Animal Models for Human Neurodegenerative Diseases

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Animal models of human neurodegenerative disease have been investigated for several decades. In recent years, zebrafish (Danio rerio) and medaka (Oryzias latipes) have become popular in pathogenic and therapeutic studies about human neurodegenerative diseases due to their small size, the optical clarity of embryos, their fast development, and their suitability to large-scale therapeutic screening.

Keywords: zebrafish ; medaka ; disease models ; neurodegenerative

1. Introduction

Neurodegenerative diseases are a major threat to human health. With the increase in the elderly population, these age-dependent diseases are becoming increasingly prevalent [1]. These disorders are devastating to families, and they represent a huge burden for society. Hence, it is urgent to develop novel and more effective therapeutic strategies to remedy these diseases. Animal models were confirmed as a useful tool to investigate the complex mechanisms of neurodegenerative diseases.

Over the past several decades, animal models, such as mice, monkeys, dogs, pigs, fruit flies, and fish, have contributed greatly to our understanding of the genetic basis of the cellular and molecular mechanisms behind neurodegenerative diseases [2][3][4][5][6]. In particular, small fish such as zebrafish (*Danio rerio*) and medaka (*Oryzias latipes*) offer several advantages as model organisms for human neurodegenerative disease studies and drug discovery. Due to their relatively small size and short lifespan, they require less space and are more cost-efficient for laboratory maintenance compared with other vertebrate model organisms, such as the mouse. In addition, they have very high fecundity, and their embryos are transparent during development, which facilitates the non-invasive visualization of its development, and complex mechanisms of neurodegeneration can be analysed more rapidly than in mouse and other vertebrate animal models [7][8][9][10][11].

Finally, drugs can be administered by intraperitoneal injection or oral gavage in adult zebrafish [12] or medaka [13], whereas in larvae or embryos, they are always administered by adding them to the water and drug solution [14]. Due to their small size, they can be easily treated in the 24-well plate, 96-well plate, or 10-cm Petri dish. This facilitates subsequent analysis of phenotypes after drug treatment. Therefore, all these characteristics make them suitable for large-scale and high-throughput drug screening scans.

On the other hand, the identity of nucleotide or amino acid sequences between zebrafish and human homologues is approximately 71% [15], which is much higher than some invertebrate animal models such as roundworms (*Caenorhabditis elegans*) (30–60%) [16] and fruit flies (*Drosophila melanogaster*) (40%) [17]. Notably, zebrafish possess a vertebrate neural structural organisation, and all of the major structures are similar to the mammalian brain. Furthermore, zebrafish also possesses a functional Blood–Brain Barrier (BBB), similar to humans [18]. Many important neurotransmitters were detected in the neurotransmitter profile of zebrafish, which is very important for neuroscientific studies [19].

Although the zebrafish is the most widely used fish model globally, medaka is also used extensively, especially in Europe and Asia [20]. Compared with the zebrafish, the embryos of medaka tolerate a wider temperature range (4–35 °C until the onset of heartbeat and 18–35 °C thereafter, compared to 25–33 °C in zebrafish) [11][21]. This provides great convenience in screens for isolation of low temperature-sensitive gene mutations and the manipulation of developmental rates [11]. In addition, medaka has a long history as a genetic model system. Therefore, a lot of inbred strains from different populations with a high degree of genetic polymorphism are available. This facilitates the generation of high-resolution genetic maps and the genetic analysis of monogenic traits and quantitative trait loci [21].

Therefore, all these factors make zebrafish and medaka of great value in studies of neurodegenerative diseases [22]. As a result, the publications in PubMed using zebrafish, the more popular model of the two, as the neurodegenerative disease

model increased sharply in recent years (**Figure 1**).

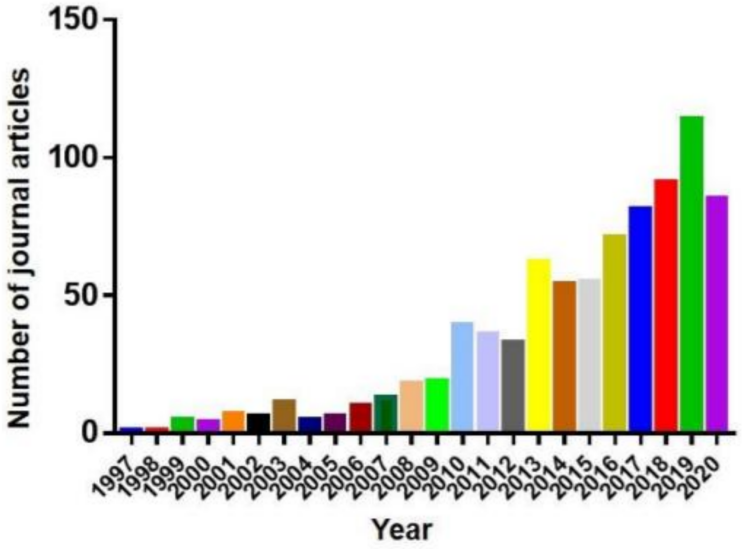

Figure 1. Absolute number of articles for zebrafish neurodegenerative diseases modelper year of publication extracted from the PubMed database.

2. Parkinson's Disease Models

Parkinson's disease (PD) is one of the most common neurodegenerative diseases that affects the motor system. Surveys, medical records, and death certificates demonstrate that the prevalence of PD has notably increased worldwide in recent years, possibly due to the growing elderly population worldwide [23][24][25]. The prevalence of PD was approximately 8.52 million and the incidence was 1.02 million in 2017 globally [26], whereas approximately 0.34 million people died from PD in 2017 globally [27]. It is predicted that the number of cases will reach 12 million by 2050 [28]. In spite of extensive studies that focus on the epidemiology and possible treatments of PD, its pathogenic mechanism has not been fully elucidated, and there is still no effective therapeutic strategy to cure this disease [29]. Compared with some traditional mammal models such as mice, zebrafish and medaka have comparative advantages for the pathological research of PD due to their short life cycles and high fecundity, which makes them particularly suitable for large scale drug screening [14][30][31][32]. In addition, as vertebrate species, zebrafish and medaka have higher genetic similarity to humans than invertebrate model animals such as roundworms and fruit flies [15][16][17][20]. In this review, we summarize several studies of PD in zebrafish, focusing on those published in recent years (**Table 1**) and several studies of PD in medaka. We discuss two main types of models: neurotoxin-induced and genetic models.

Table 1. Zebrafish models of Parkinson's disease.

Method	Phenotype	Results	Reference
MPTP induced	Motor impairments and weakened touch sensory	Reduction of locomotor activity and dopaminergic neuron, over-expression of synuclein in the optic tectum	[33][34][35][36]
6-OHDA induced	Motor impairments and anxiety	Reduction of dopaminergic neurons and morphological alternations	[37][38][39][40]
Paraquat induced	Motor impairments, various developmental anomalies	The paraquat-treated zebrafish did not recapitulate PD pathology	[41][42][43][44]
Rotenone induced	Motor impairments, anxiety, and olfactory dysfunction	In addition to motor impairments, they also show Olfactory dysfunction, which is a typical non-motor symptom of PD	[45][46][47][48]

Method	Phenotype	Results	Reference
PARK2 Morpholino	No abnormalities in swimming behavior	Loss of the DA neuron numbers in the diencephalon, whereas no abnormalities in swimming behavior	[49][50]
PINK1 Morpholino; Transgenes	Motor impairment and oxidative stress	Reduction of dopaminergic neurons, dis-organized diencephalic dopaminergic neurons, and the pink1 gene are sensitive markers of oxidative stress in zebrafish	[51][52]
LRRK2 Morpholino	Motor impairment	Loss of neuronal cells and synuclein aggregation, similar to the phenotype of PD in humans	[53][54][55][56]
PARK7 Morpholino; *CRISPR/Cas9*	Motor impairment	With aging, exhibit lower TH levels, respiratory failure in skeletal muscle, and lower body mass, particularly in the male fish	[57][58][59][60]
Synuclein Transgenes	Motor impairment	Led to cell death in larval zebrafish sensory neurons	[61]
GBA TALEN	Motor impairment	Reduction of the GBA protein, dopaminergic, and noradrenergic neurons	[62][63]
PARL Morpholino; *CRISPR/Cas9*	Motor impairment and olfactory dysfunction	Reduced DA neuronal population and dysregulation of the PINK1/Parkin mitophagy pathway	[64][65]

3. Alzheimer's Disease Models

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive memory loss, cognitive impairment, behavioural changes, and loss of functional abilities [66][67][68][69]. AD is the most prevalent form of dementia. It is estimated that nowadays more than 50 million people worldwide have dementia, and this number is expected to reach over 150 million by the 2050 [67]. AD is irreversible and it causes about 70% of all dementia cases [68]. Unfortunately, it still cannot be prevented, treated, or cured. The drug discovery for AD is very challenging, so no new drugs have been approved since 2003, when Memantine was approved [66][67][68][70]. Including four drugs that are approved by the Food and Drug Administration (FDA), at present there are only five approved drugs on the market available for the treatment of AD [68][71]. In addition, a previous study demonstrated that oxidative stress may induce behavioural and cognitive impairments in the aging zebrafish, just as it does in mammals [72]. Below, we describe previous studies of the molecular mechanisms of AD in zebrafish (**Table 2**).

Table 2. Zebrafish models of Alzheimer's disease.

Method	Phenotype	Results	Reference
Amyloid-β42 induced	Intracellular depositions	Link between aging, neurogenesis, regenerative, neuroinflammation, and neural stem cell plasticity	[73][74]

Method	Phenotype	Results	Reference
Okadaic acid induced	Cognitive and memory impairments, neuroinflammation cholinergic dysfunction, glutamate excitotoxicity, and mitochondrial dysfunction	Provide all the major molecular hallmarks of AD	[75][76][77]
Cigarette smoke extract induced	Neurocognitive dysfunction	Enhancement of the acetylcholinesterase activity	[78][79]
Aluminum chloride induced	Neurocognitive dysfunction, memory impairment	Impaired locomotor activity, learning, and memory abilities	[80]
Copper induced	Memory impairment	Reduction of the glutathione S-transferase (GST) activity in the gill	[81]
$MnCl_2$ induced	Cognition and exploratory behavior	Impairment of aversive long-term memory and distance traveled movement time	[82]
MAPT Transgenes	Motor impairment	The phenotypic abnormalities at larval stages make it suitable for high-throughput screening	[83][84]
PSEN1 ENU-mutagenized	Motor impairment	Regulation of histaminergic neuron development	[85]
BACE1/2 zinc finger nuclease; ENU-mutagenized	Hypomyelination, supernumery neuromasts, and abnormal pigmentation	Bace1 and Bace2 are proteases with different physiological functions	[86]

4. Huntington's Disease Models

Huntington's disease (HD) is an autosomal dominant, incurable, and fatal neurodegenerative disorder. Initially, HD patients display excessive movements of the limbs and face, and then gradually progress to exaggerated body movements described as chorea. Patients exhibit progressive symptoms, such as psychiatric, cognitive, and motor dysfunction, and this disease is usually lethal 10–20 years after the onset [87][88][89]. HD is caused by an expansion of the polyglutamine-coding region in the N-terminus of the huntingtin protein (HTT) [90]. HTT is a 350 kDa protein that is ubiquitously expressed, evolutionarily conserved, and likely to be involved in many cellular processes [91][92][93]. However, the precise mechanisms underlying the functions of the HTT gene remain incompletely understood.

The zebrafish HTT protein consists of 3121 amino acids and shares 70% identity with the human HTT orthologue [94]. Compared with the HTT-null mutation mice [92], HTT-null mutation zebrafish are viable, so the zebrafish is believed to be a suitable model to study the mechanisms of HD. To investigate the roles of HTT, several previous zebrafish HD models used MO to observe the effects of HTT deficiency in the early zebrafish development [95][96][97]. One study revealed that HTT-deficient zebrafish had hypochromic blood because of the decrease in hemoglobin production, despite the presence of iron within blood cells, and speculated that the disturbance of HTT's normal function in the iron pathway leads to HD pathology and especially to its neuronal specificity [95]. By use of the same HTT-deficient model, Henshall et al. reported

the effects of the loss-of-function of HTT on the developing nervous system and found obvious defects in the morphology of olfactory placode, neuromasts, and branchial arches, which led them to postulate that HTT may have a specific function that enables the formation of telencephalic progenitor cells and preplacodal cells in the forebrain [96]. Another study of the morpholino-based HTT loss-of-function zebrafish observed massive apoptosis of neuronal cells, accompanied by impaired neuronal development, small eyes and heads, and the enlargement of brain ventricles. Interestingly, it was observed that the expression of brain-derived neurotrophic factor (BDNF) was reduced. Notably, treatment of HTT-MO zebrafish embryos with exogenous BDNF rescued these defects, which suggests that increasing the BDNF expression might be a useful strategy for HD treatment [97].

In addition, some scientists established HD zebrafish models through the transgenic technology [98][99][100]. Schiffer et al. transiently expressed 102 polyglutamine repeats in the N-terminal fragment of the HTT protein fused with GFP (Q102-GFP) in zebrafish and found an accumulation of this mutant protein in large SDS-insoluble inclusions in the zebrafish embryos, thus reproducing an important feature of the HD pathology. The expression of the mutant HTT protein resulted in an increase in abnormal morphology and the occurrence of apoptosis in zebrafish embryos. A further study found that soluble mutant HTT protein forms are responsible for toxicity and aberrant polyglutamine aggregates in zebrafish [98]. The same study also found that its toxicity can be suppressed by the heat-shock proteins Hsp40 and Hsp70. Importantly, by the use of this HD transgenic model, two inhibitors of the Q102-GFP aggregation in vivo were identified, both of which are compounds of the *N′*-benzylidene-benzohydrazide class (293G02 and 306H03). In another study, a stable transgenic zebrafish line, which expressed a Q71-GFP fusion protein under the control of the rhodopsin promoter, was constructed to screen FDA-approved drugs to identify novel autophagy-inducing pathways. Three drugs (L-type Ca^{2+} channel antagonists, the K^{+}_{ATP} channel opener minoxidil, and the G_i signalling activator clonidine), which participate in a cyclical mTOR-independent pathway that regulates autophagy, were detected. This pathway has lots of candidate points to induce autophagy and reduce aggregates [99].

Cre-*loxP* system was also sometimes used to generate conditionally inducible transgenic zebrafish to study HD. For example, Veldman et al. created an inducible zebrafish HD model, in which the N-terminal 17 amino acids (N17) in the context of the exon 1 fragment of HTT were deleted, coupled with 97Q expansion (mHTT-ΔN17-exon1). That study found that, compared with the mHTT-ΔN17-exon1 line, fish with intact N17 and 97Q expansion (mHTT-exon1) had more delayed-onset movement deficits with slower progression. This model confirmed that the deletion of N17 terminal amino acids of the HTT will lead to an accelerated HD-like phenotype in zebrafish [100]. Recently, a separate study treated a transgenic HD zebrafish model with a phosphodiesterase 5 (PDE5) inhibitor and found an obvious decrease in the mutant HTT protein levels, cell death, and morphological abnormalities [101].

5. Other Neurodegenerative Disease Models

In addition to the above studies, zebrafish and medaka were also used in the investigation of some other rare neurodegenerative disorders. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by the motor neuron loss, and thus progressive muscle weakness and eventual death, primarily due to respiratory failure. The most prevalent genetic cause of ALS and frontotemporal dementia (FTD) is a hexanucleotide repeat expansion (HRE) within the first intron of the C9orf72 gene [102][103]. Shaw et al. generated two zebrafish lines to express C9orf72 HREs. This model recapitulates the motor deficits, cognitive impairment, muscle atrophy, motor neuron loss, and mortality in early adulthood that was observed in human C9orf72-ALS/FTD patients. Moreover, this stable transgenic model represents a powerful potential for the screening of therapeutic compounds [104]. In another study, several transgenic C9orf72-associated repeat zebrafish lines were generated by TOL2-mediated transposition. These models confirm the poly-GA toxicity in zebrafish. The reduction of poly-GA protein rescues toxicity, indicating its potential therapeutic value to treat C9orf72 repeat expansion carriers [105]. Conversely, Yeh et al. constructed two transient loss-of-function zebrafish larvae ($C9orf72^{u\text{-}DENN}$, $C9orf72^{c\text{-}DENN}$) using a morpholino injection. These models facilitate advances in the understanding of the functions of C9orf72 and provide potential mechanisms to elucidate the pathogenesis of ALS-FTD [106]. Mutations in the superoxide dismutase 1 (SOD1) gene were identified as another cause of ALS. In a previous study, by outcrossing the G93Ros10-SH1 line with the wildtype AB zebrafish strain, a mutant SOD1 zebrafish model was generated and used for high throughput screening to identify neuroprotective compounds [107].

Spinocerebellar ataxias (SCAs) are global neurodegenerative diseases leading to motor discoordination, which is always caused by the affected cerebellar Purkinje cells (PCs). A previous study generated a transgenic SCA type 13 (SCA13) model, which mimics a human pathological $SCA13^{R420H}$ mutation. This model exhibited neuropathological and behavioural changes similar to those manifested by SCA-affected patients [108]. Based on the same model, Namikawa et al. reported an SCA13-triggered cell-autonomous PC degeneration, which results in eye movement deficits [109]. In a previous study in our lab, we constructed an *NPC1* knock-out zebrafish model using the CRISPR/Cas9-mediated

technology [110]. This model developed symptoms similar to those observed in human patients of Niemann-Pick type C disease (NPC). We observed the loss of Purkinje cells in the cerebella of the *NPC1*$^{-/-}$ homozygous fish [110] and the aberrant motor behaviour, i.e., ataxias, a typical pathological character of human NPC1 patients (unpublished data), indicating its potential value for investigating the molecular mechanisms of NPC1.

In addition, a previous study generated a Gaucher disease (GD) model in medaka by the use of a high-resolution melting assay in the TILLING library for the *glucocerebrosidase* (*GBA*) gene [111]. In this study, it was observed that the *GBA*$^{W337X/W337X}$ (*GBA*$^{-/-}$) medaka displayed complete deficiency in GCase activity, and it showed similar pathological phenotypes with human neuronopathic GD. Importantly, compared with the perinatal death in humans and mice lacking the GCase activity, the *GBA*$^{-/-}$ medaka survived for months, enabling the investigation of the pathological progression [111].

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