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Demystifying Nervous System Regeneration: A Comprehensive Review

LEAD ARTICLE

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Abstract

Uncovering mechanisms that govern successful nervous system regeneration will help inform future development of treatments for neurodegenerative disease and brain injury. There are organisms capable of robust nervous system regeneration, but the ability to functionally repair the entire brain is rare. Planarians are freshwater flatworms capable of whole-body regeneration after nearly any injury, including that of their nervous system. Planarians were used as a model to study how successful nervous system regeneration occurs. In this thesis research, six transcription factor-encoding genes were found that are required for the regeneration and maintenance of dopaminergic neurons in the planarian central, peripheral nervous system, and pharyngeal nervous system. Work was done to develop planarians as a model for neurodegenerative disease research through targeted studies and an unbiased screen. The work reviewed here centers around one goal: demystifying nervous system regeneration.

Keywords: regeneration, dopamine, nervous system, planarian, regenerative neurogenesis, neuronal cell fate, specification, transcriptional regulation, differentiation, body patterning, neurodegeneration

Nervous System Development

Development is the process by which a single cell transforms into a complex, multicelled organism. The key stages of development typically include fertilization, cleavage, blastula formation, gastrulation, and organogenesis. Fertilization is when gametes fuse to form a zygote, which will undergo rapid cell division (cleavage) and form the blastula (Gilbert, 2000a, 2000c). During gastrulation, the cells in the blastula will spatially rearrange into three germ layers: the endoderm, mesoderm, and ectoderm (Muhr et al., 2023; Purves et al., 2001b). After gastrulation, the three germ layers will continue to divide and become specialized cell types that form all the inner organs of an organism (Muhr et al., 2023; Purves et al., 2001b). One event critical for organogenesis in vertebrates is neurulation – the process that begins development of the nervous system (Gilbert, 2000b; Purves et al., 2001b).

The vertebrate nervous system is composed of the brain and spinal cord, which make up the central nervous system (CNS), as well as the peripheral nervous system (PNS), which includes all nerves that exist outside of the CNS (Bazira, 2021). In humans, the PNS is split into two subsystems: autonomic and somatic (Bazira, 2021). The autonomic nervous system controls involuntary processes like heartbeat and blood pressure (Bazira, 2021; Gibbons, 2019). Sensory and motor neurons of the somatic PNS, by contrast, are used to carry signals to the brain or carry out commands from the brain, respectively (Bazira, 2021; Ju, 2020). The brain relies on information from the PNS to monitor the internal and external environment and then uses that information to respond to its surroundings. In humans, the enteric nervous system (ENS) is part of the autonomic nervous system in the PNS and innervates the gastrointestinal tract. The ENS acts independently of the CNS, though the ENS and CNS are interconnected through the vagus nerve (Purves et al., 2001a).

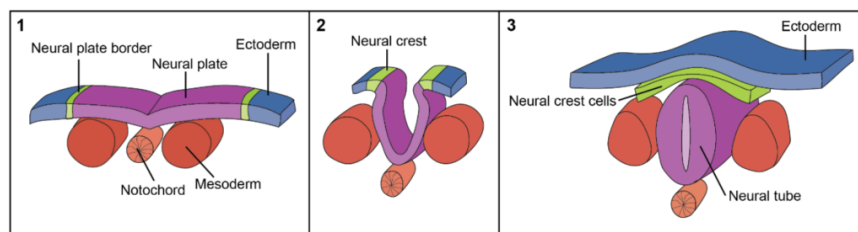
However, other animals organize their nervous systems in other ways. Cnidarians have a simple nervous system and are thought to descend from some of the first animals to possess a nervous system, along with Ctenophores (Burkhardt, 2022; Grimmelikhuijzen & Westfall, 1995; Hiroshi Watanabe, Fujisawa, et al., 2009). The basic Cnidarian nervous system organization is that of a nerve net, in which some locations can be condensed to form more complex structures (Grimmelikhuijzen & Westfall, 1995; Hiroshi Watanabe, Fujisawa, et al., 2009). Echinoderms, in contrast, have three main components to their nervous systems—ectoneural, hyponeural, and endoneuroal systems (Cobb, 1987; García-Arrarás et al., 2001). The ectoneural system has both sensory and motor functions and is composed of the nerve ring surrounding the mouth and the radial nerve cords (Cobb, 1987; Formery et al., 2021; García-Arrarás et al., 2001). The hyponeural system is primarily motor and is composed of the radial nerve cords associated with the skeletal muscle system (Cobb, 1987; Formery et al., 2021; García-Arrarás et al., 2001). Less is known about the entoneural system, which is only present in asteroids and crinoids (García-Arrarás et al., 2001; Haugh, 1975; Mercurio et al., 2024).

In vertebrate development, the nervous system begins to form early, starting with a process called neurulation (Colas & Schoenwolf, 2001; Gilbert, 2000b; Purves et al., 2001b). Neurulation in humans begins in weeks 3-4 of gestation (Chhetri & Das, 2023). During neurulation, the ectoderm is induced to become a neural plate following signals from the mesoderm (Chhetri & Das, 2023; Colas & Schoenwolf, 2001; Gilbert, 2000b). The

neuroectoderm inverts to give rise to the neural tube and, nearby, the neural crest (Chhetri & Das, 2023; Gilbert, 2000b; Purves et al., 2001b). The neural tube, which provides cells for the central nervous system, is the source of CNS neurons, oligodendrocytes (which myelinate neurons in the CNS), astrocytes, and ependymal cells (Chhetri & Das, 2023; Gilbert, 2000b; Rasband, 2015). In the neurula stage, areas of the neural tube are also further specialized into three distinct regions: the forebrain, midbrain, and hindbrain vesicles (Cowan, 1978, 1979). These three regions give rise to all the structures in the developed brain (Cowan, 1978, 1979). The neural crest gives rise to the PNS as well as a variety of other cell types and tissues, including pigment cells, cartilage, and smooth muscle (Mayor & Theveneau, 2013). The neural crest provides cells for the PNS, including PNS neurons, Schwann cells (which myelinate neurons in the PNS), and other glia (Mayor & Theveneau, 2013; Rasband, 2015). Sensory, motor, and enteric nervous systems each develop from the neural crest through distinct but interrelated processes (Mayor & Theveneau, 2013).

Figure 1

Schematic Overview of Neurulation



Note. Adapted from Development of the Central Nervous System – Spinal Cord, TeachMeAnatomy.

The nervous system is formed by neural progenitors, also called neuroblasts, that are characterized by their structure, pattern of differentiation, and transcriptional profiles (David J. Anderson, 2001; Le Douarin & Teillet, 1974). Several factors are known to influence neuroblasts to regulate the mature neuron population. After the establishment of the neuroectoderm, basic helix-loop-helix transcription factors are upregulated in pro-neural clusters of neuroectodermal cells, promoting the developmental program of neuroblasts (Hartenstein & Wodarz, 2013; Huang et al., 2014; Powell & Jarman, 2008; Quan & Hassan, 2005). Conserved mammalian SoxB family transcription factors are critical for defining cell populations that will become neuroblasts (Sasai, 2001). Transcriptional regulators like *Six3/6*, *Pax6*, *Pax3/7*, and *Nkx2.1/2.2* are also expressed early and are restricted to specific locations in the neuroectoderm. These genes play active roles in triggering neurogenic potential while inhibiting neural differentiation, thereby maintaining each cell's proliferative state (Arendt et al., 2016; Bylund et al., 2003; Elkouris et al., 2011; Sasai, 2001). Induction and patterning of early neural determinants is achieved through signaling through conserved pathways like Wnt and BMP, as well as their inhibitors (Darras et al., 2011; Marlow et al., 2013; Niehrs, 2010; Sinigaglia et al., 2013). Notch signaling also helps mediate an inhibitory feedback loop that is activated by pro-neural genes, temporally and spatially restricting formation of neural progenitors (Hartenstein & Wodarz, 2013; Kageyama et al., 2009). Neural progenitors proliferate and differentiate variably depending on the type of neural cells they will become and the

region of the nervous system in which they will be located.

Further, temporal patterning is required for proper nervous system development (Blackshaw & Cayouette, 2025; El-Danaf et al., 2023). The underlying factors controlling temporal patterning have been best studied in *Drosophila* (El-Danaf et al., 2023; Grosskortenhaus et al., 2005; Isshiki et al., 2001; Ulvklo et al., 2012). In flies and vertebrates, neuroblasts divide several times asymmetrically to self-renew, to generate intermediate progenitors, and to generate neurons of distinct fates (Doe, 2017; Holguera & Desplan, 2018). Temporal identity factors were first characterized in the *Drosophila* ventral nerve cord, where sequential expression of *bunchback*, *krüppel*, *pdm*, *castor*, and *grainyhead* maps out the temporal steps of neuroblast division and differentiation into specific neuronal subtypes (Grosskortenhaus et al., 2005; Ulvklo et al., 2012). While *Drosophila* temporal identity factors are conserved in vertebrates, specific roles in regulating the timing of neural development are mostly conserved in the eye (Elliott et al., 2008; Javed et al., 2020, 2023).

After neuronal birth, axons and dendrites must extend out along specific routes to create a network of connections between different parts of the nervous system, and connections must be adjusted and refined (Alberts et al., 2002). Typically, a neuron will have one long axon and several shorter dendrites that project toward target cells, though cell morphology can vary by species and neuronal cell type (Alberts et al., 2002). Extension of axons is driven by a growth cone that is present at the tip of the process (Alberts et al., 2002; Maloney & Bamberg, 2011; Pérez-Ferrer & Herrera, 2025; Sousa & Sousa, 2021). Axons and dendrites connect neurons to other neuronal or non-neuronal cells to form synapses (Alberts et al., 2002; Qi et al., 2022). In development, some organisms create an abundance of synapses during synaptogenesis, then use synaptic pruning to create the highly precise network of connections that is seen in the adult nervous system (Alberts et al., 2002; Faust et al., 2021; Qi et al., 2022; Sakai, 2020; Wolterhoff & Hiesinger, 2024).

Neural Diversity

Through neural development, a broad range of neurons are specified and mature, each with its own structure, function, and connections. Recent studies have shown that the human brain has over 3000 cell types, with each cell type possessing a unique transcriptional identity (Ament et al., 2023; Siletti et al., 2023). Heterogeneity in the brain is in part due to different neuron types, often identified by their neurotransmitters (Cizeron et al., 2020; Que et al., 2019; Sugino et al., 2019). In addition to several different types of neurons, the brain has a highly heterogeneous population of glial cells that vary in location, gene expression, and structure (Bisht et al., 2016; Butt & Verkhratsky, 2018; Khakh & Deneen, 2019; Oberheim et al., 2012; Silvin & Ginhoux, 2018; Stratoulis et al., 2019; Tan et al., 2020; Westergaard & Rothstein, 2020). Neural diversity extends beyond the central nervous system into all parts of the peripheral nervous system, with various neuronal and glial cell types found in the nervous system throughout the body.

Recent breakthroughs in bar-coding technologies and single-cell sequencing have allowed for lineage tagging and analysis of gene expression profiles to better understand how cellular diversity arises within the nervous system (Alemany et al., 2018; Bowling et al., 2020; McKenna et al., 2016; Raj et al., 2018). During nervous system development, neural progenitor cells initially divide symmetrically to expand the progenitor pool, followed by

frequent asymmetric division to create an intermediate progenitor pool (Ge et al., 2022; Taverna et al., 2014). It is widely accepted that neuronal fate decisions occur at the progenitor level, with more recent evidence suggesting environmental and wiring factors contribute to neuronal identity and diversification post-mitotically (Lodato et al., 2011; Lodato & Arlotta, 2015; Pla et al., 2006; Poliak et al., 2016; Pouchelon et al., 2014). Further, neurogenesis is driven by temporal and spatial patterning, with the possibility that these codes are coordinated to precisely control neuronal production (Briscoe et al., 2000; Sagner & Briscoe, 2019; Telley et al., 2019).

Dopaminergic Neurogenesis

Dopaminergic neurons are specialized neurons located in the CNS and PNS that produce and release the neurotransmitter dopamine (Chinta & Andersen, 2005; Klein et al., 2018). The identification and location of dopaminergic neurons was first confirmed in rodent tissue samples utilizing histofluorescence methods (Falck et al., 1962). Mature dopaminergic neurons are also characterized by their expression of tyrosine hydroxylase (TH), an enzyme involved in the dopamine biosynthesis pathway, though norepinephrine neurons also express TH (Blanchard et al., 1993; Moore & Bloom, 1979; Raisman-Vozari et al., 1991; Walkers & Holden-Dye, 1989). In the human CNS, the main source of dopamine is midbrain dopaminergic neurons, though dopaminergic neurons are also found in the diencephalon and olfactory bulb (Björklund & Lindvall, 1984). In the midbrain, several factors promote the development of dopaminergic neurons from stem cells and early progenitors. Sonic hedgehog (Shh) and fibroblast growth factor 8 (FGF8) signals provide essential cues for early dopaminergic progenitor cells (Hynes & Rosenthal, 1999; Rosenthal, 1997). Several early transcription factors help regulate early patterning in the ventral midbrain, including basic Helix-Loop-Helix transcription factors Hes1 and Noto3 (Kameda et al., 2011; Ono et al., 2010). Homeodomain transcription factors like Lmx1a, Lmx1b, and Msx1 help establish the identity of ventral midbrain dopamine neural precursors (Andersson et al., 2006; Failli et al., 2002; Smidt et al., 2000). Ngn2 and Nurr1 are then expressed in more specialized cells that go on to become dopaminergic neurons (Andersson et al., 2006; Hyun Jung Kim et al., 2007; Law et al., 1992; Zetterström et al., 1996).

All dopaminergic neurons in the PNS, including those in the ENS, arise from the neural crest (R. B. Anderson et al., 2013; Hao et al., 2013; Mayor & Theveneau, 2013). While little work has been done to explore the development of dopamine-producing cells in the non-enteric PNS, we do know that dopamine in the body periphery originates from a few different sources: noradrenergic neuronal fibers; neuroendocrine cells; and the adrenal medulla (Fan & Katz, 1993; Goldstein & Holmes, 2008; Katz et al., 1983; Pearse, 1969; Wahbe et al., 1982). ENS neurons come from precursors derived from the neural crest known as enteric neural crest-derived cells (ENCDCs) (Le Douarin & Teillet, 1973, 1974; Yntema & Hammond, 1954, 1955). Several factors are required for ENCDCs to enter the gut and migrate through the entire organ, including PHOX2B, RET, and SOX10 (Jaesang Kim et al., 2003; Z. S. Li et al., 2004; Marcos & Pachnis, 1996; Pattyn et al., 1999; Taraviras et al., 1999). SOX10 also works with ZEB2 to maintain the potency of ENCDCs and inhibit neuronal differentiation through EdnrB signaling (Jaesang Kim et al., 2003; Yuli Watanabe et al., 2017). Ascl1 is critical for both enteric gliogenesis and enteric neurogenesis, specifically for dopaminergic neurons (Memici et al., 2016).

In addition to vertebrate dopaminergic neurogenesis, research in invertebrates has provided insights into the mechanisms through which dopaminergic neurons arise during development. For example, identification and lineage tracing of heterogeneous populations of dopaminergic neurons in both embryonic and larval stages of *Drosophila melanogaster* have been completed (Hartenstein et al., 2016). While many factors required for dopaminergic neuron development are conserved, *Drosophila* dopaminergic neurons also require expression of genes like *sim*, *wingless*, and *gooseberry*, which encode transcription factors (*sim* and *gooseberry*) or Wnt family members (*wingless*) (Bhat, 2007; Duman-Scheel et al., 1997; X. Li & Noll, 1993; Nambu et al., 1990; Richter et al., 1998; Skeath et al., 1995).

Further, hermaphroditic *Caenorhabditis elegans* have 302 neurons, eight of which are dopaminergic (J. Sulston et al., 1975; White et al., 1986). Of these eight dopaminergic neurons, there are four different classes that arise at different times during development, are located in different regions of the nervous system, and come from distinct cell lineages (J. E. Sulston et al., 1983; J. E. Sulston & Horvitz, 1977; White et al., 1986). Though these populations of neurons are distinct, several factors impact all 8 *C. elegans* dopaminergic neurons, including AST-1 (an ETS domain transcription factor), CEH-43 (a distal-less ortholog), and several Pbx genes (Doitsidou et al., 2008; Flames & Hobert, 2009; Siehr et al., 2011). Lin-32, which is a basic helix-loop-helix transcription factor, and a PAX6 homolog also regulate dopaminergic neuron identity and cell number, respectively (Doitsidou et al., 2008, 2013). Because *C. elegans* has distinct dopaminergic neuron populations, there are likely factors that are necessary for specific sets of dopaminergic neuron populations. At least one such factor has been identified. *ztf-6* is a gene encoding a zinc finger transcription factor that regulates dopaminergic neurons in a lineage-specific manner, impacting distinct dopamine neuron-producing lineages differently (Doitsidou et al., 2018).

Dopaminergic Neurons & Parkinson's Disease

Loss or dysfunction of dopaminergic neurons is associated with neurological diseases and disorders like Alzheimer's Disease (Nobili et al., 2017), Huntington's Disease (Bédard et al., 2011; Rangel-Barajas et al., 2015), Multiple Sclerosis (Rangel-Barajas et al., 2015), and most commonly Parkinson's Disease (Bédard et al., 2011; Damier et al., 1999; Hirsch et al., 1988; Parkinson, 2002). Parkinson's Disease is a neurodegenerative disease that impacts motor and non-motor systems through loss of dopaminergic neurons in a section of the midbrain, the substantia nigra, that provides dopamine to the basal ganglia (Damier et al., 1999; Hirsch et al., 1988). Motor dysfunction is one of the earliest symptoms, with patients exhibiting tremors, hypokinesia, and rigidity (Parkinson, 2002). Parkinson's Disease was initially thought to be a sporadic neurodegenerative disorder that had greater prevalence depending on certain environmental factors; genetic mutations have been identified in some familial forms of Parkinson's Disease (Duvoisin, 1984; Lesage & Brice, 2009). The first gene mutation associated with Parkinson's Disease was a mutation in the *alpha-synuclein* (*SCNA*) gene (Polymeropoulos et al., 1997). One pathological hallmark of Parkinson's Disease is the presence of alpha-synuclein aggregates in Lewy bodies or Lewy neurites in affected neurons. Aggregates also include other components like phosphorylated neurofilaments and ubiquitin (Srinivasan et al., 2021). The genetic mutation that conveys the greatest risk of Parkinson's Disease occurs in a gene that encodes a lysosomal enzyme, *glucocerebrosidase* (*GBA*) (Sidransky et al.,

2009; Sidransky & Lopez, 2012). Other genes implicated in Parkinson's Disease include *LRRK2* and *parkin* (or *PARK2*), which contribute to the most common forms of inherited Parkinson's Disease (Matsumine et al., 1998; Paisán-Ruiz et al., 2004; Zimprich et al., 2004). While there have been several genetic risk factors identified for Parkinson's Disease, the vast majority of cases (85%) arise sporadically with no known hereditary cause (Matsumine et al., 1998; Paisán-Ruiz et al., 2004; Polymeropoulos et al., 1997; Sidransky et al., 2009; Sidransky & Lopez, 2012; Srinivasan et al., 2021; Trevisan et al., 2024; Zimprich et al., 2004). In these cases, environmental toxins and brain trauma may contribute to some, but not all, sporadic cases.

Many neurodegenerative diseases, like Parkinson's Disease and Amyotrophic lateral sclerosis, have been associated with the accumulation of protein aggregates (e.g., alpha-synuclein aggregates in Parkinson's Disease) in degenerating and dying neurons (Koszła & Sołek, 2024; Polymeropoulos et al., 1997; Sweeney et al., 2017). Whether these protein aggregates are causative or correlated with neuronal decline remains controversial, but the evidence showing the presence of abnormal protein accumulation across neurodegenerative diseases is indisputable. Cells mount defenses to help fix proteostasis problems that may arise, including protein dysfunction and misfolding (Barmaki et al., 2023; Díaz-Villanueva et al., 2015). Neuronal chaperones are proteins that aid in several processes to help prevent neuronal death due to protein aggregation (Ellis, 1988; Hartl et al., 1992; Hartl, 1996). Chaperones assist in the folding of nascent or misfolded proteins into their correct three-dimensional structures and bind to misfolded proteins to prevent harmful aggregation. When chaperones are not successful, misfolded proteins are targeted to the ubiquitin-proteasome system for degradation (Satapathy & Wilson, 2022; Heather L. Smith et al., 2015). Because of their neuroprotective roles, neuronal chaperones and components of the ubiquitin-proteasome system could be a target for treatment of neurodegenerative diseases (Luo et al., 2010; Sharma et al., 2024). Increasing activity of key proteostasis factors could slow disease progression.

Parkinson's Disease is most commonly attributed to defects in the central nervous system, but dopaminergic neurons also exist outside the CNS in the peripheral nervous system, including the enteric nervous system (Chalazonitis et al., 2022; Chinta & Andersen, 2005). The majority of research on Parkinson's Disease has focused on loss of dopamine in the CNS, specifically the substantia nigra (Barker et al., 2017; Björklund & Stenevi, 1979; Brundin et al., 1988; Damier et al., 1999; Freed et al., 2001; Nagarajan et al., 2014; Yang et al., 2008). However, as early as 1931, researchers noticed Lewy bodies in neurons outside of the CNS (den Hartog Jager & Bethlem, 1960; Hechst & Nussbaum, 1931). Braak's 6-stage theory proposes that Parkinson's Disease-associated neurodegeneration begins in the PNS (specifically the ENS) and progresses to the CNS through the vagus nerve (Braak et al., 2003; Braak & Del Tredici, 2017). The Braak staging system is based on the progression of alpha-synuclein structures in over 100 Parkinson's Disease patients presenting with alpha-synuclein aggregates (Braak et al., 2005, 2003). According to this model, the disease begins in the dorsal motor nucleus of the vagus nerve, eventually progressing and extending into and throughout parts of the brain (Braak et al., 2005, 2003). Though the clinical progression of Parkinson's Disease cannot yet be fully explained, data support a spread of the disease between different parts of the nervous system. For example, several studies demonstrated accumulation of alpha-synuclein in the enteric nervous system before the CNS (Iranzo et al., 2014; Kupsky et al., 1987; Qualman et al., 1984; Wakabayashi et al., 1988).

Parkinson's Disease has been studied for over a century, yet there is no cure, and treatment options for Parkinson's Disease revolve around managing symptoms through drugs that help increase dopamine synthesis and uptake. Levodopa has been considered the "gold standard" for treating symptoms of Parkinson's Disease, however long-term use of the drug, which is the immediate precursor for dopamine synthesis in the substantia nigra, causes adverse side effects (Fahn, 2005; Grandas et al., 1998; Melamed, 1979; Salat & Tolosa, 2013; Sethi, 2010; Tolosa et al., 1975). Alternatively, dopamine agonists can be used to activate dopamine receptors, but they also have negative side effects (Calne et al., 1974; Cotzias et al., 1970). In the past several decades, research on stem cell-based therapies emerged, with stem cells posing an attractive treatment option for introducing functioning dopaminergic neurons in affected areas. Dopaminergic neuron transplants in animal models began as early as the 1970s, with transplantation of rat fetal neurons into injured rodents (Björklund et al., 1976; Björklund & Stenevi, 1979). Pioneering work demonstrated that fetal dopamine neurons from rodents could be incorporated into a dopamine-deficient rodent brain and restore dopamine pathways, paving the way for experiments transplanting human fetal neurons in the same manner (Björklund et al., 1980, 1981; Ungerstedt et al., 1974). Grafting human fetal brain tissue into rodent models allowed functional recovery, though development and innervation of these cells took longer than the previously tested rodent cells (24 weeks opposed to 8 weeks) (Brundin et al., 1988). Not only are human dopamine neurons able to functionally recover in the immediate location of the graft, but they also extend axons over long distances to relevant cortical areas and the striatum of the transplanted rodent (Grealish et al., 2014; Moriarty et al., 2022; Wictorin et al., 1992; Xiong et al., 2021).

Early clinical trials based on grafting human fetal ventral mesencephalic tissue into human patients reported variable results and no significant changes in Parkinson's Disease patients, especially for recipients over 60 years old (Freed et al., 2001; Olanow et al., 2003). Further, a few subjects who received grafts were examined 11-24 years later, and researchers found that grafted dopamine neurons displayed alpha-synuclein pathology similar to diseased neurons (Kordower et al., 2008; Jia Yi Li et al., 2008). The presence of Lewy bodies in transplanted cells suggested that Parkinson's Disease can propagate from host cells to grafted cells, though the majority of the grafted cells were unimpaired after over a decade (Kordower et al., 2008; Jia Yi Li et al., 2008).

In the 2010s, there were breakthroughs in human pluripotent stem cell therapies, including human embryonic stem cells (Thomson, 1998) and human induced pluripotent stem cells (Takahashi et al., 2007). The first protocols for generating dopamine neurons from human pluripotent stem cells were adapted from mouse protocols and included induction of neural differentiation and exposure of cells to morphogens and growth factors like Shh, FGF8, brain-derived neurotrophic factor, and glial cell line-derived neurotrophic factor (Sánchez-Pernaute et al., 2001; Sonntag et al., 2007; Zhang et al., 2001). Surprisingly, embryonic stem cell- and induced pluripotent stem cell-derived dopaminergic neurons performed poorly post transplantation and midbrain identity was not confirmed (Jong Hoon Kim et al., 2002; Sánchez-Pernaute et al., 2001; Yang et al., 2008). Because midbrain dopamine neurons arise from floorplate progenitors marked by coexpression of FOXA2 and LMX1A, alternate protocols were then developed (Bonilla et al., 2008; Joksimovic et al., 2009; Ono et al., 2007). These adjustments, in combination with SMAD inhibition, early exposure to Shh, and Wnt pathway activation, allowed for the development of midbrain dopamine neurons that could functionally replace

disease-impacted cells after transplantation (Grealish et al., 2014; Kirkeby et al., 2012; Kriks et al., 2011). Clinical trials for dopamine cell therapy in humans began in the late 2010s and early 2020s, with two groups recently publishing results from their Phase I and/or Phase II trials (Sawamoto et al., 2025; Tabar et al., 2025). Emerging data suggest that dopaminergic cell therapies derived from either human pluripotent stem cells (Sawamoto et al., 2025) or human embryonic stem cells (Tabar et al., 2025) could be safe and could produce clinical benefits for Parkinson's Disease, including improved motor symptoms (Sawamoto et al., 2025; Tabar et al., 2025). While treatments for Parkinson's Disease have improved over the past five decades, the most recent trials still indicate modest benefits, and long-term studies will still need to confirm the efficacy and persistence of cell-based therapies. Thus, additional interventions will likely be needed for a Parkinson's Disease cure.

Regenerative Capabilities Across the Animal Kingdom

One possible approach to functionally restore cells in the case of nervous system injury could be inducing new production of neurons in the brain to replace diseased and dying cells. The ability to regenerate cells is common throughout non-human members of the animal kingdom, with many species repairing and healing neural tissue after injury through limited cell birth or de/transdifferentiation (Arenas Gómez et al., 2020; Iismaa et al., 2018; Tanaka & Reddien, 2011). Most mammals regenerate poorly, but some mammals are capable of regeneration limited to some tissues or developmental stages (Iismaa et al., 2018; Storer & Miller, 2020). For example, humans regenerate parts of organs like the liver, skin, and uterine lining (Cousins et al., 2022; Ferenczy et al., 1979; Gargett & Ye, 2012; He et al., 2021; Rowlatt, 1979; Takeo et al., 2015; Wei et al., 2021). However, there are limitations to human regenerative ability, especially when it comes to the nervous system (Iismaa et al., 2018; Varadarajan et al., 2022). While humans can repair the peripheral nervous system to an extent, the ability to recover after central nervous system injury is extremely limited (Contreras et al., 2022; Gordon, 2020; Varadarajan et al., 2022; Widodo et al., 2025). Thus, brain injuries and diseases of the CNS are often incurable. Treatments for these debilitating diseases focus on prolonging life, rehabilitation, and palliative care or symptom reduction rather than a true cure (Fahn, 2005; Grandas et al., 1998; Shusharina et al., 2023; Tolosa et al., 1975).

In contrast, some remarkable animals complete successful regeneration throughout the nervous system. Axolotls and zebrafish regenerate cells within the brain and spinal cord, though neither organism can fully reestablish perfect neuronal diversity and connectivity after injury (Amamoto et al., 2016; Caldwell et al., 2019). Zebrafish utilize a population of resident progenitors that give rise to mature cells in the locations where they are needed after injury (Grandel et al., 2006). While zebrafish and axolotls do possess incredible regenerative capabilities, the ability to regrow an entire nervous system *de novo* after injury is rare and limited to a small number of animals, including *Hydra* (a cnidarian) and planarian flatworms (Umesono & Agata, 2009; Hiroshi Watanabe, Hoang, et al., 2009). To answer questions specific to successful, whole-brain regeneration, I sought to use planarians due to their robust regeneration of the entire body, including all parts of the nervous system.

Planarians As a Model for Regeneration

Planarians are non-parasitic, freshwater flatworms of the phylum Platyhelminthes that are known for their remarkable regenerative capabilities. Though several species of planarians exist, scientists most often use two

species to study regeneration: *Dugesia japonica* and *Schmidtea mediterranea*. I used the asexual strain of *S. mediterranea* to answer questions about how successful nervous system regeneration occurs. *S. mediterranea* undergoes robust, whole-body regeneration and replenishes all tissues after nearly any injury, including the creation of the nervous system *de novo* (Inoue et al., 2004; Reddien & Sánchez Alvarado, 2004; Ross et al., 2017). Planarians accomplish great regenerative feats through a population of adult pluripotent stem cells, called neoblasts, that give rise to all mature cell types in the planarian body (Baguña et al., 1989; Morita et al., 1969; Wagner et al., 2011a; Wenemoser & Reddien, 2010). Stem cells produce new cells that differentiate to populate all mature organs in the body, as well as the connective tissue. Planarian pluripotent stem cells are found throughout the body and are only absent from the most anterior part of the head and the pharynx, the feeding organ, which are the only two parts of the animal that cannot regrow the rest of the body when isolated (Reddien et al., 2005).

Pluripotent stem cells make up approximately 20% of all cells within the planarian body and respond to signals after injury (Hayashi et al., 2006; Reddien et al., 2005; Wagner et al., 2011b). In the instance of lost tissue, stem cells respond by dividing and moving to the location of injury to replenish lost cells and tissue (Baguña et al., 1989; Takeda et al., 2009; Wagner et al., 2011b; Wenemoser & Reddien, 2010). Planarians do not have resident progenitor cells within organs, so it is necessary for stem cells and their progeny to migrate to locations where they are needed. Planarian pluripotent stem cells respond to injury with two proliferative bursts, the first of which occurs at 6 hours and the second at 48 hours post-injury (Baguña, 1976; Saló & Baguña, 1984; Wenemoser & Reddien, 2010). Pluripotent stem cells divide to replenish the stem cell population and to create cells that differentiate and eventually mature into specified cell types.

Planarian pluripotent stem cells, or neoblasts, were originally thought to be a relatively homogeneous population of cells defined by morphological characteristics like a large nucleus-to-cytoplasmic ratio, expression of *Smedwi-1*, and location in the mesenchymal tissue (Baguña, 2012; Baguña et al., 1989; Reddien et al., 2005). However, many studies have shown that the neoblast population is heterogeneous and that many neoblasts express specific markers of restricted cell fates (Molinaro & Pearson, 2016; Raz et al., 2021; van Wolfswinkel et al., 2014). Pluripotent neoblasts capable of repopulating the animal's tissue and giving rise to all cell types are termed clonogenic neoblasts, though this is a functional definition rather than a molecular one (Reddien et al., 2005). Four subpopulations have been identified that express *Smedwi-1* as well as transcription factor-encoding genes that are tissue-specific. These neoblast populations— ζ -, σ -, γ -, and ν -neoblasts—are thought to be specialized progenitors with narrower fate (van Wolfswinkel et al., 2014). ζ -neoblasts are considered specialized cells that help maintain and give rise to the epidermal lineage, and they express high levels of genes like *egr-1*, *fgfr-1*, *soxP-3*, and *zfp-1* (van Wolfswinkel et al., 2014). σ -neoblasts have a broad role in producing cells of several different lineages, including other neoblast types, like ζ -neoblasts (van Wolfswinkel et al., 2014). σ -neoblasts are characterized by high expression of genes such as *soxP-1*, *soxB-1*, *fgfr-4*, and *nlk-1* (van Wolfswinkel et al., 2014). In this same study, a third population of neoblasts, considered to be a subclass of σ -neoblasts, was identified: γ -neoblasts. This population is likely an intestine-specific progenitor pool, and it is characterized by elevated expression of genes like *gata4/5/6*, *hnf4*, and *nkx2.2* (van Wolfswinkel et al., 2014). Finally, a fourth population of neural-specific progenitors was identified and termed the ν -neoblasts. This neural-committed population of

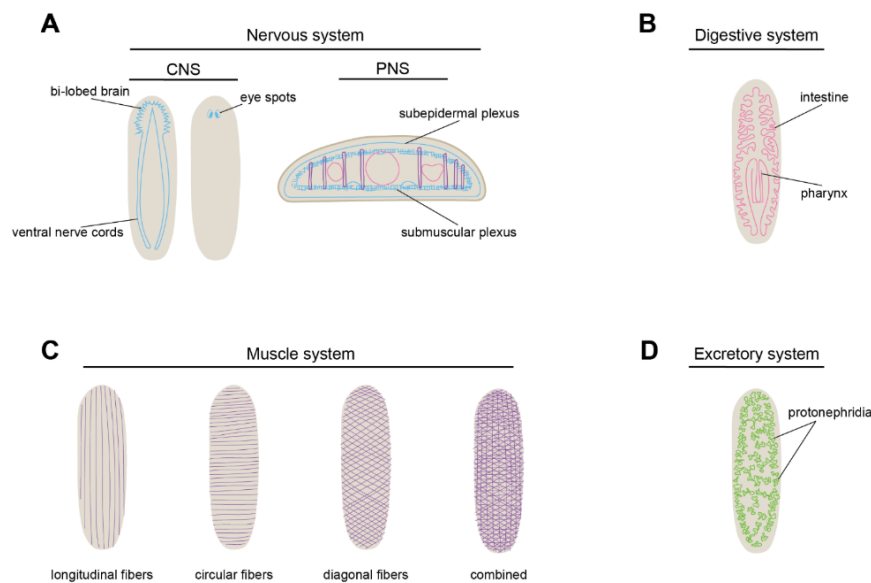
neoblasts expresses high levels of genes, including *ston-2*, *elav-1*, and *ptprd-9* (Molinaro & Pearson, 2016). Importantly, recent work indicates that stem cells with lineage-specific markers retain their potency and can return to a less specialized state after division, suggesting that pluripotency is not linked to a unique stem cell class in planarians (Raz et al., 2021). Additionally, work continues to reveal factors necessary for stem cell maintenance and function, as well as signals that tell a stem cell to differentiate and specialize into each mature cell type (Benham-Pyle et al., 2023; King et al., 2024).

Planarian Organ Systems

Planarians have complex organ systems, including nervous, muscle, digestive, epidermis, excretory, and reproductive systems that are held together by connective tissue called the parenchyma (Roberts-Galbraith & Newmark, 2015) (Figure 2A-D). For this work, I focus on the planarian nervous system, which is made up of a central nervous system, a peripheral nervous system found throughout the body, and a pharyngeal nervous system (PhNS) found in the planarian feeding organ (Roberts-Galbraith & Newmark, 2015; Ross et al., 2017) (Figure 2A-B). The central nervous system is composed of a bi-lobed brain, two nerve cords on the ventral side of the animal, and two eyespots on the dorsal side of the planarian (Agata et al., 1998; Carpenter et al., 1974; Krugelis MacRae, 1964) (Figure 2A). The brain also has brain branches that reach out laterally from the brain and relay chemosensory signals (MacRae, 1967) (Figure 2A). The peripheral nervous system is composed of nerve plexuses that sit between and around different organ systems (Figure 2B). The subepidermal nerve plexus innervates the space between the epidermis and the body wall musculature, and likely functions in sensory processes or in the regulation of epidermal motile cilia (Baguña & Ballester, 1978) (Figure 2B). The submuscular nerve plexus is located below the muscle wall, and the gastrodermal nerve plexus surrounds the intestine (Baguña & Ballester, 1978) (Figure 2B). The pharyngeal nervous system, composed of two ring-like nerve plexuses, is found solely within the pharynx and is important for pharyngeal movement in feeding behavior. While characterization of the CNS in planarians has been a focus of the field, the PNS remains poorly characterized, with sparse molecular and genetic information about the identities and developmental processes for PNS or PhNS neurons. The planarian nervous system contains dozens of neuron types, which have been defined by their gene expression and—less commonly—function. Planarian neurons produce several different neurotransmitters including acetylcholine, dopamine, GABA, octopamine, serotonin, norepinephrine, and over 50 neuropeptides (Clay et al., 2025; Collins et al., 2010; Nishimura et al., 2010; Nishimura, Kitamura, Umesono, et al., 2008; Nishimura, Kitamura, Inoue, et al., 2008; Nishimura, Kitamura, Inoue, Umesono, Sano, et al., 2007; Nishimura, Kitamura, Inoue, Umesono, Yoshimoto, et al., 2007; Ong et al., 2016).

Figure 2

Planarian Organ Systems



Notes. A) Diagram of the planarian nervous system. Central nervous system (CNS) on left, peripheral nervous system (PNS) on right. B) Diagram of the digestive system. C) Diagram of planarian musculature. D) Diagram of the planarian excretory system.

While we do not know the entire mechanism through which any neuron type is specified and differentiated, we do know some key regulators of the planarian nervous system. For example, *soxB1-2*, *coe*, and *sim* are required for broad nervous system regeneration (Cowles et al., 2013, 2014; Ross et al., 2017). *ets-1* and *hedgehog* signaling are required for proper regeneration and patterning of planarian glia, neuronal support cells (Chandra et al., 2023; Wang et al., 2016). Finally, there has been substantial work to uncover mechanisms that allow specification and maturation of serotonergic neurons, including identification of *pitx* and *lhx1/5-1* as terminal differentiation factors for neurons producing serotonin (Currie & Pearson, 2013; März et al., 2013). Importantly, additional factors required for determining the exact spatial and regional localization of neurons, and establishing neurons in the correct numbers, types, and ratios, have yet to be elucidated. Uncovering the mechanisms required for proper neuronal regeneration in the correct contexts for a single mature neuron type will likely provide critical information for differentiation pathways for other mature cell types in the planarian.

Within the nervous system, we do know the entire pathway from a pluripotent stem cell to mature eye cells, including pigment cup cells and photoreceptor cells (Atabay et al., 2018; Emili et al., 2019; Lapan & Reddien, 2011, 2012a). Planarians have two eyespots with mature cells, and a trail of eye progenitors that lead toward them (Agata et al., 1998; Carpenter et al., 1974; Inoue et al., 2004; Lapan & Reddien, 2011, 2012b). To determine the order in which transcription factors need to be active for proper eye formation, scientists completed a combination of fluorescent *in situ* hybridization experiments labeling stem cells, mature eye cells,

and transcription factor-encoding mRNAs that were thought to act in the process (Lapan & Reddien, 2011). Transcription factor-encoding genes expressed with the stem cell marker were determined to mark early progenitors, and those expressed with the mature cell type marker were determined to act later in the lineage (Lapan & Reddien, 2011).

We also know the entire pathway from a planarian pluripotent stem cell to mature epidermal cells, and we understand many of the factors at work in between (Eisenhoffer et al., 2008; Tu et al., 2015; Zhu & Pearson, 2016). The combination of 5-bromo-2'-deoxyuridine labeling with *in situ* hybridization experiments allowed lineage tracing in planarians and created a guide for determining lineage for other cell types as well (Eisenhoffer et al., 2008). Other factors have been identified in pathways of specification for different mature cell types in the planarian, including muscle, gut, and protonephridia. Proper expression of genes such as *myoD*, *foxF-1*, *nk4*, *gata4/5/6-2*, and *gata4/5/6-3* is required for proper planarian muscle regeneration (Cebrià, 2016; Lucila Scimone et al., 2017; Scimone et al., 2018). Regeneration and/or maintenance of cells in the intestine requires proper expression of genes like *gli-1*, *RREB2*, *lhx2/9-1*, *lhx1/5-2*, *LDB1*, *SSDP2*, and *gata4/5/6* (Flores et al., 2016; Forsthoefel et al., 2020; Medlock-Lanier et al., 2024; Molina et al., 2023). The planarian excretory system is governed by transcription regulators like *six1/2-2*, *hunchback*, *eya*, *sall*, and *POU2/3* (Scimone et al., 2011). Additionally, an EGF receptor, EGFR-5, is required for proper branching morphogenesis and maturation of planarian protonephridia (Rink et al., 2011).

Planarian Polarity and Body Plans

In addition to replenishing all missing cells after injury, planarians faithfully reproduce the body plan with predictable patterning, using critical polarity signals that govern the body axes. Planarians have anterior-posterior, dorsal-ventral, and medial-lateral axes that are governed by distinct mechanisms. In planarians, the anterior-posterior axis is governed by posterior Wnt signaling proteins, similar to other metazoans (Hardin & King, 2008; Logan & Nusse, 2004; Marikawa, 2006; Schier & Talbot, 2005). β -catenin functions downstream of canonical Wnt signaling and inhibits anterior pole identity. Knockdown of *β -catenin* through RNA interference (RNAi) results in ectopic head growth and regeneration (Gurley et al., 2008; Iglesias et al., 2008; Petersen & Reddien, 2008), indicating a negative regulation of brain regeneration.

The planarian dorsal-ventral axis is governed by bone morphogenetic protein (BMP) and anti-dorsalizing morphogenetic protein (ADMP) signals. *bmp4* is expressed dorsally and represses ventral *admp* (Gaviño & Reddien, 2011). In planarians, *bmp4* is expressed in clusters of cells along the dorsal midline, as well as a small number of neurons in the brain and ventral nerve cords (Molina et al., 2007; Orii et al., 1998). After knockdown of *bmp4*, planarians experience ectopic eye expression, indented blastemas, and ultimate failure of regulation at the dorsal midline (Molina et al., 2007; Reddien et al., 2007). *bmp4*(RNAi) also causes increased *admp* expression, leading to the conclusion that *bmp4* regulates *admp* through inhibitory mechanisms (Gaviño & Reddien, 2011). *admp* is expressed in cells along the ventral midline and cells at the lateral edges of the animal (Gaviño & Reddien, 2011). *admp*(RNAi) animals form indented blastemas and decreased regenerative abilities after a sagittal amputation. Knockdown of *admp* also led to decreased *bmp-4* expression, suggesting that *admp*

activates expression of *bmp-4* (Gaviño & Reddien, 2011). The dorsoventral regulators *bmp* and *admp* are also regulated by several other factors, including an expanded *noggin* family (Molina et al., 2007; Ogawa et al., 2002; William C. Smith & Harland, 1992).

Planarians' bodies are also organized along a medial-lateral axis. The medial-lateral axis is regulated by *slit* at the midline and lateral *Wnt5* through reciprocal patterning (Cebrià et al., 2007; Gurley et al., 2010). *slit* is expressed along the midline of both the dorsal and ventral sides of the planarian (Cebrià et al., 2007), and knockdown of *slit* causes misexpression of *wnt5* into the planarian midline (Gurley et al., 2010). In contrast, *wnt5* is expressed lateral to the ventral nerve cords and peripherally around the planarian body (Gurley et al., 2010). *wnt5*(RNAi) leads to expression of *slit* outside the midline and towards the lateral edges of the animal (Gurley et al., 2010).

Planarians faithfully regenerate their entire body, including their complex nervous system, after nearly any injury. Not only do planarians make the right cell types, but they do so in the correct locations, patterning, and ratios. Because of their remarkable regenerative capabilities, planarians are an ideal model with which to uncover mechanisms underlying successful nervous system regeneration. Revealing the factors required for regeneration and maintenance of their complex nervous system will not only further elucidate how planarians regrow without consequence, but could also inform research into therapies for neurological conditions, including brain injury and neurodegenerative disease.

Specification of Dopaminergic Neurons in Planarians

One of the larger goals of my thesis work was to determine the entire genetic pathway from a pluripotent stem cell to a mature dopaminergic neuron in planarians. I proposed a model in which combinatorial mechanisms specify regional location and neurotransmitter identity of dopaminergic neurons concurrently (Clay et al., 2025). However, there is likely some sort of hierarchy to dopaminergic neuron specification, even if there is overlap in the transcriptional regulation. In an effort to parse out the order in which transcription factors are turned on to create dopaminergic neurons in the peripheral nervous system, orthogonal approaches could be used to determine whether *fli1-2*, *irx-4/6*, and *soxB1-2* are expressed in the early or late progenitors. I found that *fli1-2*, *irx-4/6*, and *soxB1-2* are all co-expressed with a broad stem cell marker, *smedwi-1*, and are therefore all expressed in at least some progenitor cells (Clay et al., 2025; Eisenhoffer et al., 2008). In irradiated animals, less specialized stem cells will go away first, followed by early progenitors, late progenitors, and finally mature cell types (Eisenhoffer et al., 2008). Looking at the expression of *fli1-2*, *irx-4/6*, and *soxB1-2* in irradiated animals over a seven-day timeline will show which of these populations dies off first, providing insight into which of these transcription factor-encoding genes is expressed earliest within progenitors.

In addition to determining the order of expression of the genes I have identified, there are likely other genes that are critical for regeneration and maintenance of dopaminergic neurons in planarians. My current hypothesis is that the genes I have identified are likely enriched for the middle of the specification pathway for dopaminergic neurons. Utilizing available single-cell transcriptomic data, it will be interesting to examine transcripts that are expressed in predicted early neural progenitor populations, especially those that express high levels of *smedwi-1* mRNA (Fincher et al., 2018). Another reverse genetic screen examining transcription factors at this stage could

provide insight into the earliest fate choices in the dopaminergic neuron pathway. Further, the bulk RNA sequencing I completed will provide information as to what genes may be working downstream in the pathway of dopaminergic neuron specification. Conducting a smaller-scale screen using the bulk RNA sequencing data will help identify additional genes required for the maintenance and maturation of dopaminergic neurons.

Factors Influencing Planarian Neuronal Placement

In my thesis work, I proposed a model in which combinations of transcription factor-encoding genes help specify dopaminergic neurons, both in their neurotransmitter identity and in their regional location (Clay et al., 2025). However, there are likely other factors at play that help regulate both processes. One example is the consistent and robust body-patterning system that planarians possess (Reddien, 2018). Planarians have anterior-posterior, dorsal-ventral, and medial-lateral axes that are strictly regulated (Reddien, 2018). IRX family genes play conserved roles in vertebrates and invertebrates in mediating the dorsoventral axis (Glavic et al., 2002; Gómez-Skarmeta & Modolell, 2002; Itoh et al., 2002; Lecaudey et al., 2004). Interestingly, planarian *irx-like* has a polarized expression pattern and is only expressed on the ventral side of the animal. This raises the question of whether there are distinct factors regulating dopaminergic neurons in the dorsal and ventral PNS. *IRX-like* is a likely candidate in helping regulate ventral dopaminergic neurons, but how is this influenced by polarity signaling? Several factors have been identified as regulating polarity axes in planarians (Cebrià et al., 2007; Gaviño & Reddien, 2011; Gurley et al., 2008, 2010; Iglesias et al., 2011; Molina et al., 2007; Ogawa et al., 2002; Oori & Watanabe, 2007; Petersen & Reddien, 2008). Further characterizing the polarity of PNS cells will likely determine other factors impacting dopaminergic neuron fate and regionalization.

Planarians As a Future Model for Neurodegeneration

Unfortunately, there are currently no cures for neurodegenerative diseases, and treatment options available are used to manage symptoms (Cascione et al., 2020; Durães et al., 2018). Several models are being used to model neurodegeneration and identify potential pathways for investigation, including *in vivo*, *in vitro*, and *in silico* models (Dawson et al., 2018; Jones et al., 2022; Valadez-Barba et al., 2020). While these models have provided critical information in understanding the molecular mechanisms behind neurodegenerative diseases, with some studies resulting in clinical trials, more progress is needed. I reasoned that the use of another model system that already possesses perfect regenerative capabilities, including that of its complex nervous system, might provide complementary information and could reveal new molecular mechanisms underlying neurodegeneration.

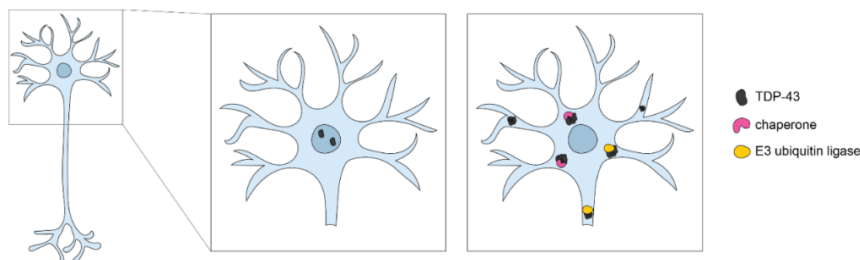
One approach I employed to model neurodegeneration in planarians was by identifying and characterizing planarian TAR DNA-binding proteins (TARDBPs). Protein aggregates are implicated in several neurodegenerative diseases, including Parkinson's Disease, Alzheimer's Disease, and amyotrophic lateral sclerosis (ALS) (Koszła & Sołek, 2024; Polymeropoulos et al., 1997; Sweeney et al., 2017). TDP-43 aggregates are specifically implicated in sporadic and genetic forms of ALS (Sreedharan et al., 2008; Suk & Rousseaux, 2020). However, the exact cause of neuron death after TDP-43 aggregation has yet to be elucidated. In one model, neurons with TDP-43 protein aggregates die due to toxicity when the protein becomes mislocalized and aggregated. In an alternate model, cellular health is primarily compromised due to the loss of healthy TDP-43

protein function. Planarians present a unique organism with which to study the cellular roles of TARDBP because planarians have five homologs of TDP-43. In other organisms with only one TDP-43 homolog, like mice, loss of TDP-43 is embryonic lethal (Kraemer et al., 2010). Because planarians have five TDP-43 homologs, we are able to knock down individual isoforms in the adult animal to examine the subfunctionality of TDP-43. Indeed, I was able to knock down each planarian homolog of TDP-43 and assess whether regeneration of the brain was impaired. I found that *tdp-4* is required for proper planarian brain regeneration. Loss of planarian *tdp-4* eventually led to animal death through lysis, which led me to examine whether *tdp-4* regulated planarian stem cells. I found that *tdp-4* causes a reduction in planarian stem cell abundance compared to controls, and I concluded that planarian TARDBPs regulate both brain regeneration and stem cell maintenance.

Currently, most planarian researchers induce regeneration through tissue amputation or other drastic injury. However, this is not physiologically relevant for modeling neurodegeneration. I hypothesized that I might be able to model neurodegeneration in planarians in a manner that is more physiologically relevant to humans. I started by looking at the literature where dysfunction in neuronal chaperones and proteasomal subunits has been implicated in neurodegenerative disease (Ellis, 1988; Hartl et al., 1992; Hartl, 1996; Satapathy & Wilson, 2022) (Figure 3). Using available single-cell transcriptomic data, I identified planarian homologs of chaperones and proteasomal subunits with enriched expression in the nervous system (Fincher et al., 2018). I narrowed this list down to twenty transcripts (e.g., *heat shock factor*, *E3 ubiquitin ligase*), which could be used for an RNAi screen to assess their impact on maintenance of brain size and function. Next, I would suggest investigating whether these RNAi conditions lead to neuronal death via protein aggregation. Utilizing TUNEL to examine cell death by apoptosis could help address the first possibility, and I have worked to develop this protocol in the lab (Kyrylkova et al., 2012). Further, a protein dye like Proteostat could be used to quantifiably examine protein aggregates in control compared to knockdown conditions (Navarro & Ventura, 2014). Developing planarians as a future model for studying neurodegeneration could prove pivotal in the field and would allow us to investigate neural loss in a system that is capable of robust regeneration to inform new approaches to tackling old questions.

Figure 3

Proteostasis Mechanisms for Neuronal Survival



Note. Protein aggregates (black) accumulate in the cytoplasm, causing toxicity to neurons. Proteins involved in proteostasis (yellow and pink) work to prevent and break up protein aggregates.

Conclusion

Throughout the body of my thesis work, I uncovered molecular mechanisms of planarian nervous system regeneration and proposed the development of planarians as a future model for neurodegeneration. Specifically, I showed that combinatorial mechanisms specify neuronal neurotransmitter identity and cellular regionalization for planarian dopaminergic neurons. For the first time in planarians, I examined the cellular roles of the five planarian TDP-43 homologs and determined their importance in brain regeneration, stem cell maintenance, and function. Finally, I provided the starting point for a fascinating avenue to develop planarians as a model with which to study neurodegeneration in a physiologically relevant manner.

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