INTRODUCTION

Parkinson’s disease (PD) is the second most common neurodegenerative disease among the elderly. It is estimated that 6.3 million people have PD worldwide, affecting all ethnic populations [1]. The main clinical features of PD are motor symptoms including resting tremor, muscle rigidity, bradykinesia/akinesia, gait disturbance and postural instability. PD is characterized by the selective degeneration of dopaminergic neurons in the pars compacta of the substantia nigra which is thought to be responsible for its motor symptoms. Cytoplasmic inclusion bodies termed Lewy bodies, composed mainly of alpha-synuclein, are histopathological hallmarks of this disease. Very recently, PD was also recognized to be accompanied by non-motor symptoms such as olfactory dysfunction, autonomic disturbances, sleep disorder, cognitive impairment and dementia. According to several studies by Braak and Tredici [2], Lewy body pathology is present even outside the substantia nigra spreading to various regions of the brain, providing compelling evidence that the widespread distribution of Lewy bodies and their related pathological changes are responsible for non-motor symptoms as well as motor symptoms.

The etiology of Parkinson’s disease (PD) is likely to involve both environmental and genetic factors. Epidemiological studies suggest that exposure to pesticides may contribute to the development of PD and some pesticides such as rotenone and paraquat have been shown to be dopaminergic neurotoxins and are frequently used to make toxin-induced PD animal models. 5–10% of PD cases are familial in form and, moreover, recent genome-wide association (GWAS) studies revealed that commonly occurring
Medaka PD Model

Genetic variants of alpha-synuclein and LRRK2 are risk factors for sporadic PD [3, 4] while a large cohort study involving several centers from 16 countries and more than 5,000 patients of different ethnicities showed that mutations in glucocerebrosidase is the number one genetic risk factor for PD [5], underlining the importance of research based on genetic models.

The establishment of animal models of PD using environmental toxins or genetic manipulation is essential in understanding the pathophysiology and pathogenesis of PD. Various animals from invertebrates such as nematodes and Drosophila to vertebrates including mice and monkeys have been used to model PD with their own advantages and drawbacks. However, an animal model that faithfully recapitulates the clinical and pathological features of PD has yet to be achieved. In this review, we would like to introduce the small teleost fish medaka as a novel and promising animal for modeling PD.

Teleost fish, among which zebrafish are the most widely used, are commonly used as model animals especially in the area of developmental biology, evolutionary biology, genetics, physiology, toxicology and pharmacology. Medaka, a small fish that is native to East Asia, are currently used as a model animals especially in Europe and Japan. These two fish share some advantages as model animals: corporal transparency, good egg production and ease of maintenance. There are now well-developed tools for manipulating these fish and information on their genome is now available: the medaka draft genome was published in 2007 [6-9]. One important trait shared by both fish is their place as the highest order of animals suitable for both forward genetics and reverse genetics: from phenotypes to genes and from genes to phenotypes.

As an animal to model human genetic disease, medaka fish have several advantages over zebrafish. Firstly, medaka have a relatively small genome (800 Mb), one-third the size of the human and less than half the size of the zebrafish genome. Secondly, the presence of highly polymorphic inbred strains makes it very convenient for mutagenesis screening and genetic mapping (Fig. 1) [9]. Furthermore, the ease of handling of both medaka and zebrafish, they both are suitable for screening.

More recently, several groups have also utilized teleost fish as disease models [10-12]. We have successfully generated medaka models of PD using genetic manipulation or toxin exposure and in this review we summarize the features of our medaka PD models and discuss future directions.

**GENERAL FEATURES OF MEDAKA DOPAMINE SYSTEM**

The dopamine system has been well studied in zebrafish [13-17]. According to these studies, teleost dopamine neurons are mainly distributed to the telencephalon and diencephalon. In contrast with mammals, the teleost mesencephalon does not have dopamine neurons. Instead, the diencephalon contains several clusters of dopaminergic neurons. Several classifications have been suggested concerning these dopaminergic neuron clusters [18, 19] but recently, an excellent review by Schweitzer et al. summarized these classifications, providing an easy way to understand the teleost dopamine system [13].

We used tyrosine hydroxylase (TH) antibody staining [20] and *in situ* hybridization using medaka dopamine transporter (DAT) mRNA (not published) to visualize the medaka dopamine system. The medaka dopamine system was similar to that of zebrafish with dopaminergic neurons distributed in clusters from the

| Zebrafish | Medaka |
|----------|--------|
| Technical name | Danio rerio | Oryzias latipes |
| Life span (years) | 2 | 2~5 |
| Generation time (months) | 2~3 | 2~3 |
| Temperature | 20~30°C | 4~40°C |
| Inbred strain | few | available |
| Genome size (Mb) | 1700 | 800 |
| Sex determination | dependent on the environment | XY chromosome |
| Freeze storage of sperm possible but not safe | safe |
| Numbers of researchers | large | small |

**Fig. 1.** Comparison of features of medaka and zebrafish. Both fish share many characteristics with some fine differences. Characters in red indicate important advantages for neurodegenerative research.

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**Fig. 2.** Distribution of TH*⁺* neurons in the adult medaka diencephalon and medulla oblongata. Cross sections at different rostro-caudal levels show the localization of TH*⁺* dopaminergic fibers and neurons in the telencephalon (B), preoptic area (C) and diencephalon (D: rostral, E: middle, F: caudal). TH*⁺* neurons were also distributed in the medulla oblongata (G). The positions of each section are illustrated by vertical lines in (A).
telencephalon to the diencephalon. In addition, we remarked the presence of a TH-positive but DAT-negative cluster in the medulla oblongata corresponding to noradrenergic neurons. Like other teleost, there were no TH-positive neurons in the mesencephalon of medaka fish. Despite the presence of a standard classification for zebrafish diencephalic dopamine clusters, we could not identify clear boundaries between cell clusters in medaka making it hard to classify the dopamine neurons of adult medaka in the same way as in zebrafish. In consequence, we preferred a simpler classification for the diencephalic dopaminergic neurons into 4 clusters: rostro-ventral, rostro-dorsal, middle and caudal clusters (Fig. 2) [20]. These clusters are distinct from each other and can easily be identified. In zebrafish, 2 distinct dopamine neuron clusters, DC2 and DC4, are the only sources of ascending projections to the subpallium, which contains structures reminiscent of the striatum [13, 21]. We believe, as outlined in the proceeding lines that these clusters correspond to the middle diencephalic cluster in medaka fish. However, which anatomical structure is the precise functional counterpart of the mammalian substantia nigra remains unanswered and further analysis of the functions and networks made by dopaminergic neurons is necessary to answer this question.

**MPTP AND 6-OHDA MODEL**

1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP) is a neurotoxin that induces PD-like symptoms [22]. Its metabolite, 1-methyl-4-phenylpyridinium (MPP+) is taken up by dopamine neurons through DAT, selectively damaging dopaminergic neurons by inhibiting the activity of the mitochondrial respiratory chain [23].

MPTP effectively induced PD-like symptoms when medaka larvae were simply exposed to this toxin by keeping the larvae in MPTP-containing water [20]. This simple exposition rapidly induced a significant reduction of spontaneous swimming movement, the images of which were obtained by a video camera positioned above the water tank and analyzed by a computer-assisted system. Spontaneous swimming distances for a period of 5 minutes were decreased by MPTP exposure in a dose-dependent manner (Fig. 3). Histochemical analysis of medaka brain revealed that the immunoreactivity of TH-positive neurons in the diencephalon almost totally disappeared. However after 3 months, the number of diencephalic TH-positive neurons recovered but remained less than that of controls. Interestingly, MPTP-induced neuronal loss was restricted to the middle diencephalic cluster leading us to hypothesize that this middle diencephalic cluster corresponds to the mammalian substantia nigra.

One question that needs to be answered is what would account for the recovery in the number of diencephalic TH-positive neurons after MPTP exposure. This recovery may be due to the genesis of new dopaminergic neurons, indeed it has been reported that in adult teleost fish there is widespread neurogenesis which may be responsible for the continuous brain growth in fishes and that new dopaminergic neurons are added in the diencephalon even in adult zebrafish [24]. Another possibility would be that the initial disappearance of TH signals was due to a functional decline of dopaminergic neuron activity which after time could have recovered without any cell loss. These possibilities should be addressed in the future.

6-hydroxydopamine (6-OHDA), another dopaminergic neurotoxin which acts mainly through oxidative stress [25], has also been used to model PD [26]. In our experiments, there was no significant reduction in the number of dopaminergic neurons when medaka were kept in 6-OHDA-containing water. Suspecting that the blood brain barrier (BBB) did not allow sufficient 6-OHDA to enter into the brain, we developed a system by which drugs can be administered directly into the cerebrospinal fluid (CSF) without passing through the BBB. Because of the presence

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**Fig. 3.** Spontaneous movement analysis of MPTP-treated medaka. Larvae are exposed to MPTP from 10 dpf to 12 dpf (2 days). Figures show representative 5 minute swimming tracks after 2 days exposure to MPTP.

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**Fig. 4.** Method of injection. (A) Simplified illustration of the agarose bed for injection. The groove allows easy stabilization of the fish. (B) Injected dye in the cerebrospinal fluid space. The blue arrow indicates the route of injection. The dorsal images were taken soon after injection of the fluorescent dye. The left image is a photograph of the whole head and on the right is that of the brain (after removal of the skull and other adjacent structures).
of a sufficiently large subarachnoid space between the skull and the brain parenchyma, we were able to administer drugs and toxins directly into the CSF of medaka. Medaka fish were first anesthetized and placed into a groove on an agarose gel plate immersed in water (Fig. 4), the fish were then held around the midportion and injected with diverse substances using a sharp glass needle attached to a Hamilton syringe [27]. Despite the non-selective administration of 6-OHDA into the CSF, selective loss of dopamine neurons was induced. Again, as we have seen with MPTP treatment, among the dopamine neuron clusters, only the middle diencephalic cluster showed robust cell loss.

Collectively, we have shown that classical dopaminergic neurotoxins can replicate PD-like features in medaka fish confirming its place as a promising PD animal model.

PROTEASOME INHIBITOR AND LYSOsome INHIBITOR MODEL

We exposed not only classical dopaminergic neurotoxins but also several other non-classical chemicals or toxins to medaka fish brain using the method mentioned above.

Previously, McNaught et al. reported that repeated systemic injections of proteasome inhibitors in rats induced dopaminergic neuronal death and the formation of inclusion bodies similar to Lewy bodies [28]. Some groups were able to replicate these results [29-31], while others have failed [32-34]. Although the reason for this inconsistency is unclear, a likely explanation is the difference in intra-cerebral drug levels depending on the site of administration. In a recent study, where mice were conditionally knocked out for a subunit of the proteasome specifically in dopamine neurons, the model mice were reported to exhibit PD-like phenotypes: selective dopamine neuronal loss, astrogliosis and alpha-synuclein positive inclusion body formation [35]. Using our CSF injection method, we found that the proteasome inhibitors lactacystine and epoxomicin produced robust inclusion bodies throughout the brain [27]. Surprisingly, although inclusion body formation was not specific to TH-positive neurons, cell death was relatively selective to TH-positive neurons. There was no significant difference in the number of cells in the optic tectum between fish treated with vehicles and proteasome inhibitors. Moreover, dopamine levels were also decreased in fish treated with proteasome inhibitors without any changes in the levels of serotonin, another monoamine. These fish also showed some movement disorders: a reduction in spontaneous swimming movement. Taken together, proteasome-inhibitors can also produce important features of PD in medaka, i.e., inclusion bodies, selective loss of dopamine neurons and locomotor impairment, supporting the idea that proteasome inhibition may present a causative factor of PD.

Recently, mutations in the gene encoding glucocerebrosidase, a lysosomal enzyme, have been shown to be significant genetic risk factors for PD [5]. Moreover, the gene responsible for autosomal recessive PD termed PARK9 has been reported to be ATP13A2, a cation transporter-like membrane protein localized in the lysosome [36]. These lines of evidence suggest that lysosomal dysfunction may also contribute to the pathogenesis of PD. We, on the other hand, have proposed that ER stress caused by accumulation of PAel-R, a substrate of Parkin, can also lead to dopaminergic cell death in autosomal recessive PD [37, 38]. To test the roles of lysosomal dysfunction and ER stress on our medaka models, we administered ammonium chloride, a lysosomal inhibitor, and tunicamycin, an ER stress inducer, into the CSF space and demonstrated that these agents caused selective loss of dopamine neurons, locomotor impairment and inclusion bodies [39].

Because it is easy to expose toxins or drugs to medaka fish, we believe that this model fish can facilitate the discovery of new environmental dopaminergic toxins, some in relation to human PD. In our studies, we effectively found ammonium chloride, which can be readily found in the environment, as a possible environmental cause of PD. Other natural substances that have inhibitory effects on lysosomal functions may in the same way be risk factors for PD, a hypothesis that we believe merits further analysis.

PTEN-INDUCED PUTATIVE KINASE 1 (PINK1) AND PARKIN

As we have mentioned earlier, another merit of medaka, besides the ease with which it can be exposed to various substances, is the wealth of information and genetic tools available: the medaka draft genome, the presence of polymorphic inbred stains and the Targeting Induced Local Lesions In Genomes (TILLING) library [40]. The TILLING library was generated and screened as outlined in Fig. 5. Founder male fish were repeatedly mutagenized with N-ethyl-N-nitrosourea (ENU), a chemical mutagen, crossed with female wild-type females, and the progeny were used to establish a permanent cryopreserved resource of 5,771 F1 males. The DNA taken from the bodies of the F1 males were used to screen for mutations. The average ENU-induced mutation frequency for the library was found to be 1 mutation per 345,000 bp.

We used the TILLING library to screen for loss-of-function mutations in human autosomal recessive PD homologous genes in medaka (Fig. 6) and identified a mutation in the homologous medaka PINK1 gene (PARK6), the PINK1 Q178X mutation.
RT-PCR and in situ hybridization analysis of PINK1Q178X homozygous mutant brains have revealed a relatively small number of PINK1 transcripts, verifying that this is a loss-of-function mutation. Homozygous mutant fish display a phenotype very close to that of human PD patients: normal development and growth, a slight shortening of life span, late-onset reduction of spontaneous movements, and a decrease in the levels of 3,4-dihydroxyphenylacetic acid, a dopamine metabolic product [41]. However, 18 month old fish did not disclose any dopaminergic cell loss similarly to a mouse PINK1 knockout model [42]. We also produced Parkin mutant medaka, but this model also did not show robust phenotype as far as the homozygous mutants are concerned according to our present data (Matsui et al., unpublished). However, the negative phenotype of Parkin mutant medaka is also similar to that of Parkin deficient mice [43].

In the future, it would be interesting to expose these genetic medaka models to various toxins or create double or triple mutants to provide further insights into PD pathogenesis. We are also currently analyzing other genetic mutants in our laboratory in the hope of creating better genetic PD models.

**CONCLUSION**

We, for the first time, developed toxin- and mutation-induced PD models in medaka fish. PD research using medaka fish is making novel and unique contributions to the understanding of the pathogenetic mechanisms and pathophysiology of PD as we have discussed in this short review article.

However, much work remains to be done and, in relation to the selective degeneration of the middle diencephalic dopamine cluster in our toxin models, further analysis of the function of the telost dopamine system should be given much importance. In parallel, the establishment of a synucleinopathy model that recapitulates clinico-pathological features of idiopathic PD will significantly help in the study of the pathophysiology and in the creation of therapeutic agents for PD. The application of transposons has made it easy to generate transgenic medaka fish [44], thus we can make not only "knock-out" models but also transgenic models including alpha-synuclein transgenic fish.

We hope that in the future the studies based on medaka fish models combined with other research using teleost fish will be instrumental in the development of effective drugs for PD as well as for other neurodegenerative diseases.

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