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Overview of the Importance and Role of Genetic Similarities and Differences of Laboratory Animal Models with Human Diseases in Experimental-medical Studies

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Abstract

Examining the genetic similarities and differences between animal models and humans is one of the most important criteria for selecting an animal model in experimental studies. This leads to a greater similarity of the animal model to humans and the possibility of generalizing the results obtained from in vivo studies to humans. In recent years, various studies have been conducted to find suitable animal models based on their genetic similarities and differences with humans. This research reviews and compares these studies, focusing on animal models, including dogs, chickens, pigs, guinea pigs, rats, Syrian mice, rabbits, monkeys, chimpanzees, and zebrafish.

Keywords: Genetic Similarity; Animal Models; Genetic Diversity

Introduction

In experimental studies, animal models simulate diseases, evaluate the method's effectiveness, and examine its advantages and disadvantages in the human body (1). Therefore, according to the subject under study, the desired animal model should be as close to humans as possible. However, most of these models are related to animals that are similar to humans in terms of genetic and physiological structure. Therefore, monkeys with more than ninety percent genetic similarity with humans are one of the most widely used animal models (2). Due to their small size, easier feeding, high reproduction rate, and of course, high genetic similarity, mice and rats are the most widely used laboratory animals (3). Other common animal models include dogs, pigs, piglets, and rabbits. Of course, among non-mammals, chicken and zebrafish are also used in various studies. Rats and mice make up 95% of the animals used in laboratories, although the mouse is the most common animal used in biomedical studies (3). Therefore, the purpose of this research is to examine the similarities and differences between common animal models and humans and to review various studies on the application of these models.

Animal models

Dog

The dog is considered the best model for understanding the morphological, behavioral, and pathological characteristics of human diseases. The base pairs in the dog genome can be sequenced with the human genome. Among the genetic differences between dogs, we can mention 31% fewer repetitive regions in the dog genome than in humans (4). By performing RNA sequencing, they made a complete transcript of the dog genome, including protein-coded genes. The results showed that the DNA and protein sequences of dogs are more similar to humans than mice (5). In another experiment, they studied and prepared gene transcripts from the microbes inside the dog's intestines. The findings show that dogs are a better model than pigs and rats for studying diets due to their microbiomes being more similar to humans (6). Cancer in dogs has many similarities with cancer in humans in terms of histological appearance, tumor genetics, molecular characteristics, biological behavior, and response to treatment (7). Another advantage of using dogs as models in cancer research is that the size of dogs and their tumors are more similar to humans. Using the biological and genetic similarity of dogs and humans, Hershey et al. studied the toxicity of antineoplastic drugs in dogs and found that the treatment could be effective in humans (8). In another study, according to the similarity between bladder cancer in humans and dogs, and according to recent studies on bladder cancer in dogs, they presented a model for the treatment of this disease in humans (9). In another study, by studying a dog model with retinitis pimentos', which was naturally caused by an autosomal dominant mutation, they showed that the phenotypes are very similar to humans (10,11). They also found in another study that due to the very similar eye size and pre-retinal light transmission characteristics between humans and dogs, ambient light is a potential accelerator of vision loss in this disease (12). Dogs are mostly used in studies of retinal diseases, cataracts, retinitis pimentos, cancer, epilepsy, and allergies (13). Dogs are suitable animal models in genetic studies, but the use of dog animal models in biomedical research has some limitations, such as multifactorial disease and diseases that have variability in drug metabolism and different pathology mechanisms. One of the ethical moral that biomedical scientists should notify to it is about dog animals often like live in sterile environment, when they contract with invasive procedure and induce disease in them, they may suffer and sense distress that should notify to this ethical moral. The researchers in this field use genome sequencing and association studies for biomedical studies.

Table 1

Medical applications	Dog animal model
Retinal studies	(14)
Cataracts	(15)
Retinitis pigmentosoa	(16)

Cancer	(17)
Epilepsy	(18)
Allergic studies	(19)

Chicken

Birds are the cause of many flu-like diseases, such as coronavirus. Due to their genetic similarity to humans, they are suitable models for making and designing vaccines (20). Among bird species, chicken embryo has a wide genetic application, including the study of genomic comparison and evolutionary relationships between different species. One of the uses of chicken is to identify non-coding elements in the human genome (21). The bird genome, having at least 70 megabases of sequence, is very similar to human functional genes. Significant reduction of repetitive sequences between parts, false genes, and duplication between parts in the genome of birds is one of the differences between their genome and humans. The size of bird chromosomes is almost twice the size of human chromosomes. Relatively, the amount of chromosomal translocations is very low in both species, while extrachromosomal rearrangements such as inversions are very common (20).

Various studies have been conducted using chickens as animal models. Schock et al.. used chicken as a model for skull research. In this review study, the structure and genetics of human and chicken skulls were compared, and the use of chickens as a human skull model was confirmed (22). Egg embryos are used in various studies as an in vivo model. In research to check the antioxidant level of nanoparticles, eggs were used, and acceptable results were obtained (23). Since the effects of hormones can cause serious damage to human and animal bodies, the side effects of natural and artificial estrogens were investigated in another experiment using egg embryos (24). Chicken models have some limitations in biomedical research, such as differences in immune system-responsiveness in that they have a less immune system in disease. The difficulty in interference that results from them to humans is another limitation, and in the end, the chickens have less genetic diversity than mammals. The ethical limitations in using these animal models are that they do not suffer when they have a disease in them and that they should not be in a distressful environment when working with them. Biology researchers use the CIRSPIR Cas9 method for the validation of their works on avian.

Table 2

Medical applications	Chicken animal model
Aging studies	(25)
Memory evaluation	(26)
Parasitology	(27)
Atherosclerosis	(28)
Reproductive studies	(29)
Infectious disease	(30)
Toxicology	(31)

Pig

Pigs are similar to humans in terms of biochemical, physiological, and genetic characteristics. Among the 112 gene loci, a great deal of genomic conservation has been identified between humans and pigs. In other words, the amino acids that create the functional proteins of human and pig diseases are very similar to each other. In this way, the homology between human and pig genes has made the genetic modification of human pathogenic alleles in the pig genome very easy to create a suitable model of the disease.

This causes a better identification of carcinogenic factors, including deletion mutations, inversions, and bilateral translocations, using the pig animal model. On the other hand, between human and pig genomes, there is between 2% and 20% sequence difference related to non-coding regions, which do not have homology with pig genome sequences. The use of specific polymorphism genetic markers shows that pigs are suitable animal models for biomedical research due to the proportional size of their organs and their metabolic similarity to humans (32). To induce the expression of cancer genes in pigs, a recombination system has been used in the specific position of the Cre-Lox locus (33). From an anatomical point of view, pig skin is more similar to human than mouse, rat, and rabbit skin, as they have the same epidermis and dermis with a thickness of 1 to 3 mm. Studies have shown that the pig is the best model for simulating the wound-healing process in humans (34). In this context, Sullivan et al. studied different animal models in wound healing studies and their similarity with human wound healing. This study showed that pig skin is physiologically and anatomically closer to human skin (35). In another study, they reviewed the genetic studies related to cytochrome P450 in pigs to determine the effectiveness of the drug its toxicity, and its similarity to the human body, and concluded that in studies to determine the dose of the drug, the pig is a suitable model for simulating the human body (36). Based on this, scientists used the pig animal model to investigate the speed of drug release and the rate of drug excretion in willows loaded with doxorubicin (37). In an experiment, they compared pig and human cranial bones and concluded that although pig bones are not very similar to human bones in terms of size, they have the same anatomy as humans and can be used in modeling ear surgeries (38). As a result, pigs can be a suitable animal model for oral, jaw, facial, orthopedic, and plastic surgeries due to their genetic similarity to humans (39). Although pigs are very suitable for biomedical research, they have some limitations in genetic research, such as having different genetic variances in comparison to humans. This issue restricts the use of pigs in human research. Another limitation is the size and anatomical difference with small animals, and financial challenges are limitations of use these animal models. Ethical considerations in apply from them is these animals are very intelligence and when they use as research model should notify to don't distress and suffer them in induce disease. One of the methods that genetic scientists use is genome tools and applications such as CARISPIR Cas9 for their research.

Table 3

Medical applications	Pig animal model
Mouth surgical	(40)
Face surgical	(41)
Orthopedics surgical	(42)
Plastic surgical	(43)

Guinea pig

Pigs are anatomically similar to humans, especially in skin, skeleton, teeth, digestive system, pancreas, liver, kidney, lung, and immune system (44,45). Due to its long lifespan and ability to move and learn, the pig is a suitable model for learning, memory, and behavioral studies (46). In addition, due to the anatomical structure of the brain similar to humans, this animal is a suitable transgene model for hypospadias syndrome. Also, the CYP3A gene in the liver and small intestine, which causes the oxidation of foreign organic molecules such as toxins or drugs and their removal from the body, is expressed similarly in both species (47). Guinea pigs are susceptible to inflammatory diseases due to their resistance to corticosteroid drugs, therefore, this animal is considered a suitable model for investigating drug resistance (48). Among the differences between humans and pigs, we can mention the lack of cholesterol ester protein transferase enzyme in pigs, the inability to metabolize lipids, the role of this enzyme in the treatment of coronary heart diseases, and the therapeutic interventions of this enzyme (49). Cholesterol ester transferase plays a central role in the metabolism

of lipoproteins, and it has been shown that different polymorphisms in the gene of this enzyme affect its activity and blood lipid parameters. Since the structure of pig skin is similar to human skin, it has been used as an animal model in various studies. In this regard, some researchers made biodegradable composite dressings to heal burn wounds. To model wound healing and observe the reduction in wound diameter as well as the disappearance of scars, they used the pig animal model, which ended with a favorable result (50). Pigs show symptoms similar to humans in lung diseases like asthma and tuberculosis (51). In another study, according to the proportionality of the transmission of infectious diseases in pigs and humans, the degree of flu contagion was investigated with the help of the pig animal model (52). The limitations of using these animals in biomedical research is susceptibility of them to specific infections, size and anatomical of them and behavioral limitations of them in genetic researches. The ethical limitation in the use of these models is that they are very sensitive to environmental changes, and biology scientists should be notified of this challenge. Biomedical researchers use the CARISPIR Cas9 method for this study.

Table 4

Medical applications	Guinea pig animal model
Tuberculosis studies	(53)
Syphilis disease	(54)
Cholesterol metabolism	(55)
asthma	(56)
Alzheimer's disease	(57)

Rat

Having 90% of the same genes, the rat benefits from a close genetic relationship with humans. In rats, as in humans, most duplications of gene fragments that are important in creating new genes are observed in pericentromeric regions. Having metacentric and telocentric chromosomes in rats is one of the differences between humans and rats (58). Due to this similarity with humans, rats are used in extensive research related to neurological diseases, kidney diseases, cancer, diabetes, lipid metabolism, cardiovascular diseases, arthritis, and immune system diseases. As an example, a group of researchers created a precise animal model using rats to simulate type 2 diabetes in humans and the effect of drugs on it (59). In another study, Liu et al... processed an accurate animal model for wrist tendon rupture with the help of rats and concluded that the created model is more similar to the human model than the rabbit model (60). In another study, due to the similarity of the cotton rat with humans in respiratory diseases, this animal model was used to investigate the performance of the influenza vaccine (61). Considering the similarity of the human brain structure with the rat brain, Cheng et al. processed a suitable animal model for the study and treatment of brain injuries caused by explosions (62). Some limitations in the use of the rat animal model in biomedical research are problems in interfacing research results of them to humans, such as drug pathways metabolism, biological variance is another limitation in applied of these animals and restrictions in reply to toxicity is another limitation in work with these animals in genetic research. Ethical issues about them is that welfare them and notice to distress and suffer them in invasive procedures with them. The researchers use engineering methods such as CARISPIR Cas9 for their genetic research.

Table 5

Medical applications	Rat animal model
Feeding studies	(63)

Genetic	(64)
Immunology	(65)
Neurology	(66)
Infectious disease	(67)
Metabolic disease	(68)
Behavioral disease	(69)

Mice

Due to their close evolutionary relationship, mice and humans have many genetic similarities. Among these similarities, we can mention the high similarity of their genomes and genomic sequences. The similar gene expression pattern in mouse and human brains has made this organism a suitable model for studying and treating Alzheimer's, aging, dementia, and metabolic diseases. The amount of somatic and germline mutations in the mouse genome is higher than that of humans. This genetic difference increases their susceptibility to genetic and acquired diseases (20,70). In 2020, a group of scientists was able to identify new genetic, autophagy, and mitochondrial pathways by using comparative bioinformatics methods using comparative transcription patterns of mouse and human pluripotent cells and comparing genetic and epigenetic pathways in human and mouse neuron cells. The results of this study showed that this model can help treat cerebellar neurological diseases (71). Some researchers found in 2003 that due to the genetic and behavioral similarity, this animal is a suitable model for discovering the genes involved in the multifactorial disease of depression and anxiety (72). In another research in 2007, the studies conducted in the field of drug administration for the treatment of stress in mice were reviewed, and by comparing with the studies conducted with other animals, they concluded that the mouse is the best animal for modeling studies related to anxiety (73). The limitations in the use of these small animals are problematic in interpreting the results from these to humans. Variability in experimental conditions, rapid reproduction, the short lifespan of these animals, and genetic variations are other limitations in the use of these animals in biomedical research. Ethical issues in the use of these animal models are noticed to not cause suffering and induce a distressful environment when working with them in biological research. Biology researchers in this study use CARISPIR--Cas9 and TALENs methods for their research.

Table 6

Medical applications	Animal model mice
High blood pressure	(74)
Diabetes	(75)
Cataract	(76)
Obesity	(77)
Epilepsy	(78)
Breathing problems	(79)
Parkinson's disease	(80)

Rabbit

The genetic sequence of humans and rabbits has about 85% genetic similarity at the level of DNA and protein (81). The DNA sequences of rabbits and humans encode proteins with lengths of 359 and 355 amino acids, respectively. Also, in the comparative study of beta-globin gene families in humans and rabbits, pairs of human-rabbit beta-globin gene structures, including beta-4-epsilon, be-

ta-3-gamma, and beta-1-beta, have been identified as similar genes in the entire gene and coding regions of the beta--globin gene, respectively.

In rabbits, the expression of alpha-beta globin genes is done simultaneously, but in humans, this process is done at different times of development. The amount of transcription of beta-globin genes is the same in both species. Gamma globin genes are very similar due to the doubling process of gene conversion. The greatest similarity is observed in the 5 regions: exon 1, untranslated region 5, intron 1, exon 2, and exon 3. Also, untranslated regions 3, epsilon, and beta are similar in both human and rabbit species. The number of silent substitutions in the rabbit genome is higher than that of humans (82). Among the differences between these two species, we can mention 10% greater divergence of rabbit nucleotides than humans, a larger human gene family than rabbits, more intergenic DNA sequences in humans, and differences in the expression pattern of their beta-globin genes. Also, rabbits have two embryonic genes, B3-B4, while humans have only one embryonic gene, epsilon. In addition, humans have many embryo-specific genes, while rabbits do not have any. Also, the rabbit B1 gene is expressed in both mature and embryonic erythrocytes, while in humans, beta and delta genes are expressed only in mature red cells. Both families contain false inactive genes between embryonic and adult genes. Rabbit intron 2 is 277 base pairs shorter than human intron due to the gene deletion phenomenon in this region. Transgenic rabbit models are used to understand the mechanism of disease pathogenesis (83). One of the main uses of rabbits as an animal model of atherosclerosis is in cardiovascular studies. In this regard, in 2004, Yanni reviewed the numerous reports made on creating a suitable animal model using rabbits in the field of atherosclerosis and hypertension (84) and concluded that the transgenic New Zealand white rabbit is a suitable model for the study of atherosclerosis in humans. One of the limitations in the use of rabbit animal models in biomedical research is inflammation when inducing disease in them and the difference in the variability of the immune system compared with humans. Another limitation in the use is the variance in pharmacokinetic metabolism in them. Ethical notification in working with them is a notice to welfare them and don't suffer and induce distress in them when evaluating one study on them. Scientists in the biology area use editing techniques such as CARISPIR-Cas9 for their study.

Table 7

Medical applications	Animal model rabbit
Atherosclerosis disease	(84)
Immunologic disease	(85)
Osteoporosis	(86)
Eye disease	(87)
Organ surgery	(88)
Pharmacologic studies	(89)
Pregnancy	(90)

Monkey

Compared to rodents, primates such as the rhesus macaque have many physiological, neurological, and genetic characteristics similar to humans. The CMP-sialic hydroxylase mutation is the only mutation that has caused biochemical and general structural differences between humans and monkeys (91). Genetic diversity in monkeys is significantly higher than in humans in many genetic loci. Many of the Pan monkeys are more genetically similar to humans than Apes. Among the human genetic differences, we can mention the location of chromosomes on DNA, many repetitive elements, reduction of the level of gene families, single genes, regulatory sequences, chromosomal rearrangements, transfer of chromosomal fragments, inversion, multiplication of transposon elements, endogenous retro-

viruses, duplication, insertion, deletion, and point mutations. Many of these types of mutations cause congenital diseases, autoimmunity, and cancer in humans (92). Due to the great genetic similarity between monkeys and humans, this animal has been used in a wide range of studies. In a study using monkeys as an animal model, scientists achieved an accurate simulation of diabetes (93). Also, the rhesus monkey has been used as a suitable model for autoimmune encephalitis, multiple sclerosis, and immune system defects in a study conducted by Levinson et al. (94). The process of gene transfer is one of the factors limiting the use of primates in experimental medical studies. With the advances made in the field of transgene technology, the first transgene monkey was produced in 2001. The results of this study showed that the monkey genome can be completely genetically modified. This caused changes in the monkey genome to express the physiological and genetic traits of human diseases (95). The first monkey model of Huntington's disease was produced in 2008. The creation of transgenic monkeys, the model of Huntington's disease, in which the pathological features of this disease were expressed, led to a suitable model for better simulation of this disease in humans (96). Monkeys have biological differences compared to humans that causes study on this. Ethical concerns in working with them is notice to welfare them and change environment in when research on them. Genetic researchers in this study use gene editing tools such as CARISPIR-Cas9 for their study.

Table 8

Medical applications	Animal model monkey
Diabetes mellitus	(97)
Autoimmune Encephalitis	(98)
Multiple sclerosis	(99)
Huntington's disease	(100)

Chimpanzee

Among primates, chimpanzees are most similar to humans. Using various methods of DNA hybridization, it was found that their mitochondrial DNA is identical, and the difference in nucleic acid sequence between them is about 1.1%. In DNA with a length of 3000 base pairs, about 33 nucleotide sequences are different between the two species. The results of DNA hybridization experiments have shown that the greatest differences between humans and chimpanzees at the genome level are 1.2%. Investigation of the similarity between human and chimpanzee macromolecules by sequencing, immunological, electrophoresis, and nucleic acid hybridization methods has shown that the molecular similarity between humans and chimpanzees is extraordinary. One of the most common chromosomal aneuploidies in humans is trisomy 21, which was detected in two cases in chimpanzees by chromosome staining, and in both cases, they had phenotypic characteristics comparable to trisomy 21 in humans. Therefore, chimpanzees can be used to achieve therapeutic goals for this disease (101). Due to differences between the chimpanzee and human genomes, chimpanzees are more vulnerable to some diseases such as falciparum malaria, epithelial cancer, Alzheimer's disease, and AIDS, so chimpanzees are considered a suitable model for these diseases (92). Chimpanzees are also used as the only animal model in studies related to hepatitis C due to their high genetic similarity to humans (102). Using the ability of chimpanzees to contract viruses such as hepatitis, Bok and colleagues studied the development of a suitable vaccine for noroviruses (103). Although chimpanzees are valuable animal models in biology research, they are not suitable for new biomedical research. One of the ethical limitations in the study of these animal models is that they are very intelligent, cognitive, and emotional. Animal biology researchers should notice this ethical concern and not distress and suffer them in study and research on them. Biological scientists use genome editing tools such as CARISPIR--Cas9 in this research.

Table 9

Medical applications	Animal model chimpanzee
Malaria falciparum	(104)
Epithelial cancer	(105)
Alzheimer's disease	(106)
HIV disease	(107)
Hepatitis disease	(108)

Zebrafish

Zebrafish is a suitable vertebrate model for mutation analysis in genetic studies. So far, about 523 genes have been mapped in zebrafish. Using complementary DNA findings, orthologous regions between humans and zebrafish have been identified, indicating 80% similarity between human and zebrafish genes (109). studies conducted, homologous gene clusters including Hox, Dix, MHC, and Hemoglobin were identified as distinct gene loci, and 400 gene regions that had no similarity to human or mouse models (110). A study conducted by researchers using SNP markers in 2006 showed that the zebrafish genome is highly variable and has many more regions of polymorphism than the human and mouse genomes (111). This animal is a valuable model for treating human diseases, including melanoma, hematopoietic, cardiovascular, and renal diseases, and for physiological genome studies. Zebrafish have provided a genetic link between vertebrates and invertebrates in evolutionary studies (109). Zebrafish are used mostly in studies related to basic and primitive body processes, including movement disorders. Therefore, scientists have reviewed studies related to modeling movement disorders using this animal (112). In addition to motor and spinal modeling, the use of zebrafish has also become important in studies related to drug discovery and drug delivery (113). The cause limitation of the use of zebrafish in biomedical research is the physiologic difference between these animals with humans that induces disease in them and interprets the results them to humans with challenging, complex nervous systems one of the limitations the use of them and rapid development lifestyle of these animal models is a problematic concern in biomedical research. One ethical issue in working with them is noticing the welfare of a place living them and not suffering them when studying them. Scientists in this study use genome-editing methods such as CARISPIR-Cas9 in their research.

Table 10

Medical applications	Zebrafish animal model
Biochemical studies	(144)
Molecular biology	(115)
Cellular biology	(116)
Epilepsy and ASD disease	(117)
Genetics studies	(118)

Conclusion

Genetic similarities and differences between humans and animals are important for determining the desired animal model. By studying these similarities, it is possible to achieve a better simulation of the desired study in the animal model, which is the most important goal of using animal models. By studying the genetic differences and similarities of different animal models, it can be seen that the animal under study to conduct an animal model should be selected depending on the intended application and study. Thus, as mentioned, monkeys and chimpanzees are the

most genetically similar animals to humans, but pigs and piglets are more commonly used in skin studies. This is because pigskin is more physiologically similar to human skin than monkey skin (35). It was also shown that although chickens and zebrafish are not mammals and have more genetic differences than other animal models, they are chosen as animal models in extensive studies. As a result, the selection of an appropriate animal model should be determined based on the similarity of the specific gene being studied. On the other hand, according to the studies conducted, it can be seen that the selection of an animal as a laboratory model is not based solely on the genetic similarity of this animal to humans, and other factors are also effective in this matter. For example, mice are more genetically similar to humans in studies of genetic mutations and cancer than dogs, but dogs are used as animal models in many applications related to tumor removal and cancer treatment. This is because dogs are closer in size to humans, and tumor tissue is more similar to human tumor tissue (7). In addition to the greater proportion of dogs in size to humans, the closer origin and living conditions of dogs to humans are other factors that have caused the physiology of dogs to be closer to humans. Animal models are generally divided into two groups: homologous and analog. When the phenotype results from a genetic change in orthologous genes in both species, the model is called homologous, otherwise, it is called analog (119). Mutations in mice are considered the best model for identifying the leptin protein and its receptor in mammalian species (120). Transgenic mice for studying mutant alleles of APOE, APP, MAPT, and PSEN1 genes are very suitable animal models for studying Alzheimer's disease. However, for studying this disease, only one animal model is sufficient to examine the defective genes and severe neurological defects (121). In hemophilia, where there is a severe deficiency in coagulation factor VIII or IX, mouse models are used, as well as other animal models, including dogs (122,123). In another genetic disease, such as Hurler disease, there is a knock-in mouse model for the most severe form of alpha-1 idoritodase mucopolysaccharidosis. Homozygous mutant mice have a much closer pathological resemblance to human Hurler disease (124). Parkinson's disease, which is often a sporadic or generalized disease, has animal models that capture some aspects of the disease. Transgenic models with increased expression of a-synuclein and knock-ins of the LRRK-2 gene are suitable models for the autosomal dominant form, while knockout models of the PINK1 and DJ-1 genes are suitable models for the recessive form. Drosophila models are being developed and have proven useful in this disease (125). Tuberculosis is a deadly infectious disease, and research on animal models such as pigs, mice, rabbits, and nonhuman primates can provide insights into drug and vaccine development, biomarker identification, and understanding of immune pathways and host effects on infection. The human body is a suitable and favorable environment for the growth of the bacterium Mycobacterium tuberculosis, so the bacterium does not need any other environment than the host body for its growth in all stages of its life cycle. This bacterium damages the airways, causing destruction and obstruction in the airways (126). During tuberculosis infection, necrosis can occur in two stages: 1- During the initial stage of lung colonization, which can result in necrosis of one or a small collection of macrophages in a primary granuloma 2- During the advanced stages of the disease, where a large area of the lung is infected by TB bacteria (127). Among the many animal models available for studying tuberculosis, mice are widely used in immunological studies of tuberculosis due to their small size, cheapness, and availability. The two strains of mice used for in vitro studies are C57BL/6 and BALB/c. The fact that laboratory mice do not have all aspects of human TB disease does not mean that mice cannot be used as valid laboratory models. Rather, researchers can create mouse models that have genetically altered characteristics consistent with human TB disease and use these animal models to analyze TB pathogenesis at the cellular and therapeutic levels. For this purpose, the C3HeB/FeJ mouse model is used to study TB wound necrosis and clinical trials of drug efficacy (128). Cancer is the result of the accumulation of several genetic changes that cause the biological transformation of cells so that they grow uncontrollably, multiply, and metastasize. By knowing these genetic changes and understanding how they function, progress can be made in the pathogenesis, diagnosis, and treatment of cancer. Therefore, animal models can play a very important role in achieving this goal. Liver cancer is the fifth deadliest cancer in the world, and in this regard, dozens of chemicals that induce liver cancer in animal models, including dogs, have been tested (129), pig (130), Hamster (131), rabbit (132), monkey (133), mice and

rat Have been reviewed (134). For several reasons, including size, lifespan, reproductive ability, genetic engineering, and similarity to hepatic lesions at the histological and molecular levels, mice are a desirable in vitro model for studying types of cancer, such as hepatocellular carcinoma (135). Mouse models are induced in different ways: 1- using chemicals 2- transplantation 3- viral models and 4- mouse models created by genetic engineering methods (Figure 1) (136). Squamous cell cancer of the head and neck is the sixth deadliest cancer in Europe and the United States and one of the most malignant cancers in developing countries (137).

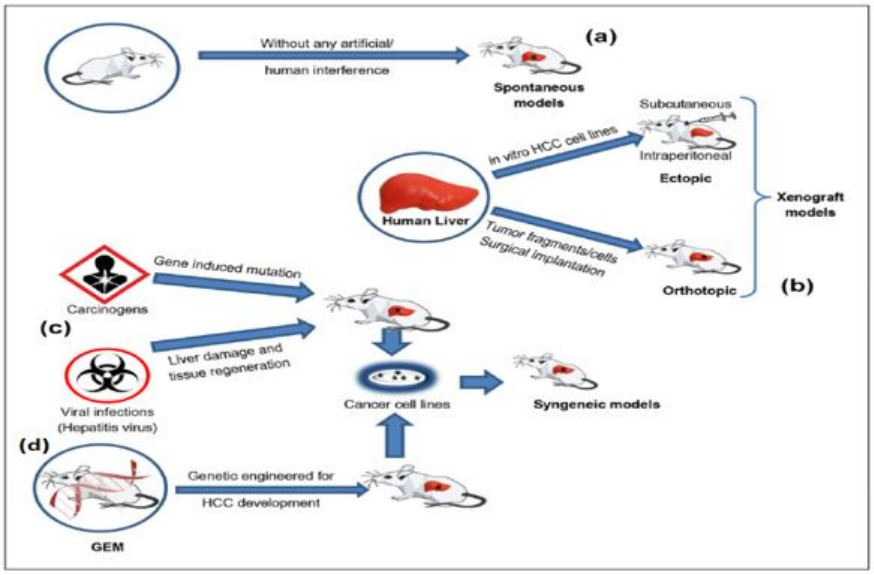

Figure 1: Mouse models of liver cancer. A – Spontaneous model B – Xenograft C – Syngeneic D – Genetically engineered mice

Various models are used to study head and neck squamous cell carcinoma. Hamsters are a carcinogenic model and are used for experiments and studies of the effects of chemotherapy, drug competition, and immune responses. Hamsters can also be used to study the interactions between the host immune system and the microenvironment because hamsters do not have immunosuppressive agents (hamsters are unable to control infection) (138). In this type of cancer, mouse and rat models are used to study the types of mutations in this type of cancer using induced chemicals. This mouse model is also used for cancer diagnosis. The disadvantage of these models is the time required, which is about 27-30 weeks, which is quite a long time. Also, this model cannot be used for metastasis studies (139). Squamous cell carcinoma of the liver is the second most common malignant tumor in dogs. For the treatment of this cancer, the combination of cisplatin with the drug piroxicam has had favorable results. Also, the metastasis process does not occur in dogs, and they can be used for phototherapy (140). 75% of all tumors in cats are oral cancer. Humans and cats have similarities in tongue cancer, but in humans, the lateral parts of the tongue are involved. This type of cancer is more common in older cats, and the best treatment for them is surgery, chemotherapy, and radiation therapy (141). The CRISPR gene editing system is one of the new approaches to gene modification. In this system, using engineered endonuclease enzymes, modification can be performed at the genome level, so this type of modification is very stable. The use of 1-cell stage fertilized embryos is the most common method for producing genetically engineered animal models. These models use microinjection and electroporation methods. Table 1 summarizes animal models of human diseases with gene editing systems (142).

تکنیک	بیماری	ژن هدف	مدل‌ها
Microinjection	tyrosinemia	Fah	mice
-	Immunologic defect	Rag1, IL2RgammaC	mice
Microinjection	Lateral meningocele syndrome	Notch3	mice
Microinjection	Osteoporosis	ATP6V1H	mice
Microinjection	Osteogenesis imperfacta	Bril	mice
Microinjection	**Compomelic dysplasia**	Sox9	mice
Electroporation	Duchene muscular dystrophy	Dystrophin	mice
Intratracheal injection	**cancer**	P53, Lkb1, KRAS	mice
Intratracheal injection	**Parkinson**	Tyrosin Hydroxylase	rat
Somatic cell nuclear transfer	**Huntington**	Huntingtin	pig
Somatic cell nuclear transfer	**Parkinson**	Parkin, Pink1	pig
Microinjection	**Duchene muscular dystrophy**	Dystrophin	monkey
Microinjection	**Muscular hypertrophy**	Myostatin	dog
Microinjection	**Muscular hypertrophy**	Myostatin	rabbit
Microinjection	**Duchene muscular dystrophy**	Dystrophin	rabbit
Microinjection	**Diabetes**	PAX4	rabbit

Table 1: Summary of animal models of human diseases using the CRISPR gene editing system

Simplicity and the possibility of creating the problem under study in an animal model are also other factors determining the animal model. As mentioned, chimpanzees are the only animal model used in hepatitis studies due to their great genetic similarity to humans. In another example, vascular occlusion occurs more rapidly in rabbits due to their greater sensitivity to cholesterol, which makes this animal widely used in cardiovascular studies. As mentioned, the egg embryo is very useful for studying the effects of hormones because hormones can cause serious harm to other animal models. Applications where there is a possibility of harm to the animal being studied are used, such as studying hormones. Another important aspect of studying the genetic differences and similarities between animal models and humans is related to the new field of genetic manipulation. As mentioned, since 2001, when the first monkey was produced with transgenic technology, there have been many advances in the field of gene transfer and modification to better suit the animal model to the subject under study.

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