Translational Models of Parkinson's Disease and Related Movement Disorders

Edited by

WAEL MOHAMED

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Dedication

I extend my heartfelt gratitude and deep appreciation as I dedicate this work to my wife, Dr. Rehab Ismaeil. Your unwavering support and limitless love have consistently served as pillars, guiding me through my academic journey and beyond. I am truly thankful for the love and motivation you bring into my life, acknowledging that none of this would have been attainable without you by my side. Your culinary expertise, featuring easy and delicious recipes in your homemade meals, not only satisfies my appetite but also nourishes my mind, providing food for thought.

Wael Mohamed
Pahang, Malaysia

Contents

3. Diagnosis and biomarkers of Parkinson's disease and related movement disorders

Mahmoud A. Ebada, Adel Mouffokes, Muhammad Imran, Mahmoud Tarek Hefnawy, Youssef Soliman, Mohamed El-Samahy, Ateeba Kamran, Tungki Pratama Umar, Basma Ehab Amer, Maged Elsayed and Mrinmoy Kundu

4. OMICS and bioinformatics in Parkinson disease and related movements disorders

Engy K. Tharwat, Hossam Hatem, Ahmed Sameh, Basmala A. Sultan, Salma Yehia and Omnia A. Abdelazeem

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Preface

Navigating the complexities of illness without the guidance of books is like sailing into the unknown, yet studying books without the experience of patients is to stay anchored in the harbor.

Sir Thomas Browne (1605–1682)

Welcome to the "Translational Models of Parkinson's Disease and Related Movement Disorders." In the realm of neuroscience, the study of neurodegenerative disorders stands at the forefront of scientific inquiry and medical innovation. This comprehensive book serves as a vital resource for researchers, clinicians, and students seeking a profound understanding of the intricate complexities surrounding Parkinson's disease.

Neurodegenerative disorders, characterized by the progressive degeneration of the structure and function of the nervous system, pose significant challenges to both affected individuals and the global healthcare landscape. The ever-growing prevalence of these conditions necessitates a multidisciplinary approach that spans basic science, clinical research, and therapeutic development.

This book is crafted with the intention of providing a state-of-the-art compendium that not only reviews the current knowledge on the mechanisms underlying Parkinson's disease but also delves into cutting-edge diagnostic methodologies and therapeutic interventions. Each chapter is meticulously curated to offer a blend of foundational concepts and the latest advancements in the field.

The journey through this book begins with a comprehensive exploration of the molecular and cellular mechanisms driving Parkinson's disease. From the intricate interplay of genetic and environmental factors to the cascading events leading to neuronal demise, readers will gain insights into the intricate tapestry of neurodegenerative processes.

Moving forward, the book meticulously examines the evolving landscape of diagnostic approaches. In an era of precision medicine, understanding the early indicators and developing accurate diagnostic tools is crucial for timely intervention. The exploration encompasses a variety of modalities, from advanced imaging techniques and biomarker discovery to innovative neuroimaging technologies.

The latter sections of the book are dedicated to the horizon of therapeutic possibilities. From traditional pharmaceutical interventions to emerging gene and cell-based therapies, this section provides a comprehensive overview of the current and potential future strategies for managing and, ultimately, halting the progression of Parkinson's disease.

Parkinson's disease and related movement disorders pose profound challenges to individuals, families, and societies worldwide. The quest to understand, treat, and ultimately conquer these conditions has been a journey marked by perseverance, collaboration, and innovation. In this volume, "Translational Models of Parkinson's Disease and Related Movement Disorders," we embark on a comprehensive exploration of the intricate landscape of these neurological conditions.

The genesis of this book stems from the collective efforts of dedicated researchers, clinicians, and advocates who have committed their expertise and passion to unraveling the complexities of Parkinson's disease and related disorders. Through translational research—bridging the gap between basic science and clinical practice—we aim to illuminate the underlying mechanisms, identify novel therapeutic targets, and pave the way for more effective treatments.

Each chapter in this volume represents a milestone in our understanding of Parkinson's disease and related movement disorders. From elucidating the molecular pathways implicated in neurodegeneration to developing cutting-edge animal models that faithfully recapitulate the clinical manifestations, the contributions herein offer invaluable insights into the pathogenesis, diagnosis, and management of these conditions.

Importantly, this book underscores the interdisciplinary nature of translational research, highlighting the indispensable role of collaboration across diverse fields—from neurobiology and genetics to pharmacology and clinical medicine. By fostering dialogue and synergy among researchers and practitioners, we aspire to accelerate the translation of scientific discoveries into tangible benefits for patients and their families.

As we delve into the pages of "Translational Models of Parkinson's Disease and Related Movement Disorders," let us reflect on the collective determination to confront these formidable challenges. May this volume serve as a beacon of hope, guiding us toward a future where Parkinson's disease and related disorders are not merely managed but conquered.

In assembling this book, my aim is to foster a deeper understanding of Parkinson's disease and to inspire collaborative efforts across disciplines. I extend our gratitude to the contributors who have shared their expertise and experiences, making this handbook an asset for researchers and practitioners navigating the intricate landscape of Parkinson's disease.

May this book serve as a beacon for those dedicated to unraveling the mysteries of PD and related movements disorders, offering a roadmap toward advancements in diagnosis and innovative therapeutic strategies, ultimately bringing us closer to a future where these devastating disorders can be effectively treated and, perhaps, prevented.

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Acknowledgments

The completion of this book, "Translational Models of Parkinson's Disease and Related Movement Disorders," represents a collaborative endeavor that would not have been possible without the contributions and support of numerous individuals and organizations. First and foremost, I express my deepest gratitude to the researchers, clinicians, and experts in the field of Parkinson's disease and movement disorders whose dedication and insights have enriched the content of this volume. Your relentless pursuit of knowledge and commitment to improving patient outcomes serve as an inspiration to us all.

I extend my appreciation to the editors, reviewers, and contributors whose meticulous attention to detail and scholarly rigor have ensured the quality and accuracy of the information presented in this book. Your expertise and scholarly contributions have been instrumental in shaping its content and scope.

I also thank the publishing team for their professionalism, guidance, and support throughout the editorial and production process. Your expertise and dedication have been invaluable in bringing this project to fruition.

Lastly, I express my gratitude to our families, friends, and colleagues for their unwavering encouragement, understanding, and patience during this project. Your support has been a source of strength and motivation, enabling us to overcome challenges and achieve our goals.

Together, we have endeavored to create a comprehensive resource that advances our understanding of Parkinson's disease and related movement disorders and fosters collaboration and innovation in translational research. It is our sincere hope that this book will serve as a valuable reference for researchers, clinicians, students, and stakeholders dedicated to improving the lives of individuals affected by these conditions.

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Chapter 13

Various zebrafish models of Parkinson's disease: What gives us hope

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1. Introduction

The selection of appropriate animal models to study neurodegenerative and neurodevelopmental disorders, including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease, schizophrenia, and epilepsy, depends on various criteria and limitations (Pienaar et al., 2010). An ideal animal model of PD should demonstrate histopathological characteristics such as progressive loss of dopaminergic neurons and nondopaminergic neurons, with symptoms appearing in adulthood (Barnhill et al., 2020). These models should also mimic clinical manifestations of PD, including motor features responsive to L-DOPA therapy, like bradykinesia, rigidity, postural instability, and resting tremor (Breger & Fuzzati Armentero, 2019; Pienaar et al., 2010). Rodent and primate models have been developed to explore disease mechanisms and enhance therapeutic outcomes using neurotoxic substances or genetic manipulation. Various toxins, such as 6-hydroxydopamine (6-OHDA), rotenone, paraquat, and 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP), have been used to selectively destroy nigrostriatal DA neurons, resulting in PD-like symptoms in animals (Burns et al., 1983; McKinley et al., 2005). Rotenone models are preferred for assessing neuroprotection due to their independent mechanism of neurotoxicity from the DA uptake transporter (DAT) (Pienaar et al., 2009; Tapias et al., 2010). Though these models offer valuable insights, they do not fully replicate all human PD symptoms. Transgenic approaches involving gene manipulation, such as overexpression, knock-out, knock-in, and knock-down of PD genes, have been used to study PD (Sfar et al., 2009; Xiong et al., 2009). However, high-throughput screenings for genetic interactions or pharmacological therapies can be costly and time-consuming when using murine or nonhuman primate models (Faust et al., 2009). As alternatives, models involving zebrafish (ZF), fruit flies, nematodes, and anurans have gained attraction due to their efficiency and contribution to understanding disease mechanisms and novel therapeutic strategies (Pienaar et al., 2010).

2. Available animal models to study and conduct research on PD

Furthermore, when selecting an animal model for preclinical research, specific criteria must be met, including information accessibility, tractability, and comparative translational potential (Dietrich et al., 2020). Model organisms are chosen based on their comparable physiology, anatomy, genetic homogeneity, and response to treatments similar to humans (Barré-Sinoussi & Montagutelli, 2015; Pienaar et al., 2010). Throughout history, researchers have introduced various animal species as study models in scientific research, including roundworms (*Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*), ZF (*Danio rerio*), rodents (*Mus musculus* and *Rattus norvegicus*), and nonhuman primates (Chia et al., 2020). In neuroscience research, conducting human-based studies is challenging and limited, mainly because experiments on the brain need to be done in vitro, often only feasible postmortem (Shamoo, 2010). Therefore, animals with significant functional similarities to humans, such as fruit flies, rodents, and ZF, offer excellent alternatives for comprehensive nervous system studies, benefiting from their impressive heart physiology and anatomy. ZF, scientifically known as *Danio rerio*,

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has been a prominent model for neuroscience-related studies for the past 3−4 decades (Razali et al., 2021). As a freshwater teleost of the Cyprinidae family, ZF 's use in neuroscience research has been optimized by developing methodologies and techniques (Razali et al., 2021). Due to its close neurofunctional and behavioral similarities to humans, ZF has become an excellent model for neurodegenerative, neurodevelopmental, and neuropharmacological studies (Razali et al., 2021). Its well-characterized nervous system positions ZF as a promising replacement for rodent models in studying PD, the second most common neurodegenerative disease after Alzheimer's (Poewe et al., 2017). As we focus on ZF in neuroscience research, particularly regarding PD studies, these aquatic creatures have gracefully established themselves as a potent animal model for investigating and combatting this chronic and progressive neurodegenerative disease.

3. What are zebrafish?

The involvement of ZF in the research world traces back to the 1950s when molecular biologist George Streisinger, based at the University of Oregon, recognized its potential (Barnhill et al., 2020). Over the subsequent decade, researchers delved into numerous investigations, mainly focusing on the development of the nervous system, leading to profound insights (Razali et al., 2021). In 1998, the National Institute of Health (NIH) established the groundbreaking Trans-NIH Zebrafish Initiative, formally acknowledging ZF as a valuable animal model in scientific studies (Razali et al., 2021). Since then, ZF have played pivotal roles as model organisms in diverse research domains, encompassing neurodegeneration, neurodevelopment, neurobehavior, toxicology, and drug discovery (Razali et al., 2021).

4. Understanding the behavioral neuroscience of zebrafish animals

Zebrafish stands out as an ideal model for behavioral neuroscience due to its diverse cognitive processes, mirroring those of humans, encompassing learning, memory, fear, anxiety, perception, social skills, and even sleep patterns (Biase et al., 2013; Pisco et al., 2013). ZF with high anxiety levels exhibit distinct behavior, spending more time at the edges and bottom of a novel tank, indicating thigmotaxis (Razali et al., 2021). Regarding learning and memory functions, ZF demonstrate remarkable capabilities in associative learning, avoidance learning, object discrimination learning, spatial learning, and more (Razali et al., 2021). For instance, the object discrimination test assesses their memory retention by introducing a novel object and observing their recognition after specific time intervals (Razali et al., 2021). Studies have revealed the involvement of specific brain regions, such as the ZF telencephalon and thalamus, in processing visual discrimination (Messina et al., 2020). Another insightful behavioral task is the avoidance learning test, where ZF learn to avoid electric shocks by refraining from swimming into a dark compartment. This test demonstrates ZF 's ability to acquire avoidance learning and encode it into long-term memory (Blank et al., 2009). Through such comprehensive cognitive assessments, ZF has proven to be a valuable model in unraveling intricate behavioral processes relevant to neuroscience research.

5. Using zebrafish as an animal model: Advantages and disadvantages

Zebrafish exhibit behaviors and phenotypes that closely resemble human behaviors. Neurotoxin-induced ZF display movement impairments like decreased swimming speed and abnormal swimming behavior, akin to bradykinesia-like symptoms observed in PD patients (Blank et al., 2009). Notably, genomic analysis reveals that the ZF genome shares 70% similarity with the human genome, with 80% of genes located in the same chromosome order, indicating conserved synteny between the two species (Blank et al., 2009). ZF's unique attributes make it an exceptional model for research. External and transparent embryo development allows real-time study of the developmental process (Ali et al., 2011), and their embryos readily absorb compounds or neurotoxins (d'Amora Silvia, 2018). Advantages over other animal models include high fecundity, with ZF laying 200−300 eggs per week, enabling larger sample sizes and more significant results (Hoo et al., 2016). ZF also reach sexual maturity in just 3−4 months and have an average lifespan of 3−4 years, contributing to shorter experimental timelines and reduced costs (Gilbert et al., 2013; Njiwa et al., 2004). Furthermore, ZF husbandry and maintenance protocols are simpler and less complicated compared to rodents and nonhuman primates (Avdesh et al., 2012). These combined advantages underscore ZF's exceptional value as a model organism, offering profound insights into various research areas with potential implications for understanding human health and disease.

6. Challenges of the zebrafish model

While ZF offer numerous advantages for research, it is essential to acknowledge their limitations as a model organism. One significant drawback is the relative scarcity of accessible information regarding ZF strains and transgenic models compared

to widely studied organisms like rodents. The availability of validated reagents, such as test kits and antibodies, that react with ZF is also limited, which can hinder postsacrifice molecular analyses. When evaluating drug efficacy, the external development of ZF embryos allows real-time observation, but variations in drug uptake, especially when administered orally, can lead to heterogeneous results. Additionally, differences in metabolism pathways and uptake rates of drugs or chemicals in ZF embryos compared to humans need careful consideration to avoid result misinterpretations (Ali et al., 2011). ZF's natural ability for regeneration and neurogenesis poses challenges for PD studies, as it complicates the establishment of a stable PD model. For instance, the dopaminergic neuronal population in the olfactory bulb of adult ZF can regenerate to normal levels within 45 days after ablation . While this regenerative ability is disadvantageous for degenerative studies, it offers valuable insights into regenerative pathways that could be potentially applied to humans.

These animals have proven to be powerful model organisms, but researchers must be aware of these limitations and consider them while designing experiments and interpreting results. By recognizing and addressing these shortcomings, the scientific community can harness the full potential of ZF research while making informed and meaningful discoveries.

7. Zebrafish as a model for Parkinson's disease

Extensive research on ZF has enabled the detailed mapping of their dopaminergic nervous system (Fig. 13.1) since their recognition as a model organism in 1998. ZF, and vertebrates like humans, share anatomical features that make them suitable for studying PD-related mechanisms. In ZF embryos, dopaminergic neurons appear as early as 19 h post-fertilization in the posterior tuberculum of the ventral diencephalon, equivalent to the human substantia nigra, and these neurons project to the ventral telencephalon, equivalent to the human striatum, resembling the nigrostriatal dopaminergic nervous system (Flinn et al., 2008). This system's resemblance to human PD pathology makes ZF a valuable model for studying related molecular mechanisms.

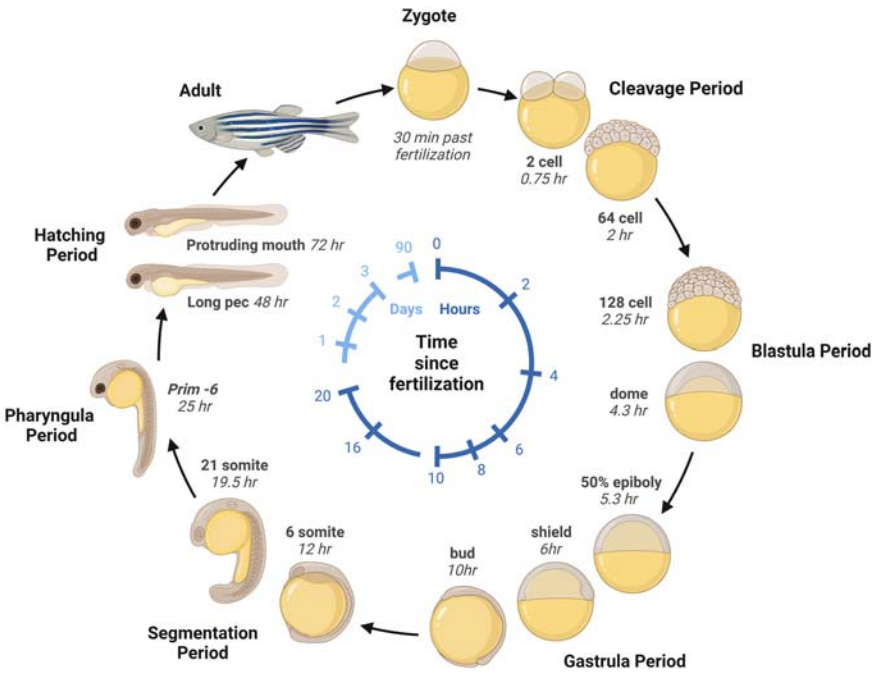

FIGURE 13.1 Zebrafish lifecycle and development. This figure illustrates the life cycle and developmental stages of zebrafish (*Danio rerio*). From fertilized embryos, zebrafish undergo rapid and transparent embryogenesis, progressing through various developmental stages, including gastrula, segmentation, and hatching. The larvae eventually mature into adult zebrafish with fully formed organs and systems, enabling researchers to study the complexities of various biological processes. Recent research advances have been integrated to researching on zebrafish such as (A) CRISPR technology: Zebrafish has become a powerful model organism for utilizing CRISPR/Cas9 gene editing technology. The precise and targeted gene manipulation facilitated by CRISPR has allowed researchers to create specific genetic modifications in zebrafish, mimicking human disease mutations and investigating gene function. (B) Drug libraries: Zebrafish has emerged as an ideal platform for high-throughput drug screening due to its transparent embryos and fast development. Researchers can efficiently test large libraries of compounds to identify potential drug candidates for various neurological disorders, including Parkinson's disease. (C) Analysis of phenotypes: Zebrafish's ease of genetic manipulation and rapid development has enabled the analysis of phenotypic changes associated with neurodegenerative diseases. By inducing specific genetic modifications or exposing zebrafish to environmental factors, researchers can study various phenotypic changes, contributing valuable insights into the pathogenesis of neurological disorders.

Zebrafish Parkinson's models encompass two main types: the neurotoxin-induced model and the transgenic model. The neurotoxin MPTP is commonly used to induce PD-like symptoms in ZF, causing the degeneration of DA neurons and reducing dopamine, norepinephrine, and serotonin levels in the brain, particularly in the posterior tuberculum of the ventral diencephalon. The ZF PD model induced by MPTP displays motor dysfunctions, including reduced swimming speed and abnormal swimming behaviors, analogous to bradykinesia in PD patients. Another frequently used neurotoxin is 6-hydroxydopamine (6-OHDA), which, as an oxidative dopamine analog, leads to mitochondrial dysfunctions and the death of DA and noradrenergic neurons (Soliman & Abdellatif, 2023; Tolba et al., 2023; Wadan & Liaquat, 2024; Wadan et al., 2024). In contrast, the transgenic model utilizes ZF with targeted mutated genes to mimic autosomal dominant or recessive PD in humans. The wealth of information on ZF dopaminergic neuronal projections and their compatibility with experimental manipulations provide this species a distinct advantage for investigating molecular mechanisms associated with PD (Mohamed et al., 2023; Sayed et al., 2024; Sanaeifar et al., 2024).

8. Neurotoxin-induced zebrafish model of PD

MPTP, 6-OHDA, paraquat, and rotenone are commonly used neurotoxins to induce PD-like symptoms in ZF. MPTP causes degeneration of dopaminergic neurons and motor dysfunction. 6-OHDA leads to selective dopaminergic and noradrenergic neuron loss and decreased locomotion and dopamine levels. Paraquat enhances oxidative stress in dopamine neurons, resulting in variable effects on behavior and dopamine levels in ZF. Rotenone acts as a redox cycler and has mixed effects on dopaminergic neurons and locomotion in ZF.

8.1 Transgenic zebrafish models of PD

Parkinson's disease does not naturally occur in animals, and due to its slow progression in humans, no single animal model can fully replicate all aspects of the disease. However, different animal models can be used to study specific aspects of PD. For instance, rodents can be used to selectively kill dopamine neurons, resulting in some motor features of PD, making them suitable for testing medicines to alleviate symptoms. Other models focus on investigating underlying molecular mechanisms, such as α-syn aggregation and dopaminergic cell loss. ZF offers distinct advantages over many other models (Barnhill et al., 2020; Guo, 2004). The transparency of ZF embryos and larvae allows noninvasive imaging techniques to study neuronal integrity, proteostasis, mitochondrial functions, and microglial activity using fluorescent reporters. ZF is also a prolific external breeder, enabling easy genetic modification without injuring the parent, reducing variation, and increasing experimental replicates. High-throughput behavioral assays can be performed in ZF larvae, serving as a powerful screening tool, although the range of behaviors that can be measured is limited (Guo, 2004).

Both genetic and toxin-induced ZF models have been utilized for PD research, but certain considerations are essential. Researchers often use embryos and larvae for their transparency, but they should be aware that the study involves a degenerative disease in a developing organism. The timing of toxin exposure is crucial due to rapid embryo development. Factors like chorion integrity and the formation of the blood−brain barrier should also be taken into account during experimentation. When conducting and reviewing ZF studies, careful consideration of these factors maximizes the benefits of using this model organism (Barnhill et al., 2020). While no model is perfect, the use of ZF in PD research has provided valuable insights and advanced our understanding of the disease.

8.2 PINK1 gene mutation

Mutations in the PINK1 gene are the second most common cause of autosomal-recessive early-onset PD. PINK1 is a ubiquitously expressed protein that contains an N-terminal mitochondrial targeting motif and a conserved serine/threonine kinase domain. PINK1 protects neurons against mitochondrial dysfunction and apoptosis induced by stress. In Drosophila, pink1-deficient mutants have mitochondrial defects that lead to degeneration of flight muscles and mild loss of dopamine (DA) neurons (Clark et al., 2006; Park et al., 2006). However, similar defects were not observed in mice with targeted null mutations in pink1 (Gautier et al., 2008; Kitada et al., 2007). In ZF, pink1 is expressed ubiquitously, and the predicted protein has 54% amino acid sequence identity to human PINK1. A previous study reported that MO knockdown of pink1 in ZF resulted in an approximate 40% reduction in the number of DA neurons in the ventral tegmental area (vDC) (Anichtchik et al., 2008). However, this phenotype has not been replicated by other studies. A study has shown that MO knockdown of pink1 in ZF does not cause large alterations in the number of DA neurons in the vDC. However, it was observed that the patterning of these neurons and their projections are perturbed (Xi et al., 2010). The pink1 morphants also show impaired response to touch stimuli and reduced swimming behavior (Xi et al., 2010). The knockdown of pink1 in ZF

also causes mitochondrial defects, such as the loss of cristae and a reduced number of mitochondria, thus affecting mitochondrial function. In addition, the DA neuron clusters of pink1-deficient ZF are more sensitive to 1-methyl-4-phenyl-1,2,3,6-tetrapyridine (MPTP) toxicity (Sallinen et al., 2010). These results indicate that PINK1 plays a role in DA neuron development and function in ZF. Developmental defects in DA neurons, resulting from PINK1 mutations, may also render DA neurons more susceptible to environmental stress. A ZF line with a nonsense mutation in exon seven of the pink1 gene was found in ENU-mutagenesis libraries (Bandmann et al., 2010). This mutation is predicted to result in a partial Pink1 protein with loss of its C terminus and part of its kinase domain. Although there were no obvious behavioral abnormalities, the larvae of this line showed a significant decrease in the number of DA neurons and a reduction in mitochondrial complex I activity. These phenotypes are similar to those observed in parkin-deficient ZF. These latter observations further support the notion that PINK1 and Parkin are in the same pathway in regulating DA neuron development and mitochondrial functions, as was previously suggested by Drosophila PD models. Hence, PINK1 plays a critical role in DA neuron development and function. Mutations in PINK1 can lead to developmental defects in DA neurons and make them more susceptible to environmental stress. This may contribute to the increased risk of PD in individuals with PINK1 mutations.

8.3 DJ-1 gene mutation

Mutations in the DJ-1 gene are a rare cause of autosomal-recessive early-onset PD. DJ-1 is a member of the ThiJ/Pfpl/DJ-1 protein family and is involved in various functions, including its role as a redox-sensitive chaperone and in mitochondria protection against oxidative stress. In Drosophila models, RNA interference-knockdown of DJ-1 led to varying degrees of degeneration of dopamine (DA) neurons and hypersensitivity to oxidative stress (Dawson et al., 2010). However, similar to parkin- or PINK1-null mice, DJ-1-null mice did not show any major abnormality in the number of DA neurons in the substantia nigra pars compacta and in the levels of striatal dopamine (Dawson et al., 2010). The ZF Dj-1 protein shows 83% overall amino acid identity to human DJ-1 (Bai et al., 2006). The amino acids affected by pathogenic mutations in PD patients are especially well conserved in ZF Dj-1. It is expressed through embryogenesis and transcripts are ubiquitously found in all adult tissues with a relatively higher abundance in the brain. MO knockdown of dj-1 in ZF did not cause a decrease in the number of DA neurons. However, DA neurons in dj-1 morphants were more sensitive to hydrogen peroxide or to the proteasome inhibitor MG132. They were also more susceptible to programmed cell death. Upregulation of dj-1 was reported in the brain of ZF subjected to oxidative stress. These findings suggest that DJ-1 has conserved functions in ZF and humans. Mutations in DJ-1 may impair the response of DA neurons to environmental stress and eventually lead to cell death. Therefore, DJ-1 plays a critical role in DA neuron protection against oxidative stress. Mutations in DJ-1 can lead to increased sensitivity of DA neurons to environmental stress and may contribute to the increased risk of PD in individuals with DJ-1 mutations (Baulac et al., 2009).

8.4 α-synuclein (SNCA) gene

The discovery of a mutation in the α-synuclein gene as a cause of autosomal dominant PD (AD PD) shed light on the significance of α-synuclein in the formation of Lewy bodies (LBs), a hallmark of PD pathology (Fig. 13.2). Increased α-synuclein expression due to gene duplication is sufficient to cause PD. While ZF lack α-synuclein expression, they do express β-, γ1-, and γ2-synuclein proteins, with γ1-synuclein shown to function similarly to human α-synuclein. Through genetic technology, researchers have created ZF transgenic models expressing human wild-type α-synuclein. Over-expression and aggregation of α-synuclein in these models led to reduced mitochondrial activity, increased reactive oxygen species (ROS), neuronal apoptosis, and cell death. Recent studies have indicated that intracellular LBs progressively disrupt dopamine neurons by affecting mitochondrial function and inducing oxidative stress, potentially contributing to early-onset PD. ZF transgenic models offer valuable insights into the role of α-synuclein in PD pathology and provide a powerful tool to study disease mechanisms and potential therapeutic interventions.

8.5 Parkinson's disease protein 2 (PARK2) gene

Mutations in the PARK2 gene are linked to early-onset PD and are the most common cause of autosomal recessive PD. The PARK2 gene encodes the Parkin protein, which functions as a ligase responsible for targeting damaged proteins for degradation through autophagy and breakdown processes. Parkin is also involved in mitophagy, degrading damaged mitochondria, and targeting α-synuclein proteins for degradation. In pathological conditions with mutated PARK2 genes, Parkin loses its degrading ability, leading to mitochondrial dysfunction, α-synuclein aggregation, and LB formation, contributing to the development of PD. ZF Parkin protein shares homology and functional similarity with the human

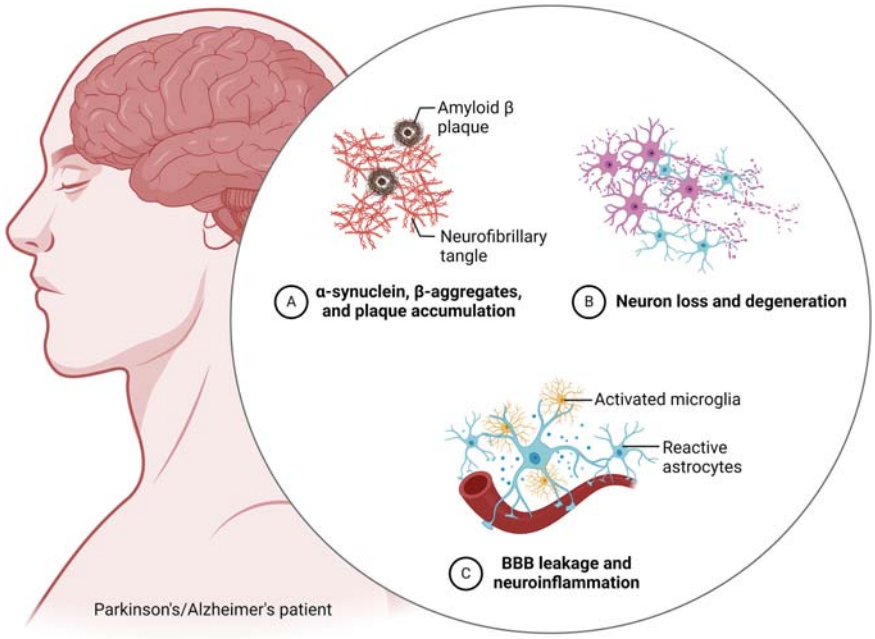

FIGURE 13.2 The hallmarks of Parkinson's disease.

counterpart. Knockdown of the PARK2 gene in ZF disrupted the mitochondrial respiratory chain, reduced dopamine (DA) neurons in the diencephalon, and increased sensitivity to toxic metabolites. The ZF model of PD with a mutated PARK2 gene indicates that the loss of Parkin function disrupts mitochondrial regulation, leading to the loss of DA neurons and perturbation of the DA system. This model offers valuable insights into the role of Parkin in PD pathology and its contribution to the disease mechanism.

8.6 Parkinson's disease protein 7 (PARK7) gene

Mutations in the PARK7 gene are associated with early-onset autosomal recessive PD. This gene encodes the DJ-1 protein, which plays a crucial role in human physiology by regulating genes involved in oxidative stress response mechanisms. DJ-1 helps cells survive oxidative stress by controlling the transcription of genes with antioxidant and antiapoptotic properties. Inactivation of DJ-1 induces the expression of genes responsible for cell apoptosis. In PD patients with inactivated DJ-1 protein, symptoms like young-onset motor disability, muscle rigidity, and tremors are observed. The ZF PARK7 gene is highly similar to human DJ-1, sharing 83% identical sequence. ZF expressing mutated DJ-1 protein exhibit characteristics resembling PD motor symptoms in humans, such as reduced swimming velocity and increased freezing bouts. Knockdown of the PARK7 gene in ZF increases ROS (ROS) production and makes DA neurons more susceptible to oxidative stress. Moreover, the knockdown of PARK7 indirectly leads to DA neuron death by not only increasing ROS levels but also inhibiting proteasomal activity necessary for the mitophagy process. The functional annotations of DJ-1 protein provide important insights into the significance of redox regulation in preventing cellular degeneration and maintaining cell survivability, contributing to a better understanding of PD pathology.

8.7 LRRK2 gene

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are a prominent cause of autosomal dominant PD, accounting for 1% of sporadic cases and 4% of familial cases. The G2019S mutation is the most common, especially in Ashkenazi Jewish people or North African Berbers, along with other pathogenic variants. Although the penetrance of LRRK2 mutations is generally low (approximately 25%), patients with these mutations exhibit similar symptoms to idiopathic cases and often have α-synuclein-containing LBs. LRRK2 is a protein with several functional domains, including a serine/threonine kinase and a GTPase domain. Most pathogenic mutations in the LRRK2 gene are believed to result in a toxic gain-of-function increase in kinase activity. Thus, inhibiting the kinase activity is considered a potential therapeutic target for both LRRK2-induced and idiopathic PD.

Zebrafish have a homolog of the human LRRK2 (hLRRK2) gene, with the protein containing all the functional domains of the human counterpart. The kinase domain is particularly conserved in ZF, sharing 71% homology with the human LRRK2 protein. While gain-of-function increase in kinase activity is the most likely mechanism leading to PD in LRRK2 mutations, ZF researchers have focused on knocking down the ZF LRRK2 (zLRRK2) gene. Morpholino (MO) knockdown of zLRRK2 in ZF results in embryonic lethality with severe morphological and neuronal defects, including the loss of tyrosine hydroxylase (TH)-positive neurons. However, the effects of targeted deletion of the Trp-Asp-40 (WD) domain of zLRRK2 using MO are less clear, with conflicting results reported by different research groups. Some studies have observed a Parkinson's phenotype with loss of TH + neurons and locomotive dysfunction, while others could not reproduce these findings despite using the same reagents. These discrepancies warrant further investigation to better understand the role of LRRK2 in ZF and its implications for PD research.

9. Defined toxins associated with PD

Zebrafish have been a valuable tool in investigating if the associations between exposure to environmental toxins, especially pesticides, and an increased risk of developing PD represent causality.

9.1 Rotenone

Rotenone, a mitochondrial complex I inhibitor, has been linked to an increased risk of PD. In rats, systemic administration of rotenone leads to α-syn accumulation, loss of dopamine neurons, and motor deficits. However, when administered systemically to adult ZF, it did not affect dopamine neurons or locomotion in one study (Bretaud et al., 2004), but other studies reported decreased dopamine levels, locomotion, and olfaction when exposed to water (Wang et al., 2017; Ünal et al., 2020). Exposure of ZF embryos to rotenone resulted in a moderate loss of dopamine neurons, decreased locomotion, and occasional cardiac defects, but the selectivity of the neuronal loss was not determined (Kalyn et al., 2019).

9.2 Paraquat

Paraquat, similar to MPTP in structure, was initially studied due to its resemblance. However, it was later discovered that, unlike MPTP, paraquat does not act as a substrate for DAT or a complex I inhibitor. Instead, it functions as a redox cycler, leading to increased oxidative stress in dopamine neurons (Bus & Gibson, 1984). Mammalian exposure to paraquat results in approximately 20% dopaminergic neuron decrease and evidence of oxidative stress. When combined with the fungicide maneb, the loss of dopamine neurons is significantly enhanced (Thiruchelvam et al., 2000). Epidemiological studies also suggest an increased risk of PD when exposed to both maneb and paraquat (Wang et al., 2011).

Studies involving ZF and paraquat have yielded mixed results. Some experiments showed no effect on embryos when treated with paraquat up to a certain concentration (Bretaud et al., 2004), while others observed decreased locomotion, dopamine, serotonin, and evidence of oxidative stress (Nellore & Nandita, 2015). Treatment with paraquat at different developmental stages of ZF resulted in a 16% decrease in dopamine neurons and altered expression of DAT and TH (Kalyn et al., 2019). In adult ZF, intraperitoneal injection of paraquat led to decreased locomotion, increased dopamine concentration, and decreased DAT expression, but no change in TH expression (Bortolotto et al., 2014). However, when adult ZF were exposed to paraquat in water for 4 weeks, no significant effects were observed (Bretaud et al., 2004).

9.3 Ziram

Exposure to ziram has been linked to an increased risk of PD (Wang et al., 2011; Chou et al., 2008). To investigate the plausibility of this association, ZF embryos were exposed to 50 nM of ziram at 24 h postfertilization (hpf), resulting in a specific loss of dopaminergic neurons and altered swimming behavior in the dark, similar to dopamine blockage (Lulla et al., 2016). Notably, the loss of dopamine neurons was found to be dependent on γ1-synuclein, as knockdown with MO provided protection. Additionally, the drug CLR01, which breaks apart γ1-synuclein fibrils, also showed a protective effect (Lulla et al., 2016).

9.4 Benomyl

Benomyl, another fungicide, has also been linked to an increased risk of developing PD. Like ziram, it selectively killed dopamine neurons in ZF (Fitzmaurice et al., 2013, 2014). The toxicity mechanism was attributed to the inhibition of aldehyde dehydrogenase, an enzyme responsible for detoxifying the dopamine metabolite DOPAL (Fitzmaurice et al., 2013, 2014).

9.5 Diesel exhaust particle extracts

Diesel exhaust particle extracts (DEPe), commonly used as a surrogate model of air pollution in health effects studies, were employed to investigate the biological plausibility and mechanisms of toxicity associated with this exposure. ZF embryos treated with DEPe for 24 h (from 24 to 48 h postfertilization) and analyzed at 5 days postfertilization showed a loss of both dopaminergic and nondopaminergic neurons, along with altered behavior (Barnhill et al., 2020; Ritz et al., 2016). Using a transgenic ZF line that measures neuronal autophagic flux (Khuansuwan et al., 2019), it was observed that DEPe inhibited autophagic flux, and enhancers of autophagy were found to be protective against neuronal loss (Alshial et al., 2023).

10. Use of gene editing technology in zebrafish (Ünal & Emekli-Alturfan, 2019)

Recent genetic advancements have made ZF an excellent model for studying neurological diseases, including PD, AD, Huntington's disease, and schizophrenia (Doğanli et al., 2013). Morpholino antisense oligonucleotide microinjection is a widely used technique for transient gene silencing in ZF. By hybridizing to the ATG initiation codon or binding to the exon−intron insertion signal before mRNA, Morpholino halts the translation of specific target mRNA in early development stages. It enables high-throughput gene silencing, but its effectiveness diminishes rapidly after 3 days and is completely lost after 5 days. However, despite being powerful and potentially efficient, morpholino microinjections may have some common issues, such as nonspecific toxicity and nontarget effects on different genes, including triggering a p53-dependent cell death pathway (Bandmann & Burton, 2010; Robu et al., 2007). The toxic effects of p53-induced morpholino exposure in ZF embryos manifest as small heads and eyes, somit and notochord abnormalities, and craniofacial disorders. Due to the limitations of the morpholino approach, interest has grown in alternative strategies for stable silencing. One such strategy is TILLING (targeting local lesions in genomes), adapted from Arabidopsis to ZF, providing stable mutant lines but with low efficiency. Zinc finger nucleases (ZFNs) are DNA-binding proteins that create double-strand breaks in specific genes for targeted genome regulation. ZFNs are injected into ZF embryos at the single-cell stage, and each ZFN contains three genetic finger tails to bind to the target gene on both strands. The Fok1 restriction endonuclease in the ZFN head results in double-strand breaks within the targeted gene, but it is a high-cost technique (Foley et al., 2009). The DNA repairs occur through nonhomologous ends (NHEJ) and homologous recombination (HR) pathways. While NHEJ causes silencing of the repaired region, HR enables genome integration. However, the inability to precisely target desired sequences remains a limitation for all ZFN-based methods (Osakabe & Osakabe, 2014).

An alternative to the ZFN system is transcriptional activator-like effector nucleases (TALENs), which require a pair of TALENs connected to the DNA strands to make cuts at the desired region. When TALENs are mutually bound, the Fok1 endonuclease cuts the targeted DNA sequence, activating DNA repair mechanisms. However, despite high specificity, nontarget mutations have been reported in genome regulation using TALENs (Joung & Sander, 2013). In ZF, the CRISPR/Cas9 system, based on periodically divided palindromic clusters, can achieve very high levels of gene silencing (Irion et al., 2014). In CRISPR technology, the Cas9 endonuclease, along with the targeted RNA sequence, is sufficient for the DNA cut. By creating the Cas9-RNA (SgRNA)-DNA complex, double-strand breaks occur in the target region (Ellakwa et al., 2024). The only prerequisite for this cut is the presence of the NGG sequence called PAM (Protospacer adjacent motif) at the 3′ ends of the target region. In a transgenic ZF model (Tg (dat: CFP-NTR)) generated by Godoy et al. (2015), which expresses cyan fluorescent protein-nitroreductase fusion protein (CFP-NTR) under DAT cis-regulatory elements' control, prodrug metronidazole exposure in 5-day-old larvae resulted in caspase three activation in CFP-positive neurons and reduction in DAT-positive cells.

11. Zebrafish models for the functional genomics of neurogenetic disorders

Zebrafish have been utilized as a model for PD research (Flinn et al., 2008; Kabashi et al., 2011). MPTP treatment in ZF embryos mimicked some PD effects, showing dopaminergic neuron loss, which could be rescued with deprenyl (Bretaud et al., 2004; Lam et al., 2005; McKinley et al., 2005). Several PD-related genes, including UCH-L1, DJ-1, and Parkin, have been studied in ZF. Knockdown of DJ-1 in ZF increased susceptibility to oxidative stress and elevated SOD1 levels, while combined knockdown of DJ-1 and p53 caused dopaminergic neuronal loss. Parkin knockdown led to a significant decrease in ascending dopaminergic neurons in the posterior tuberculum, similar to the substantia nigra in humans (Flinn et al., 2009). ZF models provide opportunities for screening compounds that promote or prevent the Parkinsonian phenotype (Boehmler et al., 2009), aided by GFP-expressing enhancer trap lines (Wen et al., 2008).

12. Conclusion

Animal models are indispensable for understanding disease mechanisms, identifying causes, and advancing treatments. ZF stands out among mammalian models due to its cost-effectiveness, transparency, and genetic manipulability. This review highlights ZF studies investigating the genetic and environmental aspects of PD, offering valuable insights transferable to mammalian models. Future ZF research is likely to involve high-throughput screenings to identify PD-associated environmental toxins and novel therapeutics. Particularly in neurodevelopmental research, Danio rerio has proven to be a valuable platform, benefiting studies on neurodegenerative diseases like PD, Alzheimer's, and Huntington's. ZF's transparent embryos, easy genetic manipulations, and short life cycles have facilitated molecular investigations, including omics studies, surpassing the limitations of primates and rodents.

Currently, ZF serves as an excellent model for studying neurobehavioral aspects relevant to humans and is widely utilized in various fields such as biology, neuroscience, pharmacology, and toxicology research. In this manuscript, we highlight its significance as a model for screening novel drugs targeting neurological disorders. Recent advancements in using ZF to analyze the pathology of PD are discussed. By manipulating the expression of orthologous ZF genes or introducing pathogenic genes linked to human neurodegenerative disorders, researchers have successfully induced morphological, physiological, and biochemical defects in specific neuronal classes, demonstrating functional conservation between human neurodegenerative disease-related genes and ZF. This supports the use of ZF as an alternative model for investigating the molecular basis of PD. With its unique attributes, ZF holds great potential as a high-throughput drug-screening vertebrate platform. Embracing the concept of precision medicine, a comprehensive understanding of disease omics (genomics, proteomics, metabolomics) can aid healthcare practitioners in tailoring treatments to individual PD patients. This patient-centered approach is believed to enhance treatment efficacy by considering each patient's specific needs. Given that most PD cases are sporadic, precision medicine knowledge can guide the selection of the most appropriate therapeutic strategies for individual patients. Although extensive research is ongoing to comprehend PD's etiology and pathophysiology, much remains to be explored, particularly at the molecular genomic and proteomic levels. In this regard, ZF has been and will continue to be an invaluable PD model, especially in studies demanding molecular investigations.

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Index

Note: 'Page numbers followed by f indicate figures, t indicate tables, and b indicate boxes.'

P

R

S

Translational Models of Parkinson's Disease and Related Movement Disorders

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The second most prevalent neurodegenerative condition following Alzheimer's disease is Parkinson's disease, marked by the loss of midbrain dopaminergic neurons and age-related motor impairments. To enhance predictability and management of Parkinson's disease risk, experimental investigations rooted in epidemiological and genetic studies are imperative. ***Translational Models of Parkinson's Disease and Related Movement Disorders*** examines the state-of-the-art methodologies for developing and validating contemporary translational experimental models of Parkinson's disease. It scrutinizes various attributes of these models, including the prion-like properties of α-synuclein, mitochondrial functions associated with the PINK1-Parkin pathway/CHCHD2, and the endolysosomal pathway linked to LRRK2, VPS35, and ATP13A2, employing cultured cells such as patient-derived induced pluripotent stem (iPS) cells. This book emphasizes the potential for introducing novel models for Parkinson's disease and related movement disorders, while also highlighting current advancements, preclinical and clinical developments, and future prospects concerning numerous model systems.

Key features

- Emphasizes the induction and validation of various existing experimental models of Parkinson's disease.
- Offers a comparative overview of different experimental models of Parkinson's disease.
- Explores the advantages and drawbacks of each model, including associated limitations.

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