***Review Article***

**ZEBRAFISH: A VERSATILE AND EFFICIENT ANIMAL MODEL FOR CANCER RESEARCH**

**ABSTRACT**

Zebrafish offer a great platform for investigating important cancer-related pathways, such as those involving oncogenes and tumor suppressor genes, because they have about 70% of human genes conserved. The great fertility and quick development of zebrafish embryos and larvae allow for large-scale, economical research, and they provide special benefits including transparency for real-time monitoring of tumor progression, angiogenesis, and metastasis. Transgenic models, which replicate particular genetic alterations seen in human tumors, and xenograft models, in which human cancer cells are implanted into zebrafish to test treatment efficacy and tumor behavior, are two examples of use in anticancer research. Studies on chemically driven tumorigenesis are additionally backed by zebrafish, which offer information on the development and spread of tumors. Zebrafish have recently emerged as an appealing option in personalized medicine, as customized medication testing and therapy optimization are made possible by patient-derived xenografts. Zebrafish models have drawbacks despite their many advantages, including variations in drug metabolism and the development of the immune system in larvae. However, their usefulness is still being increased by developments in immunocompetent mice, genetic engineering, and imaging technology. Zebrafish have enormous potential for speeding up the development of novel anticancer medications, revealing the biology of tumors, and improving precision oncology as a supplementary system to conventional mammalian models.

Keywords: transgenic models, tumor, metastasis, biomarkers, gene editing

**INTRODUCTION**

Zebrafish is an efficient animal model for studying human cancer and researching new therapeutics molecules. Many aspects led to consider zebrafish one of the most popular animal models in research, namely: high fecundity and external fertilization, fast development (at 72 h post-fertilization, all core vertebrates features are already developed), and optical clarity during the larval stage. All these characteristics set it apart from mammalian models, which require a longer time and are unsuitable for high-throughput screening (Fontana & Van Doan, 2024; Pallavi et al., 2024). Genomic changes in cells, that can be hereditary or brought on by external stimuli like radiation, chemicals, or viruses, are the first step in the development of cancer. These mutations cause unchecked cell growth by boosting oncogenes and silencing tumor suppressor genes. Cancer cells, in contrast to healthy cells, avoid apoptosis or programmed cell death, and instead persist and proliferate.[1] Tumors promote angiogenesis, the development of fresh blood vessels, to provide oxygen and nutrients and maintain their growth. Through the lymphatic or circulatory systems, cancer cells can spread to other areas of the body after infecting nearby tissues. The tumor microenvironment, which includes blood vessels, fibroblasts, and immune cells, is essential to the development of cancer and its response to therapy.[2] Generating tailored medicines requires an understanding of these processes to treat cancer.[3]

**SUITABLE ANIMAL MODELS FOR CANCER**

**MICE**: Because of their genetic and biological resemblance to humans, mice are the most often employed animal model for cancer research. From comprehending gene alterations to evaluating treatments, they provide a wide range of opportunities for investigating cancer biology. The ability to knock out or alter particular genes makes artificially created mouse models perfect for researching the functions of tumor suppressor genes like TP53 or oncogenes like KRAS.[4] Drug screening and the study of tumor progression are frequently accomplished through the use of xenograft models, in which human malignant tissues or cells are inserted into immunocompromised mice. The study of cancerous-immune system interactions is also made possible by syngeneic models, which employ murine tumor cells in healthy mice, particularly for the development of immunotherapies.[5]

Fig 1: Mice [6]

**RATS**: Due to their bigger size, which makes sample obtaining and surgical procedures easier, rats are commonly employed in cancer research. DMBA (7,12-dimethylbenz[a]anthracene) and other carcinogens are especially well suited for researching chemically caused malignancies, such as liver or breast cancer.[7] Because of their somewhat more human-like physiology than that of mice, rats are also employed to study the effects of hormones on metabolic pathways and cancer. For example, Sprague-Dawley or Wistar rats are frequently used to research liver carcinogenesis or cancers of the mammary glands. They are appropriate for long-term cancer investigations due to their bigger size and longer lifetime than mice.[8]

Fig 2: Rat [9]

**ZEBRAFISH**: The zebrafish offers many advantages over other model systems, including ease of manual experimentation and drug administration and its prolific fecundity. A great advantage for immunologists is the optical transparency of zebrafish during early development, beyond the onset of T cell ontogeny. Using transgenic zebrafish where T cells are marked with a fluorochrome, early T cell development now becomes accessible to inspection in a living organism. Furthermore, fluorescent T cells can even be visualized in the thymus and gut of adult, live zebrafish (Trede et al., 2004). Their ability to produce tumours when genetically altered or injected with human cancer cells, as well as their transparency during early development, have made them a potent model for cancer research. They are especially helpful for real-time research on cancer-related genomic pathways, metastasis, and tumour angiogenesis. Zebrafish larvae are inexpensive for high-throughput drug assessment, and because of their small size, they can test several conditions at once.[10] Furthermore, it is possible to transplant human cancer cells into zebrafish eggs, which offers a quick, easy, and visual way to examine tumour growth and medication effectiveness.

Fig 3: ZebraFish [11]

**DOG**: They differ from other animal models in that they automatically develop tumours such osteosarcoma, lymphoma, and melanoma, that are genetically, progressionally, and treatment-responsively identical to human cancers. They are frequently employed in translational research and veterinary oncology to test novel treatments, especially for tumours that develop on their own.[12] Dogs have a healthy immune system, which makes them ideal subjects for research into immune therapy and customised cancer therapy. Dog clinical trials strengthen the connection among preclinical studies and clinical studies by providing insightful information that can be applied directly to human health.[13]

Fig 4: Dog [14]

**NON-HUMAN PRIMATES**: Due to moral and budgetary concerns, non-human primates like rhesus monkeys are rarely employed in cancer research, but they are nevertheless very useful for some investigations. They are mostly employed to test cutting-edge immunotherapies or investigate tumours linked to infections caused by viruses, such as lymphomas linked to the Epstein-Barr virus (EBV). They are useful for comprehending intricate cancer networks or evaluating therapies that call for a comparable to human immune response because of their striking genetic and physiological resemblance to humans.[15] Despite their limited application, they are essential for confirming results from other models.

Fig 5: Non-human primates [16]

**ZEBRAFISH AS AN ANIMAL MODEL FOR ANTICANCER ACTIVITY**

**Zebrafish as a Model for Cancer Research**

Zebrafish are a great model for researching the genes and pathways linked to cancer because of their high level of hereditary and biological resemblance to humans.[17] Zebrafish have a well-characterized genome and many identical signalling mechanisms that control human cancer, including the Wnt, PI3K/AKT, and MAPK pathways of metabolism, are conserved in them. Zebrafish are a useful tool for researching the genetic causes of cancer because of these similarities.[18] Additionally, zebrafish have a number of benefits over other species models, including their tiny size, high rates of reproduction, and capacity to produce a large number of embryos for research. Because these embryos are readily apparent in their early stages of growth and development, scientists may track the spread and metastasis of tumours in real-time without undergoing intrusive operations. Zebrafish do have several drawbacks, though. Compared to mammals, their immune systems are less developed, which may have an impact on how immune-related tumours are modelled and how well immunotherapies work. Zebrafish continue to be a successful platform for cancer investigation in spite of these drawbacks.[19]

**Development of Cancer Models in Zebrafish**

Numerous techniques, such as chemical induction, xenotransplantation, and genetic manipulation, have been used to create zebrafish cancer models. To investigate certain genetic alterations linked to cancer, modified zebrafish models are frequently employed. In order to replicate human malignancies like those caused by alterations of the p53 or KRAS genes, these models can be modified to generate oncogenes or to knock off tumour suppressor genes.[20] The investigation of human cancer development and metastasis in an organism that exists is made possible by xenotransplantation models, which include transplanting human cancer cells or tumours acquired from patients into zebrafish embryos.[21] These models are very helpful for in vivo testing of novel treatments on human cancer cells. Furthermore, by subjecting zebrafish to cancerous substances, chemical-induced tumour models are produced, which result in the development of tumours that mimic those found in human cancers. These models are useful for evaluating possible anticancer drugs and researching environmental variables in the start of cancer.

**Molecular Pathways Studied in Zebrafish**

Zebrafish are especially useful for researching important signalling pathways linked to cancer, including Wnt (wingless/integrated pathway), PI3K/AKT (phosphoinositide 3-kinase/protein kinase B pathway), and MAPK (mitogen-activated protein kinase pathway). These pathways are essential for controlling cell division, development, and survival, and cancer is frequently linked to their dysfunction. For example, the MAPK pathway, is implicated in the survival and proliferation of cells, and it is frequently seen to be activated in a variety of malignancies. Similarly, cancer is often linked to the PI3K/AKT mechanism, which controls cell growth, metabolism, and survival.[22] Several malignancies emerge as a result of the Wnt signalling system, which controls cell fate and proliferation. Researchers can alter these pathways and examine how they contribute to the development and spread of cancer using zebrafish models.[23] Apart from these signalling pathways, zebrafish provide potent genetic technologies and tools like morpholinos and CRISPR/Cas9 that enable accurate modification of cancer-related genes. The research of gene activity and the discovery of new genes and pathways linked to cancer are made possible by these genomic tools.[24]

**Various applications in Drug testing and identification**

Since zebrafish can efficiently test a huge number of chemicals due to their tiny size, quick development, and clear embryos, they are being employed more and more for high-throughput drug testing.[25] Zebrafish are an economical and effective platform for the advancement of drugs because they allow researchers to assess the impact of several hundred or more thousand of anticancer drugs using high-throughput evaluation in a brief amount of time. Additionally, zebrafish models offer crucial information about the toxicity and effectiveness of cancer medications.[26] Researchers can evaluate the effects of medications on cancer cells and surrounding tissue by monitoring tumour growth and therapeutic response in real-time. Zebrafish models were considered utilised to find new compounds that have the potential to treat a variety of malignancies, in addition to evaluating established anticancer medications. Researchers can rank the safest and most effective options for additional development by analysing how these chemicals affect zebrafish tumours.[27]

**Anticancer Agents Tested in Zebrafish Models**

Synthetic Drugs and Natural Compounds: Zebrafish models have been used to evaluate a variety of synthetic minor molecules and natural molecules, including plant-extracted chemicals out of the sea. These investigations pinpoint possible anticancer drugs and shed light on their efficacy and modes of action. Particular Research of Anticancer Effectiveness: To assess the cytotoxic effects and possible adverse effects of particular anticancer medicines (such as paclitaxel, doxorubicin, and cisplatin), zebrafish are implemented in experiments.[28] With the added advantage of directly observing tumour responses, these studies enable researchers to evaluate how these medicines function in complicated ecosystems.

**Zebrafish as a Tool for Studying Drug Resistance**

Strategies of Drug Tolerance in Zebrafish: Drug resistance mechanisms, including changes in drug target proteins, changes in apoptotic pathways, and upregulation of efflux pumps, can be studied using zebrafish cancer models.[29] To learn more about how tumours avoid treatment, these systems can be monitored in real time. Managing Sensitivity in Cancer Therapy: By examining drug-resistant zebrafish cancer models, researchers can investigate combination therapies, new chemicals, or additional delivery forms whose services could be able to overcome resistance and improve treatment effectiveness.[30]

**Zebrafish in Specific Cancer Types**

For a range of cancer forms, zebrafish versions have been created, each providing a distinct perspective on cancer nature and treatment. Zebrafish models that replicate genomic abnormalities like BRCA1/2 or amplification of HER2 are utilised to research the course of breast cancer tumours and test novel treatments. Researchers are also learning more about the genetic abnormalities and environmental variables that contribute to the progression of melanoma through the use of zebrafish melanoma models.[31] Researchers can examine the consequences of haematopoietic stem cell alterations and test possible treatments for leukaemia and lymphoma by studying these blood cancers in zebrafish.[32] In addition to these prevalent cancer forms, zebrafish versions have been created for malignancies like colon, liver, and pancreatic cancer, giving researchers a wide range of resources to examine the scientific study associated with numerous tumours as well as the way they are treated.[33]

**Advantages of Zebrafish for Anti-Cancer Studies**

Zebrafish are a great model for oncology research because of their many benefits. Their affordability and user-friendliness rank among their most important advantages. Because of their speedy development—embryos may be produced in a matter of hours—and low maintenance costs, zebrafish allow for faster experimentation than other models.[34] Another significant benefit of embryos from zebrafish is their transparency, which enables researchers to monitor drug reactions and tumour progression in real-time without requiring intrusive procedures. This capacity to track the development of tumours over time yields important insights about the effectiveness of anticancer therapy and the response of tumours to various treatments.[35] Furthermore, high-throughput drug testing is made possible by the zebrafish's tiny size, which permits the testing of many compounds quickly. Zebrafish are a potent tool for speeding up drug discovery and cancer research because of these qualities.

**In Vivo Imaging in Zebrafish Cancer Research**

Imaging Technologies for Tracking Tumour Growth: Because zebrafish are transparent in the early stages of development, sophisticated imaging methods including bioluminescence, fluorescence imaging, and confocal microscopy can be used to track tumour growth, metastasis, and medication responses in real-time.[36] Non-invasive Monitoring of Drug Impact: Zebrafish can undergo long-term non-invasive imaging, which offers dynamic data on how anticancer drugs affect tumour growth and interactions between cells without requiring intrusive methods.[37]

**Translational Potential of Zebrafish Cancer Models**

Connecting Zebrafish to Humanity Applications: Although zebrafish models are useful for prior to clinical testing, research is still being done to see whether they can be used to treat cancer in humans. By highlighting potential medication candidates and therapeutic targets, results from zebrafish models can direct clinical trials.[38] Difficulties in Interpreting Results: Despite having numerous genetic and physiological traits in common with humans, zebrafish and humans differ significantly in terms of immunological response, medication metabolism, and cancer risk. When transferring results from zebrafish studies to human clinical settings, these issues must be resolved.

**Applications in Paediatric Cancer Research**

In the context of biology and response to treatment, paediatric malignancies frequently differ greatly from adult tumours. Acute lymphoblastic leukaemia, rhabdomyosarcoma, and neuroblastoma are among the uncommon and unusual cancers that can be studied in zebrafish.[39] Researchers can use transgenic zebrafish lines to replicate specific traits in order to gain a better understanding of the mechanism and recreate particular genetic abnormalities linked to paediatric malignancies. Using patient-derived tumour cells to create zebrafish xenografts has proven very useful for testing targeted treatments and creating individualised treatment plans for kids.[40] Furthermore, zebrafish embryos' quick development allows for quicker evaluation of possible treatment compounds for childhood cancer.

**Emerging Technologies in Zebrafish Research**

Zebrafish are now much more useful in anticancer research thanks to innovative technologies. Researchers have been able to produce zebrafish models with exact mutations present in human tumours thanks to the potent technique known as CRISPR-Cas9 gene editing. For instance, TP53-mutant zebrafish are frequently utilised to investigate tumour suppression pathways.

High-Tech Imaging: Modern imaging methods, like light-sheet and confocal microscopy, offer high-resolution, real-time visualisation of zebrafish cancer spread and progression.[41]

Omics Methodologies: Zebrafish are being utilised more and more in proteomics, transcriptomics, and genome research to find novel cancer biomarkers and treatment targets. Because of these developments, zebrafish are now a state-of-the-art platform for drug development and cancer research.[42]

**Toxicity and Side Effect Profiling**

It is becoming more well acknowledged that zebrafish embryos are a useful tool for assessing the toxicity and adverse effects of anticancer medications.[43] Because of their translucent nature, negative effects on the circulatory system, liver kidney, and neurological system may be monitored in real time. For instance, zebrafish have been used to test the cardiotoxicity and nephrotoxicity of chemotherapy medications like doxorubicin and cisplatin, respectively. Because zebrafish and humans share many physiological processes, toxicology assessment in zebrafish is not only quick but also predictive of human effects.[44] Zebrafish reduce the need for costly and time-consuming mammalian research by evaluating both pharmacological effectiveness and toxicology at the same time, which aids in the early identification of medications with desirable safety profiles.

**Zebrafish as a Platform for Combination Therapy Studies**

A key component of contemporary oncology is combination therapy, which use several medications or therapeutic approaches to attack cancer from several perspectives. Zebrafish models offer a productive and economical way to investigate these pairings. For instance, to find out whether chemotherapy, targeted medicines, or radiation have antagonistic or synergistic effects on tumour cells, embryos of zebrafish can be subjected to combinations of these treatments. The best treatment combinations for different cancer types have been found using zebrafish xenograft models.[45] In order to reduce adverse effects, these studies can also evaluate how combination medicines affect healthy tissues. Zebrafish models speed up the process of finding effective treatment plans by swiftly screening a variety of combinations. They also shed light on the mechanisms underlying drug susceptibility and coordination.[46]

**Comparative Studies of Tumor Heterogeneity**

One of the biggest obstacles to cancer treatment is tumour heterogeneity, which occurs when tumour cells through the same tumour have different epigenetic, genetic and phenotypic characteristics.[47] A dynamic and approachable system for researching this complexity is offered by zebrafish. Researchers can inject various cancer cell subpopulations labelled with unique fluorescent markers into zebrafish xenograft models to track how they interact, growth rates, and therapy responses in real time.[48] Researchers can also examine the interaction between tumour heterogeneity and the tumour microenvironment, which includes blood vessels, stromal cells, and immune cells, using zebrafish models. These investigations shed important light on the role that heterogeneity plays in cancer progression and treatment resistance. Additionally, zebrafish make it easier to test novel approaches to combat resistance brought on by heterogeneity, for focusing on cancerous stem cells or blocking particular pathways involved in hostile sub groups.[49]

**Zebrafish in Hormone-Dependent Cancer**

Dysfunctional hormonal transmission is the driving force behind hormone-dependent malignancies, including those of the breast, prostate, and endometrium.[50] The capacity of zebrafish models to replicate human hormone-regulated pathways has made them indispensable for the research of these tumours. For instance, the function of oestrogen and the androgen receptor in the formation and spread of tumours is investigated in zebrafish. Zebrafish embryos are a great model to investigate endocrine-disrupting substances that may lead to cancer because they are very susceptible to hormone abnormalities.[51] Additionally, by testing treatments that target hormonal pathways, like androgen deprivation therapy and selective oestrogen receptor modulators (SERMs), zebrafish models provide information on the effectiveness and adverse effects of medications.

**Zebrafish for Studying Tumor Hypoxia**

One of the main causes of cancer severity and treatment resistance is tumour hypoxia, a state in which cancer cells are depleted of oxygen. As the embryos they produce grow from the outside and can be exposed to regulated oxygen levels, zebrafish models are particularly well-suited for researching hypoxia. HIF-1α (hypoxia-inducible factor-1 alpha), which stimulates angiogenesis and tumour survival, is one of the molecular pathways that researchers study in zebrafish.[52] Scientists can test medications that target hypoxia-driven pathways and investigate the way cancer cells adjust to decreased oxygen settings by employing transgenic zebrafish lines that have fluorescent indicators for hypoxia-responsive genes.[53]

**Zebrafish in Cancer Biomarker Discovery**

Finding credible biomarkers is crucial for prognosis, therapy monitoring, and initial diagnosis of cancer. A dynamic approach for identifying and confirming cancer biomarkers is offered by zebrafish models. Researchers can investigate how tumours respond to host tissues or release indicators into the bloodstream by implementing human cancerous cells into zebrafish transgenic models.[54] Zebrafish models are also utilised to find molecular alterations linked to metastasis and medication resistance, which may be biomarkers. Utilising fluorescent or bioluminescent reporters, zebrafish embryos are also used to investigate non-invasive imaging indicators for real-time tumour advancement surveillance.

**Zebrafish in Studying Metabolic Pathways in Cancer**

In order to maintain fast development, avoid immunological reactions, and endure in harsh conditions, cancer cells rewire their metabolic. An inventive platform for researching these modified metabolic pathways, including glutaminolysis, lipid metabolism, and aerobic glycolysis (Warburg effect), is provided by zebrafish animals. Zebrafish can be used by researchers to study how tumour cells absorb nutrition and react to medications that target metabolic pathways.[55] Real-time visualisation of metabolic alterations in cancer cells is made possible by transgenic zebrafish that express fluorescent markers for important metabolic enzymes. Novel treatments that target biochemical shortcomings, like blockers that inhibit glucose transporters, fatty acid synthase, as well as glutaminase, are also being tested in zebrafish models.

**Zebrafish for Evaluating Nanoparticle-Based Therapies**

A possible method for more precisely and safely delivering anticancer medications is the use of nanoparticles. Because of their translucent bodies, which enable real-time visualisation of nanoparticle transportation, cellular uptake, and tumour targeting, zebrafish make an excellent model for assessing nanoparticle-based therapeutics.[56] To learn more about how nanoparticles get past biological barriers like blood vessels and build up in tumour tissues, researchers can utilise zebrafish embryos. Additionally, zebrafish are used to evaluate the toxicity and safety of nanoparticle formulations, offering vital information for improving their design. The emergence of nanomedicine for malignancy has greatly benefited from the knowledge gathered from zebrafish research.[57]

**Zebrafish in Exploring Environmental Carcinogens**

Tobacco smoke, pesticides, and industrial pollutants are examples of environmental carcinogens that significantly increase the risk of developing cancer. Zebrafish are being employed more and more to investigate how these carcinogens impact molecular and cellular pathways that result in the development and spread of tumours.[58] Zebrafish embryos are a useful tool for identifying possible carcinogens and comprehending how they function because of their heightened sensitivity to chemical exposures. Zebrafish studies have shed light on the ways that prolonged exposure to low levels of environmental pollutants can cause oxidative stress, DNA damage, and epigenetic alterations linked to cancer. In regulatory toxicology, zebrafish are also used to evaluate substances for carcinogenic potential, which helps with risk evaluation for the general public.

**Ethical Considerations in Zebrafish Research**

Zebrafish are a desirable option for preliminary cancer studies because they have clear ethical advantages over conventional mammalian models. Because zebrafish embryos are not conscious in their early stages of development, there are fewer ethical issues with testing. Zebrafish studies are also more economical and environmentally friendly due to their tiny dimensions and straightforward housing needs. Zebrafish support the 3Rs (Replacement, Reduction, Refinement) in studies on animals by lowering the requirement for mammalian models in exploratory experiments.[59] Even though there are still some ethical issues, especially with studies involving adult zebrafish, the model is still regarded as a morally sound substitute for cancer research.

**Future Directions and Challenges**

Improving Model Integrity and Dependability: Zebrafish cancer models can be used more effectively for drug screening and cancer research if their genetic fidelity is increased, for example, by producing more distinct and repeatable tumour types.[60] Better ways to replicate the heterogeneity and metastatic behaviour of human tumours are also being investigated by researchers. Combining Zebrafish with Additional In Vitro and In Vivo Models: Zebrafish models' predictive potential can be increased by combining them with other in vitro systems (like organoids and cell types) and in vivo models (like mice models). A deeper comprehension of chemotherapeutic responses to drugs and ways to resist is offered by multi-model techniques

**CONCLUSION**

By offering a special and effective platform for investigating cancer biology and assessing cutting-edge treatment approaches, Zebrafish have significantly advanced anticancer research by providing a versatile in vivo model. It has become essential for researchers all around the world due to its capacity to replicate human cancer processes and its real-time visualisation of tumour growth and metastasis. Zebrafish have a characteristic feature of allowing high-throughput drug testing at a fraction of the expense of standard mammalian models, which speeds up the search for potent anticancer drugs.

Additionally, zebrafish have advanced our knowledge of angiogenesis, tumour-stroma interactions, and the molecular mechanisms underlying the development of cancer. Zebrafish, a novel tool in personalised medicine, enable quick testing of tumours derived from patients, opening up new avenues for patient-specific therapeutic customisation.

Even Nevertheless, continual developments in zebrafish technology, such as the creation of immunocompetent models and sophisticated genomic resources, are overcoming obstacles including variations in medication metabolism and immunological responses. Zebrafish are expected to be a key component in the battle over cancer in the future, helping to close the difference between the experimental studies and therapeutic uses.

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