ISSN 2616-5791 Vol.3, Issue 2: 33-36, DOI: 10.25236/AJMHS.2022.030205

Application of Model Organism Zebrafish in Constructing Animal Models of Human Diseases

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Abstract: *As one of the most important model organisms in biological research, due to its unique advantages, zebrafish have been widely used in developmental biology, genetics, oncology, pharmacology, toxicology, environmental protection, and many other fields since the 1970s making many new important contributions. It may be expected that with the enrichment of research methods and the development of science, zebrafish will play a greater role in biomedicine as an ideal model organism and help us to understand the basic biological and human mechanisms greatly.*

Keywords: *model organism; Zebrafish; Daniorerio; Genome; model for disease*

1. Introduction

The application of model organisms in life science research region owns a century-old history and plays an irreplaceable role. Most life processes are highly conserved in the long-term evolutionary process, and model organisms have therefore become important tools for studying human development, system functions, and disease occurrence. For example, there are many similarities between model organisms and human embryonic development. In particular, the embryonic development process of vertebrates and humans is quite similar in morphology, and the signaling pathways and genes involved at the cellular and molecular levels also generally have a high degree of homology. As a new type of vertebrate model organism, zebrafish has many advantages, such as strong reproductive ability, Vitro fertilization and development, transparent embryos, short sexual maturation cycle, small individuals, and easy breeding. In particular, large-scale forward gene saturation mutation and screening can be performed. These characteristics make it one of the important model organisms in many fields of medical research. [1]

2. Development in the history of zebrafish research

The zebrafish (Daniorerio) is a bony fish belonging to the genus Danio of the Cyprinidae family of Actinopterygii. The zebrafish is native to the creeks, rice fields and the middle reaches of the Ganges River in eastern India, Pakistan, Myanmar, and Bangladesh. It is a common tropical ornamental fish since it has zebra-like longitudinal dark blue and silver stripes on its sides so it is named as the zebrafish.

In the early 1970s, George Streisinger, a famous geneticist at the University of Oregon who used T4 phage to study genetics, noticed the advantages of zebrafish, bought zebrafish from a pet store, and began to study its breeding methods, observe its embryonic development process, development Some related genetic techniques. Nearly a decade later, his research group published the first influential paper in Nature in 1981. In this paper, they reported the Vitro fertilization technology and haploid induction technology of zebrafish, established a homozygous strain, and introduced the first natural mutant of zebrafish, golden. In the following years, Streisinger and his colleagues successively reported the cleavage characteristics of zebrafish, the developmental fate of cells in embryos at different stages, and found that many neurons in the zebrafish brain are arranged simply and regularly. The report of these research results proves that zebrafish is suitable for use as a model animal, which has attracted the attention of many developmental biologists. Subsequent research reports have proved that zebrafish is the only vertebrate suitable for saturation mutagenesis so far, so it has caused great repercussions in the field of life sciences, and has attracted a large number of laboratories and scientists around the world in the following years. The use of zebrafish as a model animal has made it one of the most important model vertebrates. [2]

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3. Advantages of zebrafish as a model organism

3.1 Strong reproductive ability

The embryo of zebrafish develops rapidly, with short sexual maturity and high fecundity. The first mitosis is completed about 40 minutes after fertilization under 28.5°C culture conditions, and then it divides every 15 minutes; after 24 hours, the primordium of main tissues and organs has been formed, and each ventricle, eyes, ears, blood cells, somites, etc. are clearly visible, which is equivalent to a 28-day human embryo. Under suitable breeding conditions, the sexual maturity of zebrafish is generally about 3 months. The mating behavior of male and female fish is stimulated by light, and the spawning time can be controlled by regulating the photoperiod or controlling the contact between male and female fish. A female fish generally can lay 100 to 300 eggs at a time and can lay eggs once a week. Therefore, using zebrafish as research material can ensure that thousands of embryos can be obtained every day, which is impossible to achieve with mammals as research material, and it is also the reason why zebrafish can be used for saturation mutagenesis and precise gene mapping. [3]

3.2 Easy to observe

Embryo development in vitro, easy to observe and operate Zebrafish in vitro fertilization, the embryo develops in vitro and is transparent, so it is easy to observe. The zygote is about 1mm in diameter, making it easy to perform operations such as microinjection and cell transplantation.

3.3 Mature technology

The more perfect embryonic and genetic manipulation techniques can easily perform cell labeling and cell lineage tracking in zebrafish as in lower model animals, such as nematodes and Drosophila; cells of embryos can also be transplanted as in Xenopus. In addition, haploids and genome doublings can be cultivated. In terms of gene function research, transgenic technology, gene overexpression technology, the technology of inhibiting gene expression by antisense oligonucleotides, the technology of random and targeted gene-directed mutagenesis, and somatic cell cloning technology have been developed.

4. Application of zebrafish as a model organism

4.1 Answers to Basic Biology Questions

The life cycle involves the development, growth, the maintenance of physiological and psychological balance of embryos, as well as the generation, aging, and death of germ cells. Each process is very complex and is not only regulated by genes but also affected by external factors. The understanding of the regulation is still very limited. The main advantages of zebrafish are high fecundity, vitro embryonic development, and transparency, making them an excellent material for studying embryonic development. During embryonic development, cell proliferation, differentiation, migration, and apoptosis work together to determine the size, shape, and formation of tissues and organs of the individual. Determining the effects of genes and inter-gene interactions on these developmental processes is a major research direction.

4.2 Developmental Biology and Genetics

Zebrafish has become the most suitable model organism for developmental biology and genetics research among vertebrates due to favorable factors such as rapid cell division in the early stage of development, transparent and specific cell types, and easy identification of specific cell types. Embryonic development studies using zebrafish mainly include the following aspects: the effects of maternally-produced factors (such as proteins and mRNAs) on the initiation of embryonic development, the formation mechanism of the body axis, the induction and differentiation of germ layers, the mechanism of cell movement in the embryo, the nervous system development, organ formation, left-right asymmetric development, origin and migration of primordial germ cells, etc. At the same time, because the zebrafish is more likely to induce haploid progeny, the embryonic phenotype determined by the recessive gene can be exposed and the isogenic line of the diploid zebrafish can be rapidly cultivated. [4]

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4.3 Animal models of human disease and drug screening

Zebrafish and humans have a high degree of similarity, and the extrapolation of experimental results will be affected by species differences, zebrafish have been confirmed to be highly similar to humans in terms of genetic physiology and pharmacological effects. First is the similarity between genetics and physiology. The anatomical structure, physiology, and molecular biology of the cardiovascular, neural, and metabolic systems of zebrafish are highly similar to those of mammals. The similarity with human genomes is as high as 87%. Genetic and chemical screens have demonstrated that zebrafish can be highly representative of other organisms, including humans. Secondly is the similarity between pharmacological effects and clinical responses. The similarity between pharmacological effects and clinical responses in model animals is an important factor to measure whether the animal model is effective and usable. Therefore, it is essential to verify the similarity of its response to the drug in humans. In recent years, scholars have evaluated the efficacy of some clinical drugs in zebrafish. The research results show that the results of drug research using zebrafish as model animals have a good correlation with clinical results. The model provides data support for drug research and evaluation.

As a model organism that can quickly obtain a large population, zebrafish has many advantages such as transparent embryos, vitro development, easy genetic manipulation, and mutant screening, making zebrafish particularly suitable for the screening of drug lead compounds. Compared with other commonly used non-vertebral model organisms such as yeast, nematodes, and fruit flies, zebrafish, as a vertebrate, has great similarity with humans in anatomy, physiology, molecular level, etc. Also can obtain results that cannot be obtained in non-vertebral biological research. Zebrafish embryos and juveniles are only 1–4 mm long and can survive in cell culture plates for several days on nutrients in their yolk, making feeding simple. In addition, due to the large spawning volume, thousands of zebrafish embryos can be obtained a day in a small-scale zebrafish house, making it possible to screen small molecule compounds with high efficiency. Taking advantage of the good skin permeability of zebrafish, small molecule compounds can be directly added to water or injected directly into the intraperitoneal or cardiovascular system. The advantage of transparent zebrafish embryos allows for easy non-invasive in vivo dynamic observation, avoiding the need to kill or dissect animals to obtain test materials. The central nervous system, internal organs, blood, and visual system, especially the cardiovascular system, of zebrafish are 85% homologous to humans at the gene level. The early development of zebrafish is very similar to humans and has become the best model organism to study related disease genes. Internationally, the use of zebrafish model organisms is gradually expanding and deepening into the development, function, and diseases (such as neurodegenerative diseases, Inherited cardiovascular disease, diabetes, etc.) of various systems of life (such as the nervous system, immune system, cardiovascular system, reproductive system, etc.) research. [5]

Antibiotics are an important class of drugs, and antibiotics represented by penicillin have saved countless lives since the 1930s. However, the development of new antibiotics using traditional methods has slowed significantly in recent decades. Drug resistance in pathogenic bacteria has also prompted the search for new ways to identify drug targets, discover novel small-molecule compounds, and conduct safety assessments. Several recently emerged zebrafish disease infection models offer new avenues for the development of novel antimicrobial drugs. Compared with mouse models, the use of zebrafish allows real-time tracking of pathogenic infection processes, a better understanding of pathogenesis, and the same innate and acquired immunity to pathogenic infection, enabling high-throughput screening. Using zebrafish embryos, scientists successfully screened several cell cycle inhibitors from a library of 16,320 compounds and obtained many results not found in cultured cells. There is also evidence that zebrafish can be used as a model for antiepileptic drug screening. [6]

4.4 Toxicity test

Due to the application advantages of fish animals in toxicity experiments, the International Organization for Standardization recommended zebrafish as the standard experimental fish for toxicity experiments in the 1980s. Zebrafish acute toxicity test is one of the important means to detect industrial pollution and water pollution. Zebrafish embryos and juveniles are very sensitive to harmful substances and can be used to test the toxicity of compounds to the organism. Compared with toxicity experiments using mice or rats, zebrafish has many advantages: simple medication, only need to put the drug into the water of the cultured embryos or inject the drug quickly; the dosage is very small; the test period is short, generally not required for more than 1 week; the number of test animals can be large to ensure statistical significance; the degree of impact of the drug on many tissues and organs can be assessed.

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The Cincinnati Medical Center in the United States constructed transgenic zebrafish whose reporter genes were controlled by three response elements to detect pollutants in water. The National University of Singapore uses steroid hormone-induced priming to control transgenic zebrafish expressing fluorescent proteins to monitor steroid hormones and their analogs in the water environment; uses heavy metal-induced priming to control transgenic zebrafish expressing fluorescent proteins to detect heavy metals such as zinc, cadmium, mercury, and copper in the water environment. [7]

5. Conclusion

For nearly a century, the zebrafish has played a pivotal role in the arena of biological research and is an ideal model organism. Although the zebrafish model has unique advantages for the study of many diseases, this model still has certain limitations. First, although zebrafish have high homology with the human genome, the differences between zebrafish and human proteins inevitably lead to different drug effects. At the same time, compared with the traditional animal models of disease, the zebrafish model has a relatively simple administration method, mainly through direct immersion administration, and its dosage cannot be guaranteed to be constant. At the same time, as a common model animal, zebrafish has no unified quality control methods and specifications, so the repeatability and stability of drug research results deserve further consideration by researchers. Although studies have shown that drug distribution, metabolism, and excretion in zebrafish are similar to those in humans, few studies have so far explored these areas in depth. In addition, there are currently few zebrafish-specific molecular kits and antibodies on the market, which makes it difficult to deeply study the toxicity-related mechanisms of some drugs. But zebrafish still has its irreplaceable advantages, in general, I believe with the development of technology, zebrafish will continue to be an important model organism, widely used in various research fields of life science to explore the mysteries of life and elucidate the mechanism of disease.

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