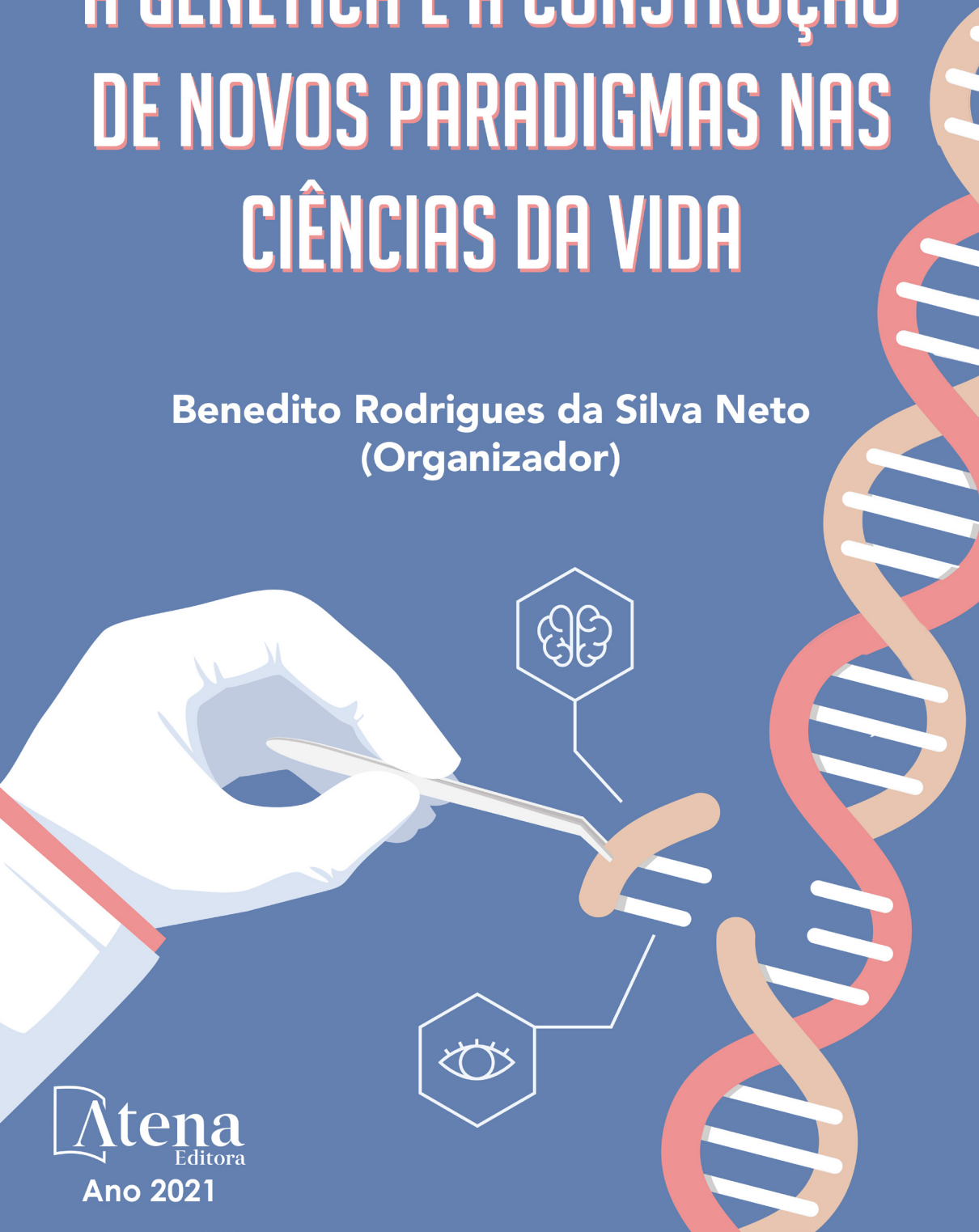
A GENÉTICA E A CONSTRUÇÃO DE NOVOS PARADIGMAS NAS CIÊNCIAS DA VIDA

Benedito Rodrigues da Silva Neto
(Organizador)



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APRESENTAÇÃO

Apresentamos o livro “A Genética e a construção de novos paradigmas nas Ciências da Vida”, um material rico e direcionado *à* todos acadêmicos e docentes com interesse pela genética.

A genética e suas aplicações tem influenciado diversas pesquisas promissoras em todo o mundo, contribuindo de forma significativa na saúde, agricultura, economia e biotecnologia. Aliada à revolução tecnológica essa subárea tem contribuído muito nos últimos anos com o avanço no campo da pesquisa. Como sabemos a genética possui um campo vasto de aplicabilidades que podem colaborar e cooperar grandemente com os avanços científicos e entender um pouco mais da pesquisa e recursos genéticos é o enfoque desta obra.

Deste modo, abordamos nesta obra assuntos relativos aos avanços e dados científicos aplicados aos recursos genéticos, o leitor poderá se aprofundar em temas direcionados à mitose, saúde e ambiente, célula e saúde, Cromossomo Philadelphia, biometria, DRESS, reações a drogas, exantema, ensino, laboratórios, extração DNA, tecidos vegetais, pureza e integridade, Stylosanthes sp., *Hylocereus*, conservação, variabilidade, RNA, método de extração, *Stylosanthes,* telômeros, telomerase, micropropagação, TCL, *Crambe abyssinica* Hochst, germinação, produção, herdabilidade, divergência genética, câncer, *Danio Rerio*, *Eye Disorders*, *Kidney Disease*, *Neurological Disorders*, *In Vivo Animal model*, dentre outros.

Esperamos que mais uma vez o conteúdo deste material possa somar de maneira significativa aos novos conceitos aplicados à genética, influenciando e estimulando cada vez mais a pesquisa nesta área em nosso país. Parabenizamos cada autor pela teoria bem fundamentada aliada à resultados promissores, e principalmente à Atena Editora por permitir que o conhecimento seja difundido e disponibilizado para que as novas gerações se interessem cada vez mais pelo ensino e pesquisa em genética.

Desejo a todos uma excelente leitura!

Benedito Rodrigues da Silva Neto

SUMÁRIO

CAPÍTULO 13

ZEBRAFISH MODEL IN THE STUDY OF HUMAN DISEASE

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ABSTRACT: Research in biological sciences relies on the use of animal models to deepen knowledge related to causes and mechanisms of human pathologies, as well as the possibility for testing innovative therapies. Zebrafish (Danio rerio) is an experimental model in areas such as oncology, toxicology, genetics, reproductive studies and regenerative medicine. The relevance of this vertebrate model relies on the small size of these animals, easy to maintain and manipulate, with a high rate of reproduction and development. The genome, physiology and anatomical structure similar to humans allows the creation of transgenic or mutant models to study several human pathologies and consequently the discovery of new therapeutic targets. In this review, we explore the zebrafish model into the study of several human pathologies, highlighting neurodegenerative diseases, cancer development and progression, ocular diseases and kidney diseases.
KEYWORDS: Cancer; Danio Rerio; Eye Disorders; Kidney Disease, Neurological Disorders; In Vivo Animal model;

RESUMO: A pesquisa em ciências biológicas conta com a utilização de modelos animais para aprofundar conhecimentos relacionados às causas e mecanismos das patologias humanas, bem como a possibilidade de testar terapias inovadoras. O peixe-zebra (Danio rerio) é um

modelo experimental em áreas como oncologia, toxicologia, genética, estudos reprodutivos e medicina regenerativa. A relevância desse modelo de vertebrado está no pequeno porte desses animais, de fácil manutenção e manipulação, com alto índice de reprodução e desenvolvimento. O genoma, a fisiologia e a estrutura anatômica semelhantes aos humanos permitem a criação de modelos transgênicos ou mutantes para o estudo de diversas patologias humanas e consequentemente a descoberta de novos alvos terapêuticos. Nesta revisão, exploramos o modelo do peixe-zebra no estudo de várias patologias humanas, destacando doenças neurodegenerativas, desenvolvimento e progressão do câncer, doenças oculares e doenças renais.
PALAVRAS - CHAVE: Cancro; Danio Rerio; Desordens oculares; Doença Renal, Doenças Neurológicas; Modelo In Vivo Animal;

INTRODUCTION

Animal models have been an invaluable tool to advance biomedical sciences research as they provide experimental avenues for cellular and molecular investigation. The zebrafish (*Danio rerio*) is an excellent alternative to mammalian models used to apply powerful experimental methods normally used in invertebrates to answer questions about development and disease (1).

The zebrafish belongs to *Cyprinidae* family, is a slightly alkaline freshwater fish, having slow water as its preferred habitat *(1,2)*. Due to the easy breeding and maintenance in the laboratory, the zebrafish has spread Worldwide, as an animal model. Studies involving this animal model grown exponentially and zebrafish model is now widely used. Methods and strategies for genetic and embryological evaluation and the induction of abnormal formative processes of internal organs can be easily applied to this model *(5)*.

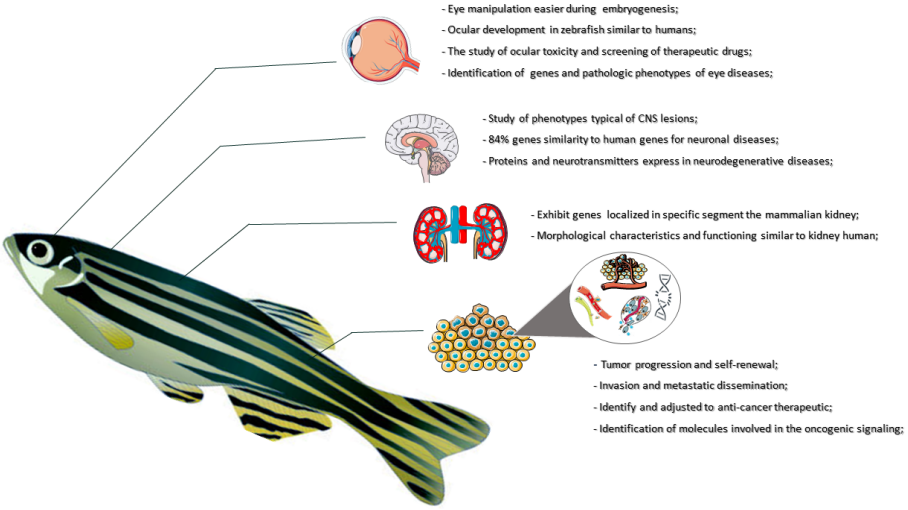
Until the beginning of its adult phase, zebrafish is transparent, which allows microscopic techniques that monitor cells *in vivo* through the different stages of its development *(1,6,7)*. This characteristic allows obtaining information regarding the animal's morphology, physiology and biochemistry *(1,6,8)*.

The zebrafish has a circulatory system, consisting of erythrocytes and platelets, which together with the operculum ensure gas exchange; a gastrointestinal system, composed of various organs such as intestine, liver, gallbladder, swimming bladder and pancreas *(1,9–12)*. The immune system is ensured by macrocytes and leukocytes from hematopoietic stem cells in which the T lymphocytes have matured in the thymus (12).

Zebrafish is a very important animal model for biology and biomedicine, once it allows the study of many human diseases, with 70% of homology to human genes (6,13). Well-established transgenic zebrafish lines with fluorescence tissues are available and add new insights into cancer cell development, dissemination and the tumour microenvironment in real-time *(8)*.

Our aim with this review is to explore the zebrafish model in the study of several human pathologies, with a focus on neurodegenerative diseases, cancer, ocular and kidney

diseases (figure 1).



Zebrafish Model in Neurodegenerative Diseases

Zebrafish model represents an optimal model to study nervoussystemalterations due to the simplicity of its nervoussystem (15,16). Its central nervous system (CNS) is similarwith other vertebrates and just like mammals,the zebrafish brain contains several progenitor cells that generate new and distinct neuronal lines, havinga greater number of active neurogenic niches(10,17–20). The blood-brain barrier(BBB)is operational 3 days after fertilization, which offers an advantagecompared to higher vertebrates(21). Zebrafish still share 84% of the genes associated with human dementias, suchas:co-orthologues tomicrotubule-associated tau protein(MAPT) gene, protein amyloid-ß (APP) and presenilins (PSEN1and PSEN2)(15,22)but alsomany proteins and neurotransmitters expressed in neurodegenerativehumans diseases (15,18,23). These characteristics make zebrafish an enriching animal model to reproduce phenotypes typical of CNS lesions or human neurodegenerative diseases(19,20).

Alzheimer Disease studies in Zebrafish Model

Several studies in Alzheimer's disease (AD) have been developed through the zebrafish model, allowing the characterization of the disease and its evolution. Several behavioural trials were necessary to identify phenotypes like the disease in humans. Several researchers observe the learning and memorization capacity of Zebrafish through different stimuli, where cognitive and memory deficits were similar to those observed in humans, as well as mobility difficulties (15,20,24).

The induction of AD status in zebrafish was explored through different substances such as aluminium exposure and β 1-42 amyloid injection or okadaic acid (OKA) (20,24). Using the induction through the aluminium exposure, a reduction in cognitive and locomotor abilities was observed (20), whereas induction using amyloid β 1-42 leads to an increase in phosphorylation and a reduction in cognitive abilities (20,25–27).

From the development of these models, we were able to understand behavioral phenotypes associated with Alzheimer's disease that can be compared to humans, as well as through the method of action to develop drugs. For example, inducing using scopolamine, a drug able to induce a phenotype similar to AD, it was possible to track cholinesterase-inhibiting treatments, such as donepezil, which will block the breakdown of acetylcholine, increasing the amount of the neurotransmitter in the synapse and consequently increasing memory retention (15). Exposure to OKA is also capable of inducing phenotypes and alterations compatible with human AD-like pathology, and cases of cerebral amyloid angiopathy (CAA) are also verified. However, in zebrafish the use of OKA to induce AD has several limitations, since OKA is a protein phosphatase 2 (PP2A) and PP2A inhibitor presents in abundance throughout the zebrafish body, besides inducing neurotoxicity (19).

Techniques such as Microinjections of antisense morpholino oligonucleotides (MOs) were also used in the creation of AD zebrafish embryos. The use of MOs microinjections in zebrafish embryos has allowed the study of several genes associated with AD such as presenilin-1 (PSEN1, presenilin 2 (PSEN2), orthologue zebrafish amyloid precursor protein (Appa, and Appb) and their role in the pathophysiology of AD (15,22,25). The Appa and Appb genes are associated with CNS cell death, a mechanism that may be responsible for cognitive decline. Two homologues (Appa and Appb) have been identified in Zebrafish for the human amyloid protein precursor (APP) gene, through which the amyloid β is synthesized (13).

Currently, the zebrafish model has been explored for drug screening. Memantine has been used in zebrafish to assess neuroprotection, however, it has no effects on locomotor behavior (15,23–25). Methylene blue (MB) was studied in zebrafish as an inhibitor of aggregation, decreasing cognitive neurodegeneration and decline, however, the results have been in constant and even contradictory (15,22).

Parkinson's Disease in the Zebrafish Model

Zebrafish model has been widely explored in the study of Parkinson's Disease (PD), due to the genetic similarity to humans and also due to the dopaminergic neurons in zebrafish's posterior tuberculum are well characterized both in the embryonic and adulthood stages *(28–31)debilitating, neurodegenerative disorder for which the current gold standard treatment, levodopa (L-DOPA*.

Several studies identified in the zebrafish model, neurons containing tyrosine hydroxylase (TH) in the ventral diencephalon homologous to mammals *(25,32)* and DP-

related proteins such as Parkin (*PRKN),* protein Deglycase (DJ-1)*, Pten-induced kinase 1 (PINK1)* and leucine-rich repeat kinase 2 (*LRRK2) (29,32).* PD can be studied in the zebrafish model through neurotoxins and genetic alterations. The neurotoxin-based models were developed through substances such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), rotenone and paraquat *(28)*.

The creation of zebrafish models associated with PD, such as the 6-OHDA model, allows testing innovative drugs for PD. Through the zebrafish 6-OHDA model, neuroprotective drugs such as isradipine, rasagiline and minocycline were screened, and the results suggest that minocycline and rasagiline can protect or restore locomotor activity deficit and the loss of dopaminergic neurons due to 6-OHDA (28).

Studies with MPTP in zebrafish result in behavioral changes, including decreased locomotor activity associated with selective loss of dopaminergic neurons in the NHS, along with decreased levels of striatal dopamine. The main limitation of the MPTP model is the absence of formation of lascivious bodies (LB), one of the most important neuropathological characteristics of PD *(30,32)rodents, zebrafish, Caenorhabditis (C.*. In turn, using 6-OHDA in different regions of the brain, different phenotypes are observed in zebrafish according to the location of the substance, since it cannot cross the *BBB (17).*

The phenotypes produced by 6-OHDA in Zebrafish range from alterations of the axonal terminals, dopaminergic degeneration of neurons in the nigra substantia, decreased levels of dopamine and norepinephrine and motor deficiencies to olfactory disorders *(21,30,32).*

The 6-OHDA in Zebrafish also allowed the tracking of some therapeutic compounds such as antioxidants and iron chending agents that demonstrated optimistic effects on the neutralization of 6-OHDA neurotoxicity *(30)rodents, zebrafish, Caenorhabditis (C.* and therapies with vitamin E, minocycline and levodopa + carbidopa where recovery of locomotor deficiencies induced by 6-OHDA was verified *(21)*.

Pesticides such as paraquat,induce oxidative stress and cytotoxicity in neurons(21,30)leading todeficiencies in spatial memory, decrease in the proportion of 3,4-Dihydroxyphenylacetic acid (DOPAC)/dopamine levels, decrease in dopamine transporter expression,decrease inmitochondrial viability, andincrease in the expression of antioxidant enzymes(21). Some authors suggest the presence of locomotor alterations or anxiolytic and aggressive behaviours depending on the genotype and sex of the fish(21,33)However, when administrated inthe water, paraquat seems to induce no parkinsonian-like phenotypes in larvaeeand adult zebrafish(30).Inturn,studieswithrotenone induce inconstantphenotypes(21,30,31).

Through different genetic silencing techniques, such as MOs, Custered Regularly Interspaced Short Palindromic Repeatsassociated protein 9(CRISPR/Cas9) several researchers studied in Zebrafish possible target therapies for genes associated with PD(21,25,30,32,34,35). One of the therapies tested in zebrafish for PD was L-3,4-

dihydroxyphenylalanine (L-DOPA) in which we verified a decrease in spontaneous swimming behaviour and a reduction in the expression of parkingenes, pink mRNA1 and TH protein (32).

Amyotrophic Lateral Sclerosis in the Zebrafish Model

The zebrafish presents many features of Amyotrophic lateral sclerosis (ALS), including decreased adult swimming endurance, loss of motor neurons, paralysis and larvael and adult neuromuscular junction defects (36–39). Currently, several studies have been developed in zebrafish to understand the aetiology of ALS, through microinjection of cDNA or mRNA (18,37,39,40) and techniques such as zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and CRISPR/Cas9 that allow easy testing in Zebrafish the loss or overexpression of genetic function associated with ALS (18,38). Most of these studies focused on genes such as TAR DNA Binding Protein (TARDBP), FUS RNA binding protein (FUS) and chromosome 9 open reading frame 72 (C9orf72) (36–38,40).

For example, ALS models generated by injection of cDNA or RNA in fertilized eggs allowed the creation of mutant SOD1 zebrafish models, associated with interneuron dysfunction. From the creation of SOD1 zebrafish mutant, it is possible to trace activating substances that regulate resistance to oxidative stress such as apomorphine and riluzole, where the neutralization of the interneuron dysfunction was observed (36).

With the development of transgenic zebrafish for ALS, it was possible to study neuronal toxicity associated with overexpression of Cu/Zn superoxide dismutase (SOD1). In zebrafish model, the SOD1 mutation demonstrated locomotor deficiency, paralysis, changes in nerve and muscle terminals, muscle atrophy, oxidative stress sensitivity and loss of motor neurons (37–39). Studies in Zebrafish using the TAR 43 protein (TDP-43) (34,36,37,39) suggested paralysis, neurodegeneration, oxidative stress in nerves and consequent deficiency of locomotion (18,23,37,38). The injection of human mutant FUS mRNA into Zebrafish resulted in the accumulation of cytosolic tension granules, aggregation of proteins in the cytoplasm of motor neurons, damage in the synaptic transmission of the neuromuscular junction, locomotor deficits and ventral root projection anomalies (18,36,37). From this model, it was possible to study the action of MB, pleiotropic molecule, used to prevent β amyloid and tau aggregation in vitro. MB in mutant zebrafish is effective in suppressing the TDP-43 and FUS phenotypes, protecting against cellular stress and conferring neuroprotective properties against the toxicity of TDP-43, a protein linked to the formation of amyotrophic sclerosis. The action of MB will reduce the stress of the endoplasmic reticulum resulting from the accumulation of mutant proteins and also restore synaptic function (22,34,38). Drugs such as guanabenz, phenanae and salubrinal were also tested in zebrafish with ALS and also revealed neuroprotective drugs (32,36).

A repeated expression of the hexanucleotide "GGGCC" in the non-coding region of the C9ORF72 gene was also studied in zebrafish associated with different forms of ALS such

as behavioural and cellular deficits related to locomotion and motor axonopathy (25,37–39).

Zebrafish Model in Neuropsychiatric diseases

The second class the neuronal diseases studied in zebrafish are Neuropsychiatric diseases. Within neuropsychiatric diseases, we can include Epilepsy, Autism Spectrum Disorder (ASD) and Schizophrenia (SCZ).

Epilepsy

In an epilepsy state, zebrafish presents similar behavior to human, from changes in locomotion, hyperactivity and spasms to electrical discharges in the CNS (18,22,25,41). Epilepsy studied in *larvael* and adult zebrafish through behavioural evaluation is possible through the administration of certain drugs and genetic alterations. The most commonly used drugs are picrotoxin, pentylenetetrazole (PTZ), kainic acid (KA) and acute caffeine (18,22,25). The behavioural alterations described were: hyperactivity, increased body cortisol, spasms in swimming, erratic movements, hyperventilation, fast whole-body clonic-like behaviour and even death (22,42). The zebrafish model was also evaluated as screening of therapeutics since these epilepsy-inducing drugs are suppressed by anti-epileptic drugs (22,25,43,44). For example, the creation of the PTZ model of adult zebrafish was crucial for the understanding and characterization of complex phenotypes of behavioural seizures, as well as in the investigation of molecular/cellular changes associated with seizure episodes.

Additionally, using the PTZ *larvael* model, it was possible to track therapeutic genes and identify modular seizure genes, using genetic lines (45). Other studies using Zebrafish have evaluated different anticonvulsant drugs and vitamin K analogues (44).

Techniques such as TALENs and CRISPR-Cas9 provide additional models for epilepsy research, creating stable genetic models targeting mutations of a single human epilepsy gene (46). Through CRISPR-Cas9 editing it was possible to create lines of zebrafish mutants with loss of functions for physiological comorbidities in syntaxin-binding protein 1 (STXBP1), aldehyde dehydrogenase 7 family member a1 (aldh7a1), among others (46). For example, the establishment of stable mutant lines for zebrafish STXBP1 homologues (stxbp1a and stxbp1b), characteristic of epilepsy, rebelled that zebrafish presents clinical phenotypes similar to those of the human syntaxin binding protein 1 mutation (47).

In recent decades, a model of epilepsy in zebrafish was also developed through the induction of N-Ethyl-N-nitrosourea (ENU), resulting in a phenotype similar to Dravet syndrome (41,43,48).

Autism Spectrum Disorder (ASD)

Zebrafish is a very social animal living in mixed-gender groups (shoals) with behavioural flexibility according to their social experience and a structured dominance

hierarchy (35,49). Zebrafish develops its social components during the first month of development, being visible at the 6th day after fertilization the first signs of shoal and later a rapid increase in the cohesion of the schoal. In less than a month after fertilization zebrafish already establishes social preferences associated with visual stimuli essential to their survival and schooling and other complex social interactions in the schoal (16,24,35,49,50).

The acquired behaviours are associated with the innate tendency of an animal to observe, mimic and approach a conspecific, characteristic preserved within the species of social vertebrates (35). To assess the emotional and social was used inhibitory prevention with cameras and paired with an aversive stimulus such as electric shock. In autism, aggression and even self-aggression behaviours are common due to the inability to process social suggestions. In zebrafish this component is observed in undulating, circular movements of the body, biting off the head, elevation of the fins, the opening of the mouth, pursuit of reflection and change of body colour. These behaviours were possible to identify through various tests with the use of mirrors (49).

The creation of zebrafish models to study ASD is possible through the disturbance of behavioural and cognitive function, by the action of drugs. For example, the use of the N-methyl-D-aspartate receptor antagonist (NMDA), which results in zebrafish in reducing the cohesion of the shoals and the exposure to nicotine which decreases the cohesion of the shoals but has a small effect on the polarization of the shoals (49).

The Zebrafish genome sequence bears high similarity to humans, with approximately 858 human genes associated with ASD being identified (49). Based on these similarities, several projects were developed based on the analysis of social behavior deficits. The ASD study, on a genetic level, was possible from the elimination of shank3b, the induction of the mutant ortholog Sam2 to the human gene *FAM19A2* and the study of the gene *centrosomal protein 41(CEP41)* (16,35,48). Using genome editing technologies such as CRISPR/Cas9-based genome editing it was possible to develop zebrafish gene lines allowing the study of phenotypes associated with ASD associated genetic variants. For example, using Cas9, it is possible to induce micro-dalicis in the ortholog of zebrafish (chd8) of the CDH8 gene of the human ASD, allowing to observe an overall increase in head size in fish, and thus mark the parallelize with the human phenotype (49). A CRISPR study also looked at risk genes for neuropsychic diseases such as schizophrenia and autism indicating significant behavioural changes in the mutants inner mitochondrial membrane peptidase subunit 2 (immp2l) and sodium channel, voltage-gated, type II, alpha (scn1lab) (35).

Schizophrenia (SCZ)

Schizophrenia is a debilitating disorder characterized by disorganized psychiatric thinking, disorientation, hallucinations, illusions and motivational decline (18,48,51). Schizophrenia is a genetically complex disease with the presence of more than one hundred variants and some quite rare and harmful. Through strategies such as the introduction of CRISPR/Cas9-mediated genome editing and other processes of suppression and

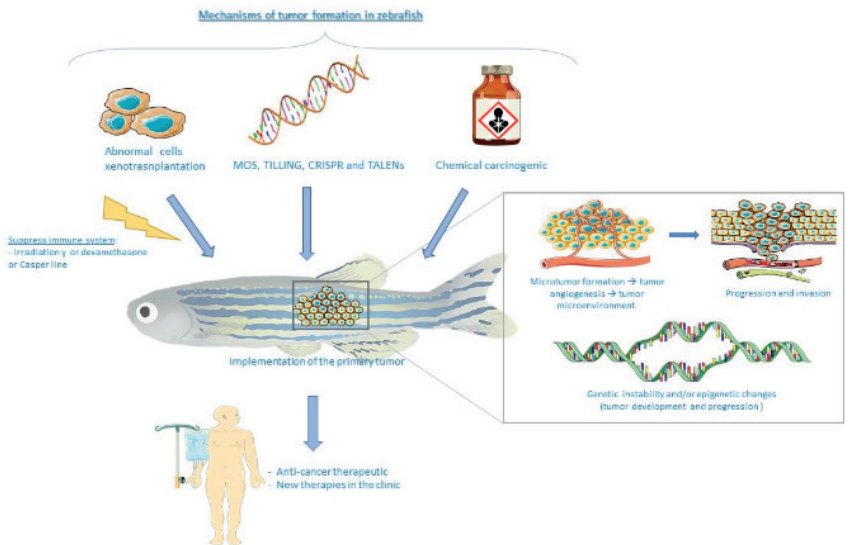
overexpression of genes easily established in the animal model, it was possible to create zebrafish models with genetic mutations or insertions directed to schizophrenia. The creation of these large-scale mutant models, due to the high fertility rate of zebrafish, allowed the study of phenotypes associated with the disease and also the screening of therapeutic potentials (25,48).

One of the applications of the mutant zebrafish model created from techniques such as CRISPR/Cas9, allowed to investigate the function of a rare gene associated with schizophrenia, the *disrupted in Schizophrenia 1(DISC1)(*17,48). Zebrafish disc1 mutants revealed an abnormal brain morphology in early stages of development, including changes in the small cerebral, hypothalamic ventricles, and stress responses in the zebrafish disc1 mutants. Changes in this gene have also been studied phenotypically where phenotypes common to schizophrenia, such as hyperlocomotion, social behaviour and memory deficits were observed (18,22,25,35,48).

Further study of dopaminergic and glutamatergic signalling will be crucial to understand the mechanisms involved in the neurological development aspects of schizophrenia (25).

Zebrafish Model in Oncology

Zebrafish model is nowadays a powerful tool to study tumoral process, from the implementation of the primary tumour to its development and development of metastases. Since the development of cancer spontaneously in zebrafish is rare, there is a need to induce tumour formation, through xenotransplantation of tumour cells, treatment with chemical exposure to carcinogenic or induction of genetic alterations and creation of mutant or transgenic models(8,52,53), as shown in Figure 2.



Zebrafish xenografts allow observation of changes in morphology, migration and cell cycle dynamics throughout tumour development. The xenotransplantation of tumour cells in zebrafish was developed in the phases of development, embryo, larvae and adult. The study in embryo and zebrafish larvae is very useful for its adaptive immune system and transparency. However, xenotransplantation in adult zebrafish allows a better analogy to human due to the tissue similarity between the mature tissues of zebrafish and the origin of xenograft. Currently, xenotransplantation in adult zebrafish is no longer compromised by the need to suppress the immune systems, through the use of techniques such as irradiation γ, treatment with dexamethasone and more recently a Casper line of transparent immunocompromised zebrafish, prkdc$^{fb103/fb103}$ il2rga$^{fb104/fb104}$ Casper-strain zebrafish (8,52,54,55). Zebrafish larvae and embryos may represent an interesting alternative to adult zebrafish because they allow the analysis of microtumor formation, tumour-induced angiogenesis and cell invasion. The study of tumour angiogenesis is also possible, due to its vascular embryonic system. Techniques such as fluorescence microscopy in transgenic embryos facilitate macroscopic and microscopic observation of the entire angiogenesis process (52–54,56).

Other studies on zebrafish have allowed tumour development and progression by creating genetic instability and/or epigenetic changes, a common feature in human tumours (52). Genetic instability in zebrafish is possible through reverse genetic approaches to generate loss-of-function phenotypes, such as MOs, targeting induced local lesions in genomes (TILLING), CRISPR/Ca9 system and transcription activator-like effector nucleases (TALENs) (8,53,56–58). The characterization of mutant and transgenic zebrafish lines allowed identifying chemical inhibitors of mutant phenotypes using chemical suppressor screens. For example, using a cell cycle stop mutant as a crash&burn (crb) it was possible to identify oncogenic genes (59). The zebrafish model has also been used in the study of tumour progression and self-renewal through cells in its microenvironment as called tumour-propagating cells (TPCS) which are responsible for initiating metastasis, relapse and stem cell-like population (52,53).

The complex and heterogeneous tumour development comprises interaction of multiple signalling pathways. The zebrafish model through chemical genetics has allowed the identification of molecules involved in the oncogenic signalling pathways and the discovery of new targeted therapies (8,59,60).

The zebrafish model allowed the development of small molecule screens, resulting from a procedure in which small molecules are tested for their ability to activate or modify a target or a biological process of interest. For example, inhibitors of oncogenic pathways including Wnt/b-catenin and Ras; metastasis of cancer including lymphamnesis and angiogenesis; and cell cycle aberrations were found (8,59). Regarding the study of tumour metastasis in Zebrafish, several tumours were studied, such as liver carcinoma, glioblastoma, breast cancer, rhabdomyosarcoma, melanoma, neuroblastoma, among

others(14,52,58). All the stages of the metastatic process were able to be studied including the beginning, approaching, clustering, invading, migrating, transmigrating and metastatic colonization (52,54,58,61). Several techniques are used to observe invasion and metastatic dissemination, such as the fluorescent zebrafish model and the development of transparent Casper adult zebrafish. For example, the fluorescent zebrafish model evaluates the progression of T-lymphoblastic lymphoma (T-LBL) to acute lymphoblastic leukaemia (T-ALL) and the transparent Casper adult zebrafish to evaluate the graft and proliferation of pigmented melanoma cells (8,52,54,58,62).

Fluorescence transgenic zebrafish allow the detection of genes or alterations in the signaling pathways involved in tumor development, allowing the implementation of new therapies, through suppressive drugs, such as vascular endothelial growth factor (VEGFR) inhibitors, inhibition of SMYD3 (promotes cancer invasion), cell division cycle-associated protein 7 (CDCA7) and protein human MutT Homolog1 (MTH1) (54,63).

Due to their small size, zebrafish embryos and larvaee are ideal systems for large-scale screening of pharmacological molecules in culture plates and studies in vivo in cancer research, several molecules can be identified and adjusted to anti-cancer therapeutic strategies and drugs (59,62–64). Researchers studied chemical libraries variations based on the time and duration of exposure, chemical concentration and general toxicity. The most used are the *Chembridge DIVERSetE* collection of synthetic compounds and the LOPAC collection of bioactive (59). The zebrafish larvae and embryo has also been useful to identify specific therapies against cancer stem cells that contribute to metastasis and relapse (59,65). Currently, several drugs have been studied in zebrafish for various types of cancers such as *Dasatinib Quisinostat or Crizotinib* for Melanoma, Indenum[1,2-b]quinoxaline derivatives for hepatocellular carcinoma, Visfatin for breast cancer, among many others with significant results (54,66,67).

Zebrafish Model in Kidney diseases

Zebrafish is increasingly used in kidney diseases, as they are genetically tractable and have basic renal anatomy comparable to mammalian kidneys with tubular filtration processing and glomerular filtration (68–72). Genetic studies by Wingert et al. have confirmed that many genes that are localized to a specific segment in the mammalian kidney were also expressed in zebrafish prone, such as an expression chloride voltage-gated channel K gene (clcnk) associated chloride channel in mammals in the distal regions (68,70).

Given the morphological characteristics and functioning of the zebrafish kidneys, this animal model has been used in the study of several of these pathologies. About renal acute injury (AKI), Zebrafish has been used to study the effect of nephrotoxic agents such as gentamicin and cisplatin (70,72). The induction of AKI in zebrafish allowed to identify possible targets for nephrotic recovery therapy, with for example the analogue of 4-(phenylthio)-butanoic acid, which is an inhibitor of histone deactylase and is related to the reduction of

cell cycle arrest and consequently renal proliferation in the context of abrupt and protracted injury (72). Zebrafish ise also used in the study of glomerular diseases. Genome-associated studies (GWAS) identified phosphatase acid 1 (ACPI) and the SOS Ras/Rho guanine 2 nucleotide (SOS2), which were associated with renal function and development based on the estimated glomerular filtration rate (eGFR) (70). Genetic studies revealed several mutations associated with renal filtration and cell growth (70).

With the use of transgenic zebrafish, it was possible to identify several mutations associated with kidney diseases, such as underlying mutations in the FAT atypi-calcadherin1 gene (FAT1) in inoculant in steroid-resistant nephrotic syndrome (SSR) and also a specific transgenic line of podocyte Tg (podocin:GFP) (70–72). Polycystic kidney disease and cylopathy were also studied in this model, where it was possible to identify 12 genes causing human cystic kidney disease in a panel of zebrafish mutants with cystic phenotypes (70–73). Some scientists studied the relation between renal disease and apolipoprotein 1 (APOL), suggesting that zebrafish model is beneficial in the study of APOL eliminating the potential redundancy effect because zebrafish have only one APOL orthologue and the primates are up to five APOL genes (70). The screening and testing of drugs through the zebrafish model, is now possible, by the knowledge of the renal physiology of zebrafish and by laboratory procedures such as genetic screens that allow the breeding and detection of a mutant organism (70,72).

Zebrafish Model in Ocular diseases

Ocular development in zebrafish is like humans and other vertebrates. Zebrafish has predominantly cone-mediated vision like the human macula resulting in color vision with a cone density close to humans. The retina in zebrafish and humans also share the same layout, with the ganglion cell layer, the outer nuclear layer, the inner nuclear layer and two synaptic layers. Moreover, the retinal architecture is characterized by photoreceptor subtypes spatially arranged in a highly organized photoreceptor mosaic. Besides, the eyes of the zebrafish are large relative to the overall size of the fish, allowing eye manipulation easier during embryogenesis (74).

The characteristics mentioned above, and the great genetic homology enable a widespread investigation of human ocular diseases in this vertebrate model (75). Several researchers search for genetic modifications in Zebrafish. They have identified genome editing technologies, such as TALENs, MOs, the clustered regularly interspersed short palindromic repeats CRISPR-/Cas 9 system and zinc-finger nucleases (ZFNs) (74–76). The MO knockdown technique allowed the identification of genes associated with Joubert syndrome (JBTS). The JBTS is a type of human diseases associated with numerous ciliopathic defects, ataxia, cognitive impairment and retinopathy (75,77). ZFNs have been extensively studied in DNA manipulation, allowed to induce gene expression in zebrafish for further mechanistic studies of eye phenotypes. The use of ZFNs allowed the study of

hereditary mutations and somatic mutations. Using ZFNs it was possible to create clarin 1 (clrn1 gene) mutants, associated with syndrome type III, which leads to progressive loss of vision in patients (75,78). From 2011, several studies were developed using TALENs, which can be more easily designed than ZFNs. With the use of TALENs it was possible to establish a link between eye diseases and target genes, such as elongation Factor Tu GTP Binding Domain Containing 2 (EFTUD2 *gene), beta 3-glucosyltransferase (B3GLCT gene), mab-21 like 2 (MAB21L2 gene), abelson helper integration site 1 (AHI1) and paired like homeodomain 2 (PITX2 gene) (75,79*–81).

Currently, studies have been conducted on the modeling of human eye diseases with CRISPR/Cas9 system in zebrafish (75,82). Using CRISPR-Cas9 it was possible to establish a line of zebrafish with elimination of the mutation in the frame in the chaperonin containing TCP1 Subunit 2 (cct2 gene). As heterozygous mutations composed in CCT2, result in symptoms such as sunken eyes, early-onset blindness, photophobia and oculodigital signs, well characteristic of Leber Congenital Amaurosis (LCA). Through the retina of the homozygous mutant, we can associate cct2 with the significant death of the cell in the developing neural retina, a phenotype similar to that of retinal pathology in human patients of LCA (75,83). Associated with each phenotype of eye disease, these zebrafish genes homologous to humans were identified through zebrafish mutant/morphant establishment. For example, associated with Coloboma we identified mutant adenomatomas polyposis coli (apc) homologous to the human gene APC and associated with Corneal dystrophies and cataract we identified laminin α1 (Lama1), homologous to the human LAMA1 gene(74).

The Microphthalmia was studied in zebrafish identifying genes such as SRY (sex-determining region Y)-box 2 (SOX2 gene), the gene most associated with this disease, and the patched 1 (PTCH1) gene. Using CRISPR/Cas9- mediated knockout zebrafish, it was possible to identify the characteristic phenotype of patients as defects of the terminal nerve and ethmoid plate and decreased eye size (74,75). In Arhinia Microphthalmia Syndrome, we used CRISPR/Cas9 edited smchd1 knockout zebrafish in which phenotypes such as ethmoid plate defects, eye size and terminal nerve were observed (75). Mutant zebrafish models were used in the study of ocular coloboma, allowing to understand the optic fissure morphogenesis and orthologues of the human ocular coloboma, characteristic of retinal and lens defects. The creation of mutant zebrafish models allowed to better understand ocular coloboma. For example, homozygous mutant zebrafish for the paired box gene 2 (pax2) mutation is associated with a defect in the closure of optic fissure and recessive mutations in genes such as laminin-γ1 (lamc1), laminin-β1 (lamb1a), growth factor and growth differentiation 6 (gdf6a), adenomatous polyposis coli (apc), patched1 (ptc1) and n-cadherin (ncad). These mutations were associated with pathological changes in the extracellular matrix position compromising tissue function and persistence of optic fissure (74,75). In retinal degeneration, a model expressed a human RHO transgene with a truncated mutation Q344X, associated with the autosomal dominant form of the disease and the pde6c zebrafish

mutant, that cause changes in zebrafish vision (84).

However, many other studies in pathologies such as Glaucoma (74,80), Cyclopia (74), Corneal dystrophies (74), Cataract (74,85), Ocular albinism (74), retinitis pigmentosa (74,84), genetic correlations and pathologic phenotypes were also identified (74). The Zebrafish model is used in the study of ocular toxicity and screening of therapeutic drugs for eye diseases. Unlike other animal models, Zebrafish has an unusual characteristic, the retina can regenerate (74,86).

CONCLUSION

The study of the anatomical structure and metabolism of the zebrafish model revealed an intimate connection with the human, suggesting that this model is desirable for the study of various human pathologies. Although zebrafish do not spontaneously develop diseases similar to humans, their genetic and behavioral homology allows the induction of the pathological state. The establishment of genetic screens and the easy manipulation of the genome allows basic and transactional investigation of cell biology and pathogenesis. This animal model proved important in the identification, testing of inhibitors, and genetic or chemical suppressors associated with phenotypes of different diseases. The transparency of the embryo and zebrafish larvae make this model unique for the direct visualization of cellular dynamics, allowing a better understanding of the development and progression of complex diseases such as cancer and neurodegenerative diseases. In recent years, the zebrafish model has proven satisfactory results regarding the diagnosis and prognosis of human diseases, as well as in the discovery of new therapies. Being a low-cost model, comparing with other models used widely, shares a high genetic similarity with the human, high fecundity and easy chemical absorption makes zebrafish a powerful model in the screening of new drugs and therapies directed to human diseases.

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ÍNDICE REMISSIVO

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A GENÉTICA E A CONSTRUÇÃO DE NOVOS PARADIGMAS NAS CIÊNCIAS DA VIDA

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