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In the context of biomedical research, rabbits are perhaps most often thought of as bioreactors for the production of monoclonal and polyclonal antibodies and more recently recombinant proteins. However, rabbits are increasingly becoming a valuable experimental model in their own right and are in some cases, the translational model of choice. [1]

Rabbit models do not have the litany of advantages afforded by rodent, or for that matter invertebrate, models in terms of their short life spans, short gestation periods, high numbers of progeny, low inter-individual variability, low cost, advanced genomics and proteomics, and broad availability of reagents. However, rabbits do have many advantages and serve to bridge the gap between these small animal models, which are perhaps best suited for discovery phases of research, and larger animal models often required for pre-clinical, translational research. Rabbits are relatively inexpensive to purchase, house, and maintain as compared to larger animal models. They are easy to breed and handle and are a well-established model in terms of being recognized by the scientific and regulatory communities. Rabbits are phylogenetically closer to primates than rodents and further offer a more diverse genetic background than inbred and out-bred rodent strains, which makes the model a better overall approximate to humans. Further, rabbit genomics and proteomics are advancing rapidly and several transgenic lines have been created and characterized and are readily available. With more researchers using rabbits in their experiments, industry is catching up to their needs and offering an expanding range of rabbit-specific products and services to support them. [1]

Perhaps most importantly, there are some human conditions that cannot be adequately modeled by invertebrate or rodent species and in some cases, the special characteristics of rabbit anatomy and physiology make it uniquely suitable for the study of particular human diseases. [1] Some of the fields for which the rabbit often serves as a primary experimental model include atherosclerosis, Alzheimer's disease, eye research, osteoarthritis, and tuberculosis. Below is a brief description of how rabbits are crucial to furthering research in these selected areas. This review is intended to be neither comprehensive nor definitive, rather an overview of selected biomedical research fields that employ the rabbit model.

Atherosclerosis
Atherosclerosis naturally occurs only in humans, a few non-human primates, and pigs. Rabbits, being herbivores, do not develop atherosclerosis naturally, but do consistently develop an atherosclerotic condition that very closely resembles clinical observations

when manipulated via dietary or genetic interventions. The rabbit hypercholesterolemia model is perhaps the most well-know of the models and is typically produced by feeding intact rabbits a high-cholesterol diet. After only a few weeks on a modified diet, rabbits develop notable vascular lesions. This rabbit model is highly reproducible with minimal variation between animals in a single laboratory and between laboratories. Two spontaneous lipid metabolism mutants have been characterized and also used extensively in atherosclerosis research – the Watanabe heritable hyperlipidemic (WHHL) rabbit (LDL receptor deficient) and the St. Thomas' Hospital rabbit (VLDL, IDL, and LDL elevated) serve as models for familial hypercholesterolemia and familial combined hyperlipidemia, respectively. Homozygous WHHL rabbits and St. Thomas' Hospital rabbits predictably develop atherosclerotic lesions on normal diets. Finally, there are at least 19 transgenic rabbit lines now available specifically for the study of cardiovascular disease that express a wide variety of human transgenes many of which code for proteins implicated in atherosclerosis. [1-3]

These rabbit models closely approximate a variety of aspects of human atherosclerosis and are commonly used to study atherogenesis, plaque instability and rupture, and myocardial infarction. Relative to rodent models, rabbits are much more clinically relevant as many aspects of rabbit lipoprotein metabolism are very similar to humans. Perhaps the most notable differences are that rabbit vascular lesions are more fatty and more inflammatory (as measured by numbers of macrophages present) and rabbit circulating cholesterol levels are higher. An additional advantage to rabbits over rodents is that human transgenes expressed in rabbits produce the expected human-like symptoms while the same transgenes expressed in rodents fail to do so. Further, rabbits are capable of tolerating longer experimental protocols that require monitoring and/or sampling over a period of time whereas individual rodents often can only contribute to a single time point in a study. [1-3]

Rabbit is the first and classical model for human atherosclerosis research and will continue contribute pre-clinical, translational evidence for the safety and efficacy of novel therapies. Perhaps the only animal models that have in some cases surpassed the value delivered by rabbits are the swine models. [1-3]

Alzheimer's Disease
As a result of the rarity of spontaneous Alzheimer's disease (AD) development in non-human species, animal models mimicking various aspects of this disease have only recently been innovated – typically via dietary, pharmacological, or genetic manipulations. Of these new experimental AD models, the rabbit hypercholesterolemia model, originally developed for the study of atherosclerosis (described above), has a variety of advantages that make it one of the leading models for AD research as well. [4]

Physiologically at the cellular and molecular levels, rabbits fed high-cholesterol diets display many of the neuropathologies observed in humans with AD. The brains of these rabbits show increased levels of cholesterol and Amyloid β (Aβ) and decreased levels of acetylcholine, increased Aβ, tau, and ApoE immunoreactivity, Aβ plaques in the extracellular space, a breakdown in the blood-brain barrier, and an increase in microglial and decrease in neuronal cell populations. The phylogenetic proximity of rabbits and humans is reflected in the 97% amino acid sequence conservation observed between the two species' Aβ proteins and is a major advantage over other models of AD including fruit flies, mice, and rats. Anatomically, rabbits have larger brains relative to the aforementioned species allowing for greater flexibility in testing for cognitive impairment. Cognitively, rabbits with hypercholesterolemia-induced AD display age-dependent deficits in associative learning that closely parallel those observed in humans. As measured by impairment of eyeblink classical conditioning, these deficits are beyond those observed with normal aging, are specific to AD (i.e., not observed in Parkinson's Disease or Huntington's disease), and are relieved upon administration of drugs that improve cognition. No other experimental animal model of AD boasts such an extensive body of existing data by which to judge cognitive impairment as the classically-conditioned eye blink response of rabbits. [4]

Eye Research

The main advantages to using rabbits as experimental models in eye research are the large size of the rabbit eye relative to its body and the several hundred years worth of accumulated data on the anatomy and physiology of the rabbit eye and its similarity to the human eye. Added to that, the fact that rabbits are easy to handle and breed and the most economical of the larger breed models, makes them ideal for ophthalmic research. [5]

The main avenues of eye research using the rabbit as a model are related to surgical interventions including cataract removal, intraocular lens insertion, corneal transplantation, laser refractive procedures, glaucoma shunt implantation, and intra-vitreal drug delivery. Strain selection is an important consideration for these experiments as the strain most commonly available is albino (New Zealand White [NZW]). Other strains are available that more closely approximate human ocular pigmentation (New Zealand/Dutch Belt or Dutch Belt) for experiments were pigmentation is important. Though there are no differences among male and female rabbits studied using these types of procedures, there are significant age-related differences. For example, young rabbits are commonly used because they have a more robust post-operative inflammatory response, which has been described as similar to that clinically observed in small children. [5]

Other areas of active biomedical research using the rabbit eye as a model include retinal detachment and proliferative vitreoretinopathy (PVR), retinoblastoma, and retinitis pigmentosa (RP). PVR is an abnormal wound healing process that takes place commonly after retinal detachment or other ocular trauma, resulting in a highly

inflammatory environment within the eye. Treatment of PVR by vitrectomy or non-specific pharmacological prevention of cell proliferation are only marginally successful. Understanding intra-ocular inflammation is critical to developing new therapeutics for PVR and the rabbit PVR model will undoubtedly facilitate that effort. [6] A new model of retinoblastoma, created by injection of cultured human retinoblastoma cells into the sub-retinal space of immunosuppressed rabbits, displays intraocular tumors after one week that are remarkably similar to those observed in humans and that continue to grow for up to eight weeks. This model also has the advantage of developing viable vitreal tumor seeds when the retinal tumor is still only mid-sized. These vitreous seeds only develop very late in mouse models and are thought to be the cause of treatment failures in humans. This model presents the opportunity to test potential novel chemotherapeutics as well as delivery methods. [7] A new model of RP has been developed via creation of transgenic rabbits bearing a point mutation in the rhodopsin gene. The model has been characterized histologically and electrophysiologically and determined to display progressive retinal degeneration as a result of loss of rod function. While other animals currently serve as models for RP, this new rabbit model will offer additional options for testing therapeutic strategies including implantation of devices or prosthetics and local delivery of drugs or gene therapy. [8]

Osteoarthritis

In humans, osteoarthritis (OA) develops either idiopathically and progresses slowly with age or secondarily to trauma and progresses rapidly. OA is associated with changes to all joint tissues including articular cartilage, subchondral bone, synovium, ligaments, and muscles. Clinically, OA-mediated joint damage results in reduced mobility, pain, and fatigue. While several disease modifying OA drugs are in various stages of development, none have yet been approved for human use. Concurrent research in humans as well as experimental animal models will be important for the discovery of new therapeutics. Since no single experimental model provides the complete picture of OA in humans, a variety of animals have served to advance OA research including mouse, rat, guinea pig, rabbit, dog, and horse. [9,10]

A broad range of rabbit OA models have been used extensively and continue to offer specific advantages over other models for OA research. The gross anatomy of the rabbit knee is very similar to that of humans. Moreover, the rabbit knee joint is large enough to enable the harvest of adequate volumes of tissue for histopathological analysis, a major limitation of smaller animal models. In adult humans, the growth plates in the long bones no longer retain the capacity for growth and are termed "closed." This is also the case in skeletally-mature rabbits. By contrast, mouse and rat growth plates do not normally close completely and longitudinal bone growth can be reinitiated even in mature animals. This is a complicating issue for data interpretation and limits the translatability of research performed using mice and rats. [10]

Most often, skeletally-mature, male, NZW rabbits are used for OA studies in an attempt to ensure bone growth plate closure, reduce hormone fluctuation, and control for potential inter-strain variability. OA does not occur spontaneously in rabbits, but can be induced via surgical intervention (i.e., meniscectomy or anterior cruciate ligament transection [ACLT]), mechanical manipulation (i.e., impact or immobilization), or chemical application (i.e., IL-1β, collagenase, etc.). The majority of rabbit OA studies employ the ACLT model as it offers several advantages. ACLT-modified rabbits very quickly develop a wide variety of cartilage lesions post-surgically, which closely approximate many aspects of human OA. The histopathology of the rabbit ACLT model has been studied extensively and a standardized nomenclature and scoring scheme for evaluating and comparing alterations in joint structures, including changes in cartilage, synovium and bone, have been proposed. Further, a sizeable body of data derived from this model has already been amassed describing OA pathogenesis including imaging studies and effects of various potential pharmacological applications. [10]

Tuberculosis

The three main animal models employed for the study of tuberculosis (TB) pathogenesis in humans are rabbits, guinea pigs, and mice. All three of these species have the advantages of closely approximating clinical observations as they can be infected by inhalation, display both innate and adaptive immune responses, and generally control the infection initially before it finally becomes fatal. Human TB pathogenesis is a very complex process and no one animal model represents all aspects of the disease. However, rabbit models of TB have the further advantages of displaying cavitation and arrested infection. [1,11]

Rabbit is the only experimental model in which pulmonary cavitation occurs. Pulmonary cavities in rabbits and humans contain huge populations of TB bacteria (~108), which have access to the bronchial tree and therefore the external environment. Given that the degree of contagiousness of TB in humans is typically judged by bacillary burden in sputum culture, the study of cavitation in rabbits is critical to our understanding of TB transmission in humans. Further, the immune systems of rabbits are capable of arresting infection such that they display a latent, or paucibacillary, state similar to humans and in some cases are capable of controlling TB infection so effectively that the bacilli appear to have been completely cleared. While reactivation from a latent state is spontaneous in humans, rabbit reactivation requires immunosuppression. These features make rabbit an important model for the study of human latent TB. [1,11]

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