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Review Article

Zebrafish Brain Regeneration as a Model for Neurorepair in Parkison's Disease

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Abstract: Parkinson's disease (PD) is the fastest-growing neurodegenerative disease in the world. Despite extensive research, its aetiology and pathogenesis remain poorly understood, often leading to delayed or missed diagnoses, especially in early-onset cases. One of the important hallmarks of PD is the progressive loss of dopaminergic neurons in the substantia nigra, which underlies the manifestation of motor symptoms. Current therapeutic interventions, which primarily offer symptomatic relief, do not alter the deteriorating course of the disease. These limitations have led to a greater emphasis on regenerating dopaminergic neurons as a potential approach for PD management. Mammals, however, exhibit limited reparative capacity in renewing cellular components of the central nervous system (CNS), making mammalian-based models unsuited for the understanding of neuroregeneration. As such, the zebrafish (*Danio rerio*) has emerged as a powerful model for neuroregeneration studies given its robust neurogenic potential, high proliferative capacity, and significant genetic and structural homology to the human brain. This review aimed at highlighting current findings on zebrafish neuroregeneration, with particular emphasis on 1) cellular

responses and neuroinflammation following the loss of neurons and 2) brain repair through the regeneration of new neurons through sequential stages of progenitor cell proliferation, migration, and differentiation at the injured brain regions. The latest findings on the conserved neuroregenerative mechanisms in zebrafish further imply translational potential into novel therapeutic strategies against PD, such as drug discovery and activation of endogenous repair pathways. By contrasting the mammalian limitations, this review underscores advances in zebrafish neuroregeneration which could provide new therapeutic avenues for PD.

Keywords: Parkinson's disease, zebrafish, neuroregeneration, dopaminergic neurons, immune cells

1. Introduction

Parkinson's disease (PD) is the most common movement disorder and the second leading neurodegenerative disease in the world, affecting an estimated 8.4 million people globally in 2019 [1, 2]. This number is projected to reach 25.2 million by 2050 due to the ageing of the global population [3]. In many developing nations, a demographic shift is underway, with the proportion of older adults expected to rise from 7% to 14% between 2020 and 2043. This demographic trend raises significant concerns for healthcare systems, as the ageing population is particularly susceptible to age-related diseases [4]. As such, PD presents a growing healthcare burden, with a mortality rate nearly three times that of the general population [2, 5-7]. While the aetiology and pathogenesis of PD remain poorly understood, the progressive loss of dopaminergic neurons underpins the motor symptoms of PD [8, 9]. The loss of dopaminergic neurons is associated with ageing (a major risk factor for PD [10, 11]), whilst genetic mutations [e.g., Synuclein Alpha (*SNCA*), Leucine-Rich Repeat Kinase 2 (*LRRK2*)] [12-14], environmental exposures (e.g., pesticides, diet) [15, 16], and emerging evidence of gut microbiota alterations could potentially contribute to disease susceptibility [17, 18].

Current PD treatments, such as levodopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, and deep brain stimulation (DBS), offer only symptomatic relief but do not alter disease progression [19]. Levodopa, the gold standard, has a short half-life and gives rise to side effects, whereas DBS is associated with surgical risks [20-23]. An emerging strategy against PD is cell replacement therapy, which aims at preventing dopaminergic cell loss and restoring dopamine production by implanting functional dopamine neurons into the striatum [24]. However, this approach not only yielded inconsistent results due to challenges in

producing mature neurons from grafts, but is also associated with safety concerns, immune responses destroying grafted tissue, complex graft preparation, and high treatment costs [4, 25]. Alternatively, there is also an attempt at drug discovery using botanical extracts such as *Nicandra physaloides*, *Pinus succinifera*, and *Piper longum*. These extracts regulate autophagic processes, including initiation, elongation, maturation, and selective degradation, demonstrating neuroprotective effects in neurological models [26]. Baicalein, a flavonoid from *Scutellaria baicalensis*, also exhibits antioxidant, anti-carcinogenic, and neuroprotective properties, with potential benefits in PD patients [27]. However, the clinical efficacy of these extracts remains under investigation and requires further clinical trials.

Given the lack of disease-modifying treatments against PD, current research efforts are directed towards neuroregeneration as an alternative therapeutic strategy. This approach aims at restoring neuronal function through cellular mechanisms, beginning with injury response, followed by proliferation, migration, and differentiation of progenitor cells into damaged brain regions. However, neuroregeneration in adult mammals remains rare and inefficient. The investigation of mechanisms underlying this process in mammalian models is particularly challenging given neurogenesis is largely restricted to specialised niches which include the hippocampus and subventricular zone [28]. Furthermore, neuronal loss in mammalian models persists, and strategies such as foetal dopaminergic cell transplantation or glia-to-neuron reprogramming remain unsuccessful due to immune rejection, poor survival and integration of transplanted cells, as well as incomplete functional recover [29, 30]. Owing to its exceptional capacity to regenerate lost neurons, the zebrafish model has recently emerged as a valuable tool for elucidation of the cellular and molecular mechanisms underlying neural repair [31, 32]. The zebrafish model is highly regarded for its various advantages, including rapid development, ease of maintenance and handling, cost- and space-efficiency, high-throughput screening capabilities, high genetic homology to humans, and conserved brain architecture and physiological functions [33].

Although zebrafish are widely used to study neuroregeneration, most studies focused on developmental neurogenesis or neuroregeneration following spinal cord injuries or developmental neurogenesis [34-38]. As such, the specific cellular mechanisms driving the zebrafish ability to regenerate lost neurons following brain lesions remain to be fully elucidated. Given the distinct responses of mammalian and zebrafish neural stem cells to injury, along with the complexity of neuroregeneration, specific investigations that uncover the pathways that drive the intrinsic regenerative capacity of the injury-induced zebrafish model are essential. That said, there remain considerable knowledge gaps regarding cellular changes following brain lesions. This review aimed at addressing these gaps by highlighting

the cellular mechanisms of injury response and neurogenic repair in zebrafish models, in contrast to mammals.

This review first outlined the pathological cascade of PD, focusing on oxidative stress, mitochondrial dysfunction, and neuroinflammation. It then compared the mammalian glial and immune responses (which featured the microglia- and astrocyte-mediated glial scar formation that restricts neuronal regeneration) with the regenerative responses observed in zebrafish. This comparative framework underpinned the analysis of zebrafish neuroregeneration, emphasising the role of neurogenic niches in driving key regenerative processes, which include progenitor proliferation, migration (involving neuroblasts), and differentiation.

2. Cellular Responses and Neuroinflammation Following Dopaminergic Neuron Damage in PD

PD is marked by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [39, 40]. The dopaminergic neurons project to the striatum via the nigrostriatal pathway, which is essential for motor control [41]. Although the exact mechanisms underlying the pathogenesis of PD remain elusive, it is widely hypothesised that oxidative stress, mitochondrial dysfunction, and neuroinflammation collectively contribute to irreversible cellular damage [16]. Due to their high metabolic demand, dopaminergic neurons are particularly susceptible to oxidative stress, which in turn exacerbates mitochondrial dysfunction [42]. Mitochondrial dysfunction causes reduced mitochondrial complex I (MCI) activity, elevated reactive oxygen species (ROS), adenosine triphosphate (ATP) depletion, and the activation of caspase-3-mediated apoptosis [42-47]. Mitochondrial dysfunction also contributes to α-synuclein aggregation and iron accumulation, which further exacerbate oxidative stress and neuronal damage [48]. Moreover, mitochondrial stress activates inflammatory pathways, promoting the release of pro-inflammatory cytokines such as Interleukin-1 (IL-1), IL-6, and Tumor Necrosis Factor alpha (TNF-α). Mitochondrial deoxyribonucleic acid (DNA) leakage further drives neuroinflammation [44, 49].

Recent research highlighted the pivotal role of neuroinflammation in the pathophysiology of PD and other neurodegenerative disorders [50], where it contributes to the onset and progression of cognitive impairments, including deficits in learning and memory [51]. Initially, immune cells such as microglia and astrocytes infiltrate the central nervous system (CNS) and interact with cytokines, chemokines, and the complement system to facilitate tissue repair and counteract a range of pathological stimuli, including cellular damage, α-synuclein aggregation, environmental toxins, infections, genetic mutations, and

mitochondrial dysfunction [52, 53]. However, chronic activation of these immune responses exacerbates neuroinflammation, compromising blood-brain barrier (BBB) integrity and increasing the brain's susceptibility to neurotoxic agents, ultimately accelerating disease progression by amplifying neuronal damage and hastening the deterioration of neuronal function [54].

2.1. Neuroimmune Responses in Mammalian PD Models: Roles of Glia, Glial Scarring, and Adaptive Immunity

2.1.1. Microglia

Microglia, the primary resident immune cells in the CNS, appear to play a crucial role in the pathophysiology of PD [55-59]. In the event of neuronal injury, microglia undergo proliferation, morphological changes, and activation into a reactive state (i.e., microgliosis) that can be broadly classified as follows [60]:

- M1 phenotype (pro-inflammatory/cytotoxic) which releases cytokines and ROS, driving neuroinflammation and neuronal loss.
- M2 phenotype (anti-inflammatory/neuroprotective) which promotes debris clearance, tissue repair, and regeneration.

In PD, microgliosis predominantly favours the M1 phenotype, thereby driving excessive inflammation and neuronal damage [61]. Activated microglia further modulate astrocytic responses via mediators such as IL-1α, TNF-α, and Complement Component 1q (C1q), establishing a critical signalling axis [60, 62]. Basically, this crosstalk shifts astrocytes toward the neurotoxic A1 reactive phenotype, which compromises normal astrocytic functions [63, 64]. Upon excessive activation, astrocytes undergo hypertrophy, upregulate glial fibrillary acidic protein (GFAP), and form glial scars [52]. These changes impede axonal regeneration and obstruct the infiltration of oligodendrocyte progenitor cells (OPCs) to the lesion site, thereby inhibiting effective neuronal regeneration following injury [65, 66] (Figure 1).

2.1.2. Astrocyte

The reactive astrocyte-driven glial scar formation is a major obstacle to CNS repair following injury in mammals [68]. The glial scar plays a crucial role in stabilising the injured tissue by restoring the physical and chemical integrity of the CNS, re-establishing the BBB, and limiting non-CNS cell infiltration. It also creates a physical and molecular barrier that inhibits axonal regeneration. Axonal regeneration is hindered by myelin-associated inhibitors,

including chondroitin sulphate proteoglycans (CSPGs), Neurite Outgrowth Inhibitor-A (Nogo-A), myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMGP), which are produced by glial scars [69]. This inhibitory effect is compounded by the inefficient clearance of myelin debris by microglia [70].

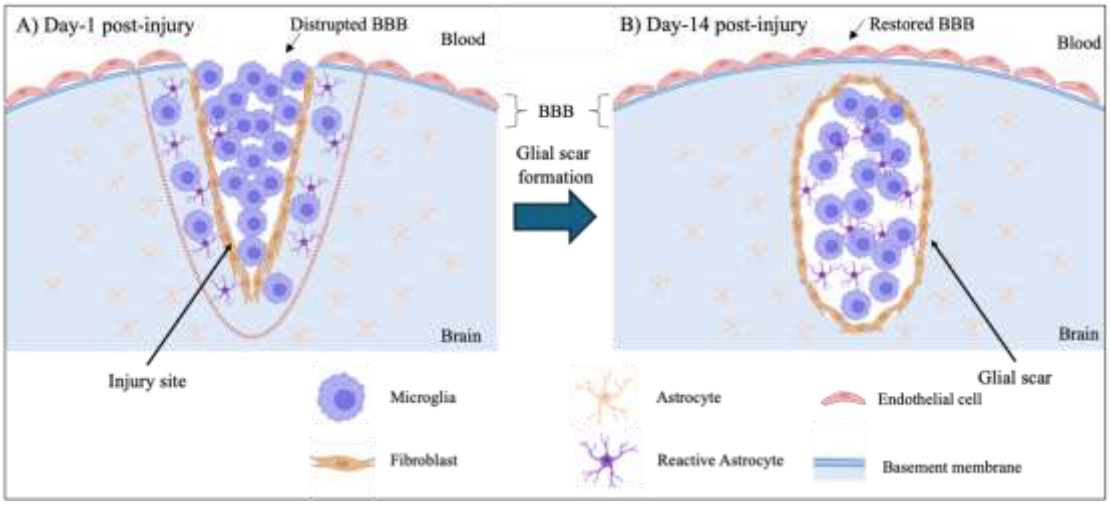

Figure 1. Schematic illustration of scar formation in a lesioned mammalian brain. (A) Following mammalian brain injury, disruption of the blood brain barrier (BBB) triggers macrophage infiltration, astrocyte activation, and fibroblast invasion to the lesion site. (B) Fibroblasts proliferate to form a fibrotic scar, while astrocytic processes restore the BBB integrity and seal the lesion with glia limitans. The resulting glial scar isolates the injury but blocks neuronal regeneration in mammalian brain. Source of information: [67]. Remark: Part of this image was created with BioRender (BioRender.com).

2.1.3. Oligodendrocyte

Recent studies of postmortem PD brain tissue demonstrated significant co-localisation of oligodendrocytes, with alterations in these cells occurring before the onset of motor symptoms and pathological changes in the SNpc [71, 72], suggesting their potential involvement in the pathophysiology of PD. While the association between oligodendrocytes and PD is increasingly recognised, the precise molecular mechanisms underlying oligodendrocytes' role in immune responses remain poorly understood, as their involvement was previously overlooked [73, 74]. Oligodendrocytes are essential for maintaining neural function by producing the myelin sheath around nerve fibres. As such, oligodendrocytes are likely to play a role in neurodegeneration through interactions with microglia and astrocytes, which release cytokines that regulate oligodendrocyte survival and differentiation, thus influencing myelin formation [60, 75]. Damage to or reduced production of oligodendrocytes disrupts myelin production, impairing electrical impulse transmission and contributing to the progression of neurodegenerative diseases [76].

Additionally, growing evidence highlights the involvement of dendritic cells, B cells, and T cells as potential biomarkers and therapeutic targets in PD. These cells are integral to both the initiation and modulation of immune responses. Dendritic cells have been shown to capture and process α-synuclein into small peptides, which are then presented on their surface in association with co-stimulatory molecules to T cells, thereby initiating an adaptive immune response that targets dopaminergic neurons [77]. Chronic inflammation in PD suggests that T cell immunity is critical for disease onset and triggering humoral responses, while humoral immunity contributes to further disease development [78-80].

2.2. Roles of Glia and the Absence of Glial Scarring following Injury in the Zebrafish Brain

The zebrafish brain demonstrates a strong regenerative response to injury, driven by immune cell-progenitor cell interactions. Following neuronal loss in the zebrafish brain, a complex series of cellular events is initiated, involving the recruitment and/or proliferation of various cell types, including microglia, peripheral immune cells, oligodendrocytes and endothelial cells. Understanding the immune responses is critical, as it plays a central role in regulating the zebrafish regenerative response to injury, particularly by influencing the behaviour of neural stem cells and progenitor cells.

While the neuroinflammatory response in zebrafish shares several parallels with that of mammals, a key distinction lies in the temporal dynamics of resolution: inflammation in zebrafish is rapid and transient, avoiding the formation of a permanent glial scar, a hallmark of CNS injury in mammals [81]. This regenerative permissiveness is attributable to several unique features. Firstly, microglial activation is short-lived, with early pro-inflammatory responses (e.g., TNF-α, IL-1β) peaking within 1-3 days of injury, followed by a swift transition to anti-inflammatory states characterised by the release of mediators such as Transforming Growth Factor-β (TGF-β) and IL-10 [82, 83]. This rapid switch facilitates efficient debris clearance while limiting chronic inflammation. Secondly, unlike mammals, zebrafish lack stellate (protoplasmic) astrocytes. Instead, GFAP-positive radial glia persist throughout adulthood, functioning not only as neural progenitors but also as regulators of the immune microenvironment [84, 85]. The presence of radial glia cells enables injury-responsive proliferation without astrocyte-driven scarring. Thirdly, astrocyte-like scarring is absent; zebrafish resolve inflammation without forming permanent scar tissue, thereby maintaining a permissive environment for axonal regeneration and progenitor integration [86-88] (Table 1).

Table 1. Comparison of neuroinflammation response of glial cells after brain damage in mammals and zebrafish.

Glial cells	Mammals	Zebrafish
Microglia reactivity	Present	Present
Presence of astrocyte	Present	Absent
Proliferation of radial glia cells	Absent	Present
Glial scar formation	Present	Absent
Oligodendrocytes precursor cells (OPC) proliferation	Present	Present but dependent on site of injury

In mammals, microglia and astrocytes contribute to a pro-inflammatory environment and glial scar formation, which restricts regeneration. On the contrary, zebrafish lack astrocytes and glial scarring but exhibit robust radial glia proliferation, supporting a regenerative milieu. Although oligodendrocyte progenitor cells (OPCs) proliferation occurs in both species, it is injury-site dependent in zebrafish, reflecting a more context-specific regenerative strategy. These distinctions underscore why zebrafish provide a valuable model for studying neuroregeneration, offering insights into mechanisms absent or limited in mammals. Source of information: [86].

On another note, even though the mechanisms governing the crosstalk between immune cells and ependymal glial cells have been studied, the specific role of OPCs in the critical time window that facilitates neuronal integration during regeneration remains less well understood. In zebrafish telencephalic impaired models, injuries along the rostro-caudal axis did not induce significant proliferation or recruitment of OPCs to the damaged site. In contrast, dorso-ventral injuries led to a prolonged accumulation of OPCs at the injury site. This differential response suggests that the nature of the injury influences OPC activation and accumulation, potentially impacting regenerative outcomes. Further investigations revealed that Toll-like receptor 2 (TLR 2) and chemokine receptor 3 (Cxcr3) played critical roles as regulators of OPC proliferation. Specifically, interference with these innate immune signalling pathways resulted in the alleviation of excessive OPC accumulation at the injury site, which not only promoted more efficient wound healing but also enhanced restorative neurogenesis [89].

3. Adult Neurogenesis Potential in Mammalian and Non-Mammalian Brains: Insights into Zebrafish Neuroregeneration

The belief that the adult brain is incapable of regenerating new cells persisted in neuroscience until Altman and Das [90] discovered neurogenesis in the hippocampus of adult rodents. This groundbreaking finding was later supported by numerous studies, establishing that adult neurogenesis occurs in various species, even though at varying degrees of efficiency [91-95]. In PD, for instance, more than 80% of dopaminergic neurons in the SNpc may be lost before symptoms appear, showcasing the remarkable functional compensatory capacity of the

human brain. This compensatory mechanism triggers a cascade of growth-related events, enabling surviving neurons, both near and distant from the lesion site, to survive, repair, and form new connections. Although endogenous repair mechanisms are present in the adult mammalian brain, their regenerative potential is limited, leaving many patients with neurodegenerative diseases or brain injuries living with enduring deficits. These regenerative processes are also inefficient in other mammalian models, such as mice, with only 0.2% of neurons differentiating into mature cells [28].

Given these limitations in cellular recovery in mammals, considerable attention has been directed towards non-mammalian models to investigate successful neuroregeneration. Neurogenesis in non-mammals occurs over a longer period and is significantly more extensive than in mammals. However, despite evidence of regeneration in the CNS and Peripheral Nervous System (PNS) of non-mammals, newly formed neurons in species like salamanders and newts do not show functional restoration due to a lack of innervation [96]. Among the non-mammalian models, zebrafish have emerged as an excellent model for studying neurogenesis, owing to their significant brain homology with humans and their remarkable ability to fully regenerate lost neurons following brain injury. Neurogenesis is a tightly regulated process involving proliferation, migration, and differentiation, coordinated by signals from neighbouring cells. This cellular recovery in zebrafish is also accompanied by the restoration of sensory and motor functions, with neurogenesis occurring continuously throughout their lifespan [97].

3.1. Proliferation of Newly Generated Cells in the Neurogenic Niches of Mammalian and Zebrafish Brains

Research has identified specific neuronal populations or neurogenic niches within the brain that contribute to adult neurogenesis [98, 99]. These areas, rich in neural stem cells with stem cell-like properties, can generate new neurons in response to injury, aiding recovery by integrating into existing neural circuits [100, 101]. However, neurogenic niches vary across species, influencing neuroregeneration efficiency in different injury contexts [102, 103].

In the mammalian models, adult neurogenesis does not occur throughout the brain area and is highly restricted to two regions, the subependymal zone (SVZ) of the lateral wall of the ventricle and the subgranular zone (SGV) of the hippocampus [96] (Figure 2a). Both the SVZ and SGZ house heterogeneous populations of active progenitor cells, predominantly glial cells, which maintain homeostasis and support neural tissue [104, 105]. Studies show that glial cells in these regions function as neural stem cells, generating neurons through intermediate stages of cell differentiation [106]. The SVZ, located in the telencephalic lateral ventricle, is the primary

site of adult neurogenesis, with progenitor cells migrating to the olfactory bulb where they differentiate into neurons and integrate into the granule and periglomerular layers into neural networks. In rodents, these neuroblasts travel via the rostral migratory stream (RMS), but in humans, the SVZ differs morphologically, lacking a prominent RMS [107, 108].

Similar to mammalian cells, adult zebrafish brain cells retain stem cell-like properties [68]. However, non-mammalian brains, like those of zebrafish, contain embryonic-like pockets of cells that serve as intermediate stages between the germinal zone of the developing brain, contributing to greater neuroregeneration compared to mammals [109]. Zebrafish regeneration is not restricted and occurs widely across 16 distinct neurogenic niches, where new neurons are continuously generated and integrated into other brain regions. The presence of these areas explains why the high rate of proliferating neurons in the zebrafish brain is about double the amount in the adult mammalian brain [110] (Figure 2b). Notably, the dorsal and ventral pallium of zebrafish share substantial homology with mammalian neurogenic niches, making them key areas for studying regenerative processes [111]. Within these proliferative domains, two distinct populations of label-retaining cells were identified: (a) slow-cycling cells along the ventricular surface, and (b) fast-cycling cells organised mainly in a subpallial cluster. Both populations indicate the presence of self-renewing neuronal precursor cells, crucial for sustaining continuous neurogenesis in the adult zebrafish brain.

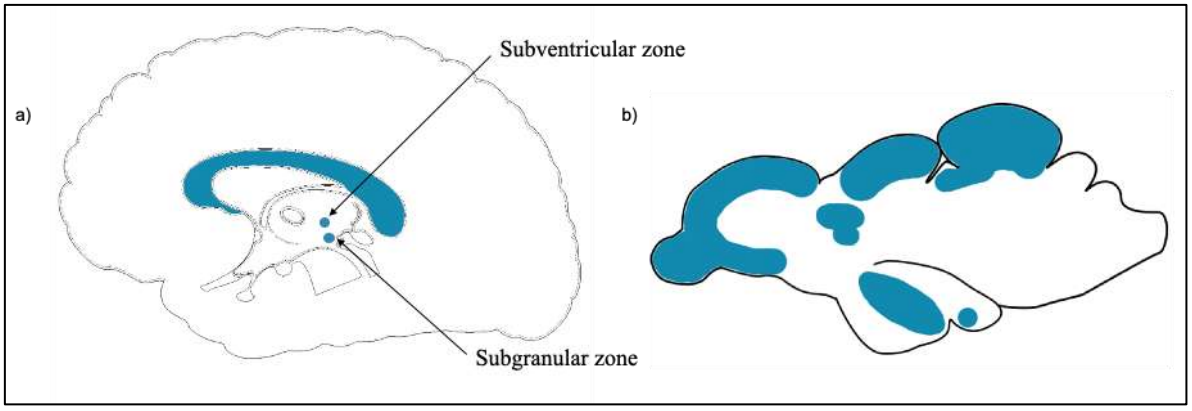

Figure 2. Different neurogenic niches (in blue) in the brains of adult (A) mammal and (B) zebrafish. Source of information: [96]

Various signalling pathways, such as Sonic Hedgehog (Shh), Wingless-related integration site (Wnt) and Notch, are recognised as key regulators of progenitor cell proliferation during adult zebrafish neurogenesis, with Notch signalling being one of the most prominent [112] (Figure 3). Notch receptors, particularly Notch3, play a crucial role in modulating progenitor cell activity and neurogenesis in the adult zebrafish brain. These receptors are predominantly expressed in proliferating glial cells across multiple neurogenic

niches, including the dorsal and ventral telencephalon, hypothalamus, optic tectum, and cerebellum. Notch receptors are essential for the maintenance and activation of progenitor cells, with their expression varying regionally and cell-specifically. Notch3 appears to be more closely associated with promoting glial characteristics in progenitors and glial cells, while Notch1a and Notch1b likely modulate progenitor proliferation in a dose-dependent manner. The combinatorial activity of these receptors is crucial for maintaining neural stem cells populations, as evidenced by a study that demonstrated that inhibition of Notch signalling via γ-secretase inhibitors significantly reduced progenitor cell proliferation in the adult zebrafish brain [103]. Furthermore, Notch signalling is implicated not only in neurogenesis but also in processes such as neuronal maturation, oligodendrogenesis, and vascular homeostasis, highlighting its multifaceted and indispensable role in zebrafish brain regeneration [113].

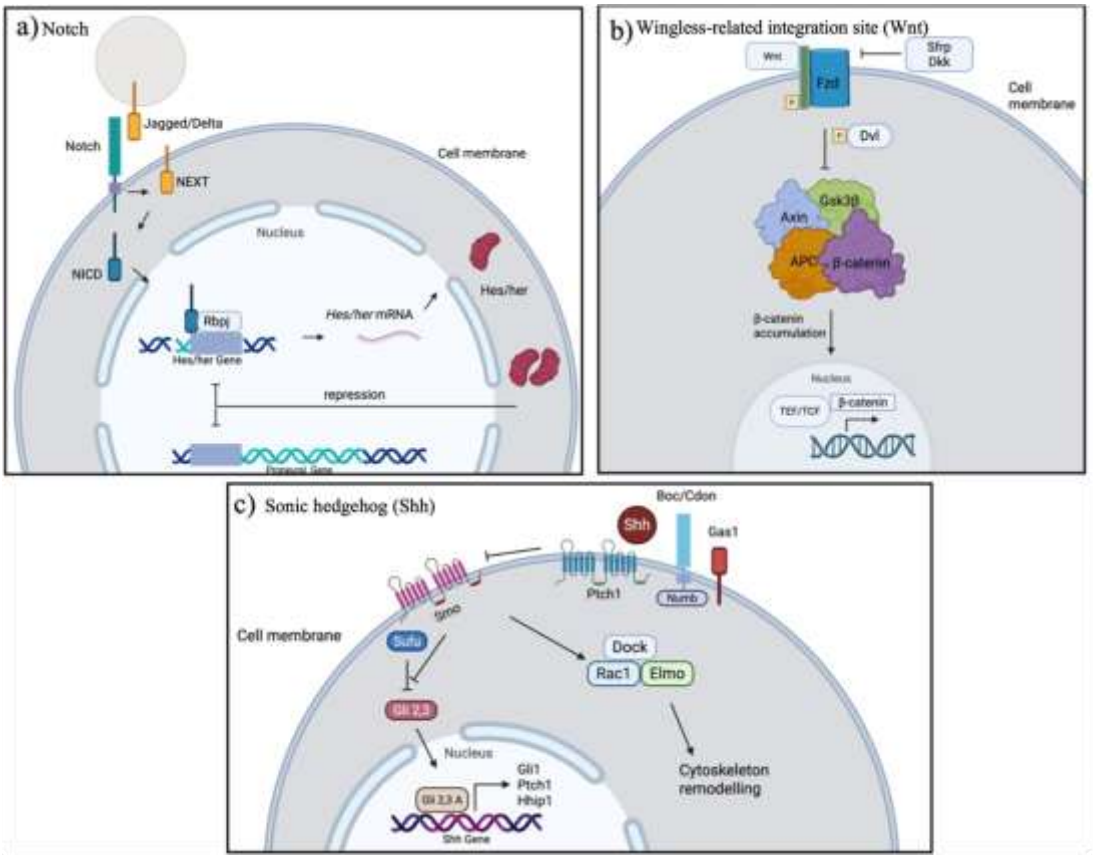

Figure 3. Signalling pathways that regulate progenitor cell proliferation during adult zebrafish neurogenesis. (a) Notch signalling: Binding of Delta/Jagged ligands activates the Notch receptor, releasing the Notch intracellular domain (NICD), which translocates to the nucleus, binds Recombination Signal Binding Protein for Immunoglobulin Kappa J Region (*Rbpj*), and induces Hairy and Enhancer of split/Human Epidermal Growth Factor Receptor (*Hes/Her*) transcription factors that repress proneural gene expression. (b) Wingless-related integration site (Wnt)/β-catenin signalling: Binding of Wnt to the Frizzled (Fzd) receptor activates Dishevelled (Dvl), inhibits the destruction complex [Axin, Adenomatous Polyposis Coli (APC) and Glycogen Synthase Kinase 3 Beta (GSK3β)], and promotes β-catenin accumulation. Stabilised β-catenin enters the nucleus, binds Transcription Enhancer Factor / T-cell Factor (*TEF/TCF*), and drives transcription of proliferation-associated genes. (c) Sonic Hedgehog (Shh) signalling: Binding of Shh to Protein patched homolog 1 (Ptch1) relieves inhibition of Smoothened (Smo), activating downstream Glioma-associated

oncogene (*Gli*) transcription factors that regulate Shh target genes. Additional interactions with Biregional Cdon-binding protein/ Cell adhesion molecule-related/down-regulated by oncogenes (Boc/Cdon), Ras-related C3 botulinum toxin substrate 1 (Rac1), Dedicator of cytokinesis (Dock), and Engulfment and cell motility (Elmo) influence cytoskeletal remodelling during progenitor responses. Source of information: [114-117]. Remark: Part of this image was created with BioRender (BioRender.com).

Rather than functioning in isolation, the Wnt/β-catenin signalling pathway operates as part of a complex regulatory network, interacting with other key pathways such as Transforming Growth Factor-β/Bone Morphogenetic Protein (TGF-β/BMP), Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT), Notch, and Shh, through intricate cross-regulatory mechanisms that directly or indirectly influence the expression of downstream genes associated with these pathways. Wnt ligands bind to Frizzled (FZD) receptors and lipoprotein-related receptors 5 and 6 (LRP5/6) co-receptors, activating Dishevelled (DVL) and inhibiting the β-catenin destruction complex composed of Axin, Adenomatous Polyposis Coli (APC) and Glycogen Synthase Kinase 3 Beta (GSK3β). This inhibition stabilises β-catenin, allowing its accumulation and nuclear translocation. In the nucleus, β-catenin associates with T cell factor/lymphoid enhancer factor family (TCF/LEF) transcription factors to activate target genes such as MycProto-Oncogene Protein (c-Myc), Cyclin-Dependent Kinase Inhibitor 1D (cyclin D1), Cyclooxygenase-2 (COX-2), and Matrix Metalloproteinases (MMPs), which drive cell proliferation and migration [118].

The Shh pathway, another major regulatory axis, is mediated by Patched (Ptch1/2) and Smoothened (Smo). In the absence of ligands, Ptch inhibits Smo activity. Ligand binding relieves this inhibition, allowing Smo to activate the Glioma-associated oncogene (*Gli*) transcription factors. function primarily as activators, while Gli3 acts mainly as a repressor, thereby regulating the expression of Shh target genes [119]. These Shh-responsive cells subsequently function as rapidly proliferating, multipotent neural progenitors that give rise to new neurons [120] .

3.2. Mechanisms of Neuroblast Migration in Mammalian and Zebrafish Brain Injury Repair

Following brain injury in both mammalian and non-mammalian species, neuronal precursor cells migrate to the damaged area, where they attempt differentiation and repair [86]. This migration is a complex process that involves a combination of cellular structures, signals, and cues, primarily directed by neuroblasts [121]. Neuroblast-derived migration is guided by a series of steps involving the extension of the leading process, centrosomal migration, and somal translocation. Importantly, targeted migration in zebrafish is orchestrated by chemotactic cues, most notably Stromal cell-derived factor 1 / C-X-C motif chemokine ligand 12 (SDF1/Cxcl12), which interacts with its receptor C-X-C chemokine receptor type 4 (Cxcr4)

on migrating neuroblasts. This signalling axis directs cells along the injury-induced chemokine gradients, thereby ensuring efficient recruitment of progenitor cells to the lesion sites [122].

The movement is regulated by both cytoskeletal dynamics and external guidance cues such as growth factors [insulin-like growth factor I (IGF-I), vascular endothelial growth factor (VEGF), and fibroblast growth factor 2 (FGF2)] and cell adhesion molecules. These neuroblasts utilise scaffold-like astrocytic processes, blood vessels, and extracellular matrix components to aid in their migration. Brain-derived neurotrophic factor (BDNF), which is secreted by blood vessels, plays a crucial role in promoting neuroblast migration by binding to the p75 neurotrophin receptor (p75NTR) receptor, thereby increasing the number of migratory cells. It also facilitates the transition of neuroblasts from a mitotic to a motile state, thereby enhancing their displacement over greater distances. During migration, neuroblasts are directed along the RMS within glial tubes formed by astrocytes, which help maintain their confinement, prevent dispersion, and ensure proper guidance [123].

The mechanisms underlying neuronal migration are conserved across vertebrates, with neuroblasts exhibiting analogous migratory behaviours in both mammals and non-mammals. However, the intrinsic repair mechanisms of the mammalian brain are largely ineffective, particularly when dealing with large lesions, as migration is typically limited to short distances or impaired in mammalian neurodegenerative animal models [124]. In contrast, newly generated cells in the zebrafish brain have been shown to undergo lateral migration of neural progenitors from the telencephalic ventricular zone towards the injury site on dorsolateral domain of the telencephalic hemisphere [103], as well as migration from the neurogenic regions of the telencephalon and olfactory bulb to the diencephalon [125].

3.3. Differentiation of Newly Generated Cells into Mature Neurons in Non-Mammalian Brains

While there is an increase in proliferating neurons after the cessation of protein aggregate expression, these neurons do not differentiate into mature neurons, a limitation that is often observed in mammalian neurogenesis models of brain pathology [31, 126]. As such, neuroregeneration in mammals is highly restrictive and thus makes it an unsuitable model to understand the differentiation process [127, 128]. Conversely, in injured zebrafish, newly regenerated cells, following significant proliferation and migration, are capable of differentiating into mature neurons. This is evidenced by the expression of the postmitotic marker HuC/ELAVL3 and HuD/ELAVL4 neuronal RNA-binding proteins (HuC/D) and polysialylated neural cell adhesion molecule (PSA-NCAM), a marker of early neuronal differentiation, after the cells migrate to the lesion site [115].

Although the regulation of differentiation in adult neurogenesis is not fully understood, a variety of pathways and neurotrophic factors, including Glial cell line-derived neurotrophic factor (GDNF), BDNF, Fibroblast Growth Factor (Fgf), Shh, Wnt, Notch, and BMP (Bone Morphogenetic Protein), are hypothesised to play key roles in modulating this process [115]. Additionally, transcription factors such as Paired-like homeodomain transcription factor 3 (*pitx3*), LIM homeobox transcription factor 1 beta (*lmx1b*), Nuclear receptor subfamily 4 group A member 2 (*nr4a2a*), Forkhead box protein A2 (*foxa2*), and Orthopedia protein (*otpb*) are also critical for dopaminergic differentiation (Table 2).

Table 2. Key transcription factors that regulate dopaminergic neuron differentiation in zebrafish.

Transcription Factor	Role in Dopaminergic Differentiation	References
Paired-like homeodomain transcription factor 3 (*pitx3*)	• Regulates terminal differentiation and survival of dopaminergic neurons; • • Tyrosine Hydroxylase (TH) expression • Maintenance of mature dopaminergic identity	[129]
LIM homeobox transcription factor 1 beta (*lmx1b)*	• Essential for dopaminergic progenitor specification • Interacts with Glial cell line-derived neurotrophic factor (GDNF) signalling to promote differentiation	[130]
Nuclear receptor subfamily 4 group A member 2 (*nr4a2a*)	• Controls expression of dopaminergic markers such as TH and Dopamine transporter (DAT) • Necessary for dopaminergic neuron maturation	[131]
Forkhead box protein A2 (*foxa2*)	• Regulates early patterning and dopaminergic neuron lineage commitment • Cooperates with nr4a2 in specification	[132]
Orthopedia protein (*otpb*)	• Promotes differentiation of diencephalic dopaminergic neurons • Implicated in progenitor cell fate determination	[133]

A study of GDNF-deficient zebrafish larvae showed a significant reduction in dopaminergic neurons, confirmed by Enhanced Green Fluorescent Protein–positive / Tyrosine Hydroxylase–positive (EGFP+/TH+) neuron counts and impaired locomotor activity. Further investigation into how GDNF influences dopaminergic neuron specification and differentiation revealed its potential interaction with key transcription factors such as *lmx1b.1* and *otpb*, which likely regulate dopaminergic progenitor cell fate [130].

4. Conclusion and Future Perspective

PD remains a significant global health challenge due to its increasing prevalence and the lack of disease-modifying therapies. Despite advances in pharmacological treatments, current therapeutic strategies primarily alleviate symptoms rather than halt disease progression. Neuroregeneration has emerged as a promising therapeutic strategy, with zebrafish serving as a valuable model for understanding the cellular and molecular mechanisms of neuroregeneration. In contrast to mammals, which exhibit limited regenerative capacity, zebrafish demonstrate the ability to regenerate lost neurons and restore function through a highly efficient process involving proliferation, migration, and differentiation of progenitor cells. This review highlights the significance of understanding the cellular responses to injury, neurogenic niches, and transcriptional pathways involved in zebrafish neurogenesis, providing valuable insights into promoting the regeneration of dopaminergic neurons.

Comparative analyses with mammalian systems highlight critical barriers to regeneration in humans, including the formation of inhibitory glial scars and limited progenitor areas. Insights gained from zebrafish models are increasingly informing strategies aimed at promoting neuroregeneration in the mammalian brains. Further research into the interaction between immune cells (particularly microglia, astrocytes and oligodendrocytes) will be vital for advancing regenerative treatments for PD. Moreover, uncovering the role of conserved signalling pathways, such as Notch, Wnt/β-catenin, and Shh, in regulating progenitor fate decisions may offer translational potential for guiding cell-based therapies. Harnessing the regenerative capacity of the zebrafish brain offers promising avenues for developing therapies to restore dopaminergic circuits in PD. Future research efforts, which include Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-mediated perturbation of Notch3 to define its role in progenitor maintenance, high-resolution *in vivo* imaging to track immune-progenitor interactions during regeneration and single-cell transcriptomic mapping to resolve the molecular heterogeneity of neurogenic niches, can be performed to elucidate the molecular basis of zebrafish neuroregeneration and thereby yield insights into the design of regenerative therapies for PD. However, translating the findings from zebrafish to mammals remains challenging. Some of the key obstacles include differences in neurogenic niche organisation, limited progenitor availability, inhibitory glial scar formation, and the difficulty of scaling up regenerative mechanisms to the complexity of the human brain.

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