from a WHHLMI rabbit monitored immediately before sudden decease showed an elevation of ST-segment and deep Q-wave which are the typical changes of acute myocardial infarction in humans. The coronary lesions of WHHLMI rabbits show various types, vulnerable plaque (large lipid core covered with thin fibrous cap), macrophage-rich plaque, complicated plaque and fibrous plaque, all similar to human coronary plaques. However, rupture of coronary plaque and/or formation of thrombosis were not observed. The next theme is the development of acute coronary syndrome in WHHLMI rabbits, with the coronary plaque rupture and the generation of thrombosis.

Figure 7.1 summarizes the characteristics of WHHLMI rabbits and their implementation in translational researches. LDL accumulates in the plasma due to LDL receptor deficiency, the low HDL-cholesterol and the metabolic syndrome-like

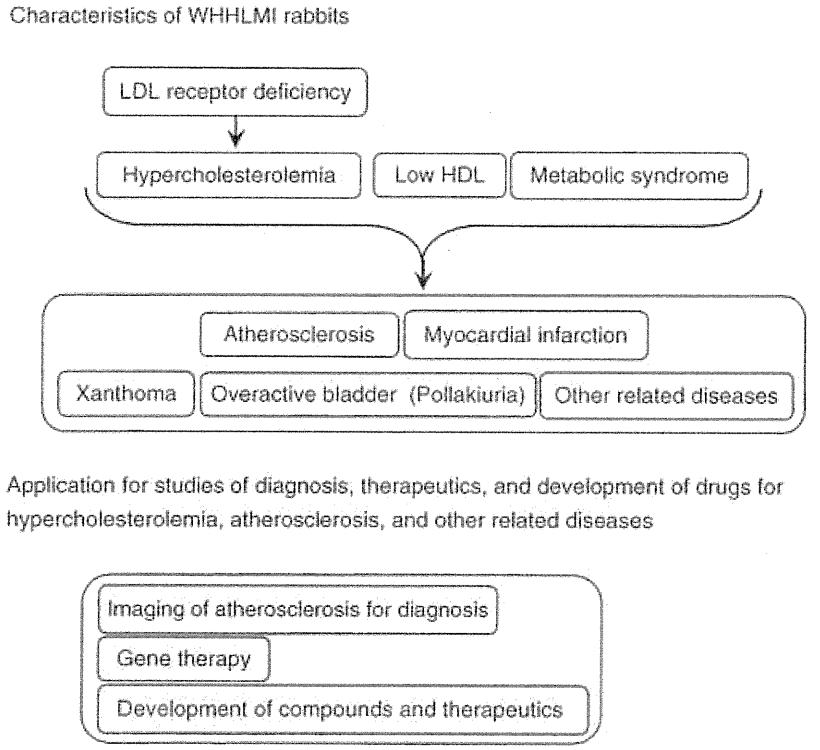

Fig. 7.1 Characteristics of WHHLMI rabbits and the application

feature (accumulation of visceral fats and hyperinsulinemia) which cause the development of atherosclerotic lesions in aorta, coronary arteries, pulmonary arteries, carotid arteries, cerebral arteries and other arteries. Myocardial infarction occurs due to coronary occlusion by atherosclerotic lesions. In addition, xanthoma, overactive bladder and other diseases appeared related to hypercholesterolemia and atherosclerosis.

Ideally, it is essential that animal models should contribute not only to the mechanistic study of human diseases but also to the development of new drugs, devices, or techniques for therapeutics. As mentioned above, several hypocholesterolemic drugs have been developed and the anti-atherosclerotic effects of some of them could be proved. Statin is an inhibitor of HMG-CoA reductase, a rate-limiting enzyme in the cholesterol biosynthesis pathway. Lipid-lowering effect of statin was initially detected in WHHL rabbits and it is the most potent drugs to prevent acute coronary syndromes (Naghavi et al. 2003). Studies using WHHL rabbits contributed to understand how the reduction of the serum cholesterol levels stabilized atherosclerotic lesions (Shiomi et al. 1995). Recently, WHHLMI rabbits have been

used in studies based on imaging of atherosclerotic lesions by MRI (Meding et al. 2007; Steen et al. 2007), PET (Ogawa et al. 2006; Ishino et al. 2007) and intravascular ultrasound (IVUS) (Iwata et al. 2007). These techniques are promising for the identification of patients with coronary atherosclerosis to prevent acute coronary syndromes. In addition, WHHL (Kobe colony) and WHHLMI rabbits also showed metabolic syndrome-like metabolic disorders, including the accumulation of visceral fats (Shiomi et al. 1999b), insulin resistance (Zhang et al. 1991; Shiomi et al. 1999b) and mildly hyperglycedemia. Some WHHLMI rabbits also showed overactive bladder and keratopathy (Garibaldi and Goad 1988).

7.3.3 Other Rabbit Models for Human Lipid Disorders

In 1987, La Ville et al. (La Ville et al. 1987) developed a rabbit strain characterized by hypercholesterolemia (394 ± 100 mg/dl) with moderately increased or normal triglyceride levels. This rabbit strain showed elevated endogenous lipoproteins (very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and low-density lipoprotein (LDL)) cholesterol and LDL triglyceride levels due to over-secretion of VLDL from the liver. The LDL receptors functioned normally. Atherosclerosis developed in the aorta of these animals. These rabbits resemble human familial combined hyperlipidemia, which is one of the most common discrete hyperlipidemic disorders. Later on, this rabbit strain was bred into a new colony, the St. Thomas' mixed hyperlipidemic (SMHL) rabbit (Ardern et al. 1999). In SMHL rabbits, the serum cholesterol levels were 264 ± 68 mg/dl, and the triglyceride levels were 290 ± 55 mg/dl in feeding of very low cholesterol containing diet (0.08% cholesterol enriched diet) (De Roos et al. 2005). SMHL rabbits also showed insulin resistance (De Roos et al. 2001).

Ito and coworkers developed postprandial hypertriglyceridemic (PHT) rabbits (Kawai et al. 2006), which showed postprandial hypertriglyceridemia and metabolic syndrome-like feature. In PHT rabbits, the preprandial plasma triglyceride levels (4.55 ± 1.32 mmol/l) were about tenfold higher than in normal JW rabbits. After 15 h of continuously available feed of normal standard chow, the plasma triglyceride levels were markedly increased (15.9 ± 2.7 mmol/l) compared with the normal Japanese white rabbits (0.71 ± 0.01 mmol/l). In PHT rabbits, accumulation of visceral fat was prominent and insulin resistance was observed. These rabbits may also be important for the study of hyperlipidemia and metabolic syndrome.

7.4 Rabbit Models for Other Human Diseases

Rabbits also contributed to studies of cardiac function, infectious diseases, orthopedic surgery, cardiovascular surgery, and neoplastic diseases.

7.4.1 *Transgenic Rabbit Models for Prolonged QT and Sudden Cardiac Death in Human*

Recently, Brunner et al. (Brunner et al. 2008) reported that the expression of pore mutants of the human genes KCNQ1 and KCNH2 in rabbit hearts led to the generation of transgenic rabbits (LQT1 and LQT2) with a long QT phenotype. KCNQ1 and KCNH2 are genes encoding repolarizing K^+ channels. The human long-QT syndrome is characterized by delayed ventricular repolarization, prolonged QT-interval, ventricular arrhythmia and sudden cardiac death. Current murine transgenic animal models of long-QT syndrome are limited by substantial differences in cardiac electrophysiology. LQT2 rabbits showed a high incidence of spontaneous sudden cardiac death (>50% at 1 year) due to polymorphic ventricular tachycardia. Optical mapping revealed increased spatial dispersion of repolarization underlying arrhythmia. These transgenic rabbits have been used as a model to detect the channel-blocking properties of some anesthetic agents (Odening et al. 2008). The transgenic LQT1 and LQT2 rabbits are thus suitable animal models for studying the human prolonged QT syndrome.

7.4.2 *Rabbit Models for Thrombogenesis*

An important event after plaque rupture is thrombogenesis. Development of thrombus under physiological conditions is rare in animal models. Recently, Yamashita et al (Yamashita et al. 2004) reported that a blood flow reduction after thrombus propagation related to arterial thrombogenecity in rabbit model after single and repeated balloon injuries. In their study, after balloon injury of the normal femoral artery of normal rabbits, the blood flow was reduced. As a result, increased vascular wall thrombogenicity together with a substantial blood flow reduction are crucial for occlusive thrombus formation and the von Willebrand factor plays an important role in thrombus propagation. Finally, they speculated that reduced blood flow at plaque disruption sites might contribute to thrombus propagation leading to acute coronary syndromes. In coronary thrombi obtained by an aspiration device from patients with acute myocardial infarction, Hoshiba et al. (2006) observed co-localization of the von Willebrand factor with platelet thrombi, the tissue factor, platelets with fibrin and the consistent presence of inflammatory cells (CD16-positive neutrophils, CD45-positive mononuclear cells and CD34-positive blood progenitor cells). These studies suggest that, to propagate an arterial thrombus after a plaque rupture, a reduction of blood flow is important as well as the growing of the thrombus with inflammatory cells and erythrocytes. Therefore, rabbits are useful models for studies of thrombogenesis. Development of transgenic rabbits for factors of thrombogenesis may also play an important role.

7.4.3 *Rabbit Models for Infectious Diseases and Deficiency of Immunological System*

Manabe et al. (Manabe et al. 2008) showed that New Zealand white rabbits are useful animal for human latent tuberculosis. The global epidemic of tuberculosis claims more than two million lives yearly. *Mycobacterium tuberculosis* latently infects one third of the world population. They examined aerosol-infected rabbits with *Mycobacterium tuberculosis* and showed the formation of caseous lung granulomas which are strikingly similar to tuberculous lung lesions in humans. The lung burden of infection peaked at 5 weeks after aerosol infection followed by a host containment of infection that occurred in all rabbits. Corticosteroid-induced immunosuppression initiated after the disease containment resulted in a reactivation of disease. They also characterized the lung cellular immune response to inhaled *Mycobacterium tuberculosis* in the susceptible inbred Thorbecke rabbit (the genomically sequenced strain) and compared it to outbred, *Mycobacterium tuberculosis*-resistant, New Zealand white rabbits (Mendez et al. 2008). The development and severity of the immune reconstitution inflammatory syndrome was dependent on the antigen load at the time of immunosuppression and the subsequent bacillary replication during the corticosteroid-induced immunosuppression. This corticosteroid model is the only animal model to study the immune reconstitution inflammatory syndrome. The lung granulomas of inbred rabbits had a significantly higher number of cells expressing MHC Class II and CD11b, and a lower number of CD8 + T cells than the outbred controls. Effective utilization of this rabbit model could lead to a new tuberculosis diagnostic as well as to the elucidation of important correlates of protective immunity.

Human papillomavirus infections result in more than 250,000 deaths from cervical cancer in women worldwide. Hu et al. (2007) established a rabbit transgenic model expressing the human major histocompatibility complex (MHC-I) gene (HLA-A2.1). These transgenic rabbits expressed the HLA protein at a high level and HLA-A2.1 restricted rabbit CD8 cells were induced in these animals. Southern blot analysis demonstrated that the HLA-A2.1 gene was integrated into the rabbit genome and similar expression patterns of HLA-A2.1 and rabbit MHC class-I was observed in the three lines of transgenic rabbits. They demonstrated that HLA-A2.1 transgenic rabbits showed a susceptibility to cottontail rabbit papillomavirus infection akin to that of normal domestic rabbits. They also reported that a human papillomavirus type 16 E7 epitope can be engineered to be introduced into the cottontail rabbit papillomavirus E7 gene of the rabbit papillomavirus genome. This hybrid genome retained the ability to initiate paplillomas. The cottontail rabbit papillomavirus/HLA-A2.1 rabbit model has the potential to be used to screen HLA-A2.1-restricted immunogenic epitopes from human papillomaviruses in the context of in vivo papillomavirus infection. These studies suggested that rabbit is an excellent model to assess both natural and induced immunity to papillomavirus infections and that the transgenic rabbits may have utility for assessment of immunity to other human pathogens that are permissive in rabbits.

Rother reported the existence of a mutant rabbit which was deficient in the sixth component of complement (Rother et al. 1966). Current studies based on the use of the 6 complement-deficient rabbits suggested that this component is involved in the activity of the immune system, the activation of the inflammatory response and the hemolytic activity. Chartrand et al. (1979) demonstrated that delayed rejection was observed in the puppy hearts engrafted to C6-deficient rabbits. Schmiedt et al. (1998) suggested that C6-deficient rabbits delayed the development of atherosclerosis by cholesterol feeding due to the weak inflammatory responses of arterial cells. Therefore, C6-deficient rabbits may contribute to study human diseases related to the immune system and the inflammatory responses.

7.4.4 Rabbit Models for Human Articular Lesions and Therapeutics

Patients with articular cartilage lesions caused by injury or degenerative joint diseases become increased recently and these defects do not repair spontaneously. Studies using rabbits have been contributed to tentatively develop therapeutics against the diseases. Ikeda et al. (2009) showed that rabbits are useful to examine the effect on porosity and of the mechanical properties of a synthetic polymer (DL-lactide-coglycolide) scaffold on repair of osteochondral defects. They treated rabbits suffering from osteochondral defects in the femoral condyle with three types of scaffolds. Their study suggested that higher porosity allowing bone marrow cells to migrate to the scaffold is important in repairing osteochondral defects. Nakayama et al. (2009) performed a mechanical analysis of the effects of fibroblast growth factor-2 (FGF-2) on autologous osteochondral transplantation in an artificial rabbit model. They induced a full-thickness cartilage defect in the right femoral condyle and treated with osteochondral transplantation using an osteochondral plug taken from the left femoral condyle. Autologous osteochondral grafts transplanted with gelatin hydrogel containing FGF-2 acquired adequate stiffness at early postoperative phase. In addition, Ishida et al. (2007) demonstrated that platelet-rich plasma enhances the healing of meniscal defects in rabbits. These studies demonstrate that rabbits are useful for studies to develop therapeutics about human articular lesions.

7.4.5 Rabbit Models for Vascular Surgery

Rabbits are also useful for studies to develop technique for vascular and respiratory surgery. Kawanishi et al. (2007) showed that the prevention of back-bleeding from intercostal arteries and lumbar arteries during thoracoabdominal aortic surgery was considered to reduce spinal ischemic injury. They examined the effects of back-bleeding in spinal cord by comparing rabbits without back-bleeding from

the lumbar arteries by draining from the aorta during aortic clamping with rabbits in which back-bleeding was not drained. Forty-eight hours later, the number of TUNEL-positive cells in rabbits draining back-bleeding was significantly smaller than those in rabbits with back-bleeding. Hasegawa et al. (2007) implanted autologous fibrin-coated vascular prostheses and/or xenologous fibrin-coated vascular prostheses in the bilateral carotid arteries of JW rabbits. As a result, autologous fibrin coating in thrombin-free fibrin-coated vascular prostheses improved antithrombogenecity. Their study suggested that autologous fibrin coating in thrombin-free fibrin-coated vascular prostheses have a potential for clinical use in hybrid small-caliber vascular grafts.

7.4.6 Rabbit Models for Tumor Study

Several transplantable rabbit tumors have been reported and VX2 tumor has been used in some studies. The VX2 carcinoma arose as the result of spontaneous transformation of a virus-induced skin papilloma in a domestic rabbit (Kidd and Rous 1940) and is a type of dermatological squamous cancer induced by the Shope virus. In general, the VX-2 tumor had a high malignant potential, with capacity for rapid reproduction, infiltration and metastasis. VX2 tumors have been transplanted into lung, liver, and other organs in rabbits. These rabbit VX2 tumors have been studied for establishing therapeutics and diagnostics. Virmani et al. (2008) demonstrated that hypoxia caused by transcatheter arterial embolization of VX2 liver tumors activates the hypoxia-inducible factor-1 alpha, a transcription factor that in turn regulates other pro-angiogenic factors. Jiang et al. (2008) reported that the hemodynamic changes in the liver caused by rabbit VX2 liver tumor can be detectable after tumor inoculation and that functional CT can evaluate the physiological characteristics of early angiogenesis. In addition, Ohira et al. (2008) demonstrated that FDG-PET was useful for monitoring the early effects of radiofrequency ablation in VX2 rabbit tumors implanted into the back muscles. These studies have demonstrated that rabbits are also useful for studies of tumor.

7.5 Conclusions

Genetically modified mice is playing an essential role in the clarification of the expression and functions of individual gene. However, to translate or extrapolate the results of animal studies to humans, it is necessary that key gene expression and function are equivalent to human rather than the outward features or phenotype. For example, to study human hypercholesterolemia, not only the hyperlipidemia itself, the characteristics of the lipoprotein profiles and enzymes in the lipoprotein metabolism of animal models is vitally important for translational researches. In addition, histopathological and/or immunohistochemical features similar to humans are

also important. Several rabbit models for some human diseases described in this chapter are useful in translational researches. Applying these animal models in translational researches will contribute to elucidation of the mechanism of human diseases and development of novel compounds, therapeutics, or diagnostic instruments containing lesion imaging techniques.

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