The importance of fasciculation and elongation protein zeta-1 in neural circuit establishment and neurological disorders

Introduction

The fundamental underpinning of our brain function lies undeniably in its dense and complex networks of interconnected neurons. The estimated 100 billion neurons contained in the normal human brain are systematically and intricately organized into functional units ranging from local networks connecting neighboring neurons to long-range networks that span across different brain regions (Richards and Van Hooser, 2018). Formation of neural circuits is organized into distinct phases stretching over 20 years (Birnbaum and Weinberger, 2017). Neurogenesis and neuronal migration, the earliest phases, occupy only a small fraction of this process (Molnar et al., 2019). In comparison to this, functional wiring (synaptogenesis) and optimization (synaptic pruning) of the neural circuits extend into young adulthood, reflecting the incredible complexity involved in their establishment, wiring and optimization. Indeed, perturbations affecting these two critical phases of brain formation (i.e. initial wiring and subsequent optimization) are believed to be the origins of neuropsychiatric disorders including schizophrenia and autism-spectrum disorders (Birnbaum and Weinberger, 2017). Functional wiring is a dynamic and highly complex process regulated by a diverse assortment of seemingly disparate signaling pathways to coordinate axon and dendrite specification, elongation, arborization and guidance. These events eventually lead to synaptogenesis when the two processes come into contact. Functional wiring is closely tied to the completion of neuronal migration and begins when differentiating neurons project axons and dendrites to their relevant cellular connections, guided by both extrinsic and intrinsic cues (Ledda and Paratcha, 2017). Upon reaching their cellular targets, additional signaling by trans-synaptic signaling molecules allow contacting axons and their target dendrites to initiate synapse formation (Sudhof, 2018). Strikingly,
many of these pathways ultimately converge to modulate cytoskeletal dynamics and intracellular transport. This intersection is critical given that the rapid elongation of both types of processes and the subsequent formation of up to ten thousands of synapses in each neuron must be efficiently coordinated and supported by the synthesis and delivery of an incredible amount of biological raw materials to the sites of neurite expansion and synapse development (Rizalar et al., 2021). Indeed, defects in many proteins involved in these pathways are linked to human neurological disorders with severe mental disabilities, mostly involving cognitive and motor dysfunctions (Sleigh et al., 2019).

One protein that has been inextricably linked to many of the abovementioned processes is known as fasciculation and elongation protein zeta-1 (FEZ1). UNC-76, the nematode homolog of FEZ1, was first discovered in *Caenorhabditis elegans* (*C. elegans*) as a protein essential for normal development of its nervous system (Desai et al., 1988; Bloom and Horvitz, 1997). Since then, other studies have highlighted its importance in neuronal development, and the formation and maintenance of synapses in both the central as well as peripheral nervous system. These findings strongly indicate that loss of FEZ1 in neurons can trigger alterations that affect the formation and maintenance of central and peripheral neuronal networks that underlie neurodevelopmental and neurodegenerative disorders. This review highlights recent advances in our knowledge of FEZ1’s function and its relevance in causing neurological disorders.

### Search Strategy and Selection Criteria

Articles cited in this review published from 1974 to 2021 were searched in the PubMed database using the following keywords: fasciculation and elongation protein zeta 1, UNC-76, neuronal development, neurodegeneration, neurodevelopmental disorders, schizophrenia, Jacobsen syndrome, autophagy. Results were further filtered by title and abstract.

### Fasciculation and Elongation Protein Zeta-1 Is Selectively Expressed in Nervous Tissues

*Unc*-76, the *C. elegans* homolog of the mammalian FEZ1 gene, was first identified as part of a group of genes associated with locomotory behavior in a series of elegant studies (Brenner, 1974; White et al., 1976). Subsequent studies determined that the gene is essential for axon outgrowth and guidance and further highlighted its restricted expression to nervous tissues at all stages of development (Hedgecock et al., 1985; Desai et al., 1988; Bloom and Horvitz, 1997). In mammals, a similarly restricted pattern of expression to nervous tissues is observed (Fujita et al., 2004; Honda et al., 2004; Sakae et al., 2008). In rodent brains, FEZ1 could already be detected prenatally and increases with development. High levels of FEZ1 expression persist in both rat and human adult brains (Whitehouse et al., 2002). Within the brain, regional differences in expression are observed, with the prefrontal cortex and cerebellum expressing the highest levels of the protein (Sakae et al., 2008; Gunaseelan et al., 2021). FEZ1 is also notably well-expressed in the spinal cord. Both neurons and astrocytes appear to express FEZ1 (He et al., 2009; Butkevich et al., 2016; Gunaseelan et al., 2021). Mammalian genomes contain a separate gene encoding the related FEZ2 that has a much broader expression but whose function is much less understood (Fujita et al., 2004). A word of caution – it should be noted that FEZ1/UNC-76 is often erroneously confused with another mammalian gene named LZTS1 (unfortunately also known as FEZ1) in the literature as well as public databases. Careful examination shows these genes are distinct from each other and located on different chromosomes. Sequence comparisons of their gene products (i.e., mRNA and protein) do not show any significant alignment. As an example, annotations of the human orthologs of both genes as derived from the NCBI Gene database is shown in Table 1.

| Official gene symbol/Full name | Synonyms | Chromosomal location (aa) | Major function |
|--------------------------------|----------|---------------------------|---------------|
| FEZ1 Fasciculation and elongation protein zeta 1 | UNC-76 | 11q24.2 | 392 | Kinesin-1 adapter |
| LZTS1 Leucine zipper tumor suppressor 1 | F37; FEZ1 | 8p21.3 | 596 | Transcription factor |

### Fasciculation and Elongation Protein Zeta-1 Is a Kinesin-1 Adapter for Intracellular Transport in Neurons

Possibly the most studied function of FEZ1 relates to its role as a Kinesin-1 adapter. Concomitant binding of FEZ1 and JIP1 to the tail of Kinesin-1 was reported to activate the motor (Blasius et al., 2007). Other studies have confirmed the FEZ1/Kinesin-1 interaction and further identified mitochondria as well as synaptic proteins as major cargoes of the FEZ1/Kinesin-1 motor complex in neurons (Gindhart et al., 2003; Ikuta et al., 2007; Toda et al., 2008; Chua et al., 2012; Butkevich et al., 2016; Sure et al., 2018). In all instances, binding to motor and cargoes require the coiled coiled domain of FEZ1.

The role of FEZ1 in axonal transport is regulated by kinases. In particular, phosphorylation of the conserved Serine residue (positions 58 and 143 in mammalian and *Drosophila* FEZ1, respectively) by ATG1/UNC-51 or microtubule affinity regulating kinases is required for axonal transport of synaptic cargoes (Toda et al., 2008; Butkevich et al., 2016; Malikov and Naghavi, 2017). Additionally, PKCζ phosphorylates FEZ1 at its C-terminal region although its relevance to transport remains unknown (Kuroda et al., 1999; Lanza et al., 2009).

### Fasciculation and Elongation Protein Zeta-1 Is Required for Axo-Dendritic Development

During brain development, developing neurons send projecting axons and dendrites to their targets. Transport of biomolecules is crucial to support the growth of rapidly extending neuronal processes and, thus, indispensable for the formation of neural circuits (Aiken and Holzbaur, 2021). Early studies on UNC-76 in *C. elegans* first illustrated its importance in axonal outgrowth and guidance. In particular, chemosensory neurons of *unc-76* mutant worms exhibited ectopic branching with enlarged axonal terminals that terminated prematurely (Hedgecock et al., 1985). Moreover, similar defects in axonal outgrowth and bundling were observed in the hermaphrodite-specific neuron motor neurons of *unc-76* mutant worms, where the axons failed to grow in normal fascicles (Bloom and Horvitz, 1997). The role of mammalian FEZ1 in axo-dendritic development is evolutionarily conserved (Figure 1). Using nerve growth factor-treated PC12 cells as a model for neurogenesis, expression of FEZ1 temporally coincided with the appearance of neurites in a manner dependent on its phosphorylation by PKCζ as well as ubiquitylation by the U-box-type ubiquitin ligase E4B (Kuroda et al., 1999; Okumura et al., 2004). More importantly, recent studies employing CRISPR-based strategies further demonstrate that both axon and dendrite development in developing hippocampal neurons are significantly impaired when FEZ1 expression is abrogated (Chua et al., 2021). In particular, total axonal length and the length of the longest axon were significantly shortened in FEZ1-deficient
FEZ1 is critical for neurodevelopment. In CNS and PNS neurons, FEZ1 participates in both axo-dendritic development as well as synapse formation and organization. (1) FEZ1 acts downstream effector of guidance cue signaling pathways to regulate axo-dendritic development and migration. FEZ1 also interacts with DISC1 or ZNF804A to modulate dendrite length, branching and short spine density. (2) FEZ1/Kinesin-1 complexes transport synaptic components essential for synapse formation and organization. (3) Likewise, FEZ1 roles in transporting synaptic components during motor neuron development is essential for proper formation of neuromuscular junctions (NMJ).

Loss of FEZ1 in these processes eventually leads to neuronal network perturbations and potentially contributes to neurodevelopmental disorders.

**Fasciculation and Elongation Protein Zeta-1 Contributes to Synapse Formation and Organization through the Delivery of Synaptic Proteins**

Chemical synapses play predominant roles in most neural circuits. It consists of two juxtaposed components from two adjacent neurons, namely the presynaptic specialization (in axon) and postsynaptic density (in dendrite) (Chua et al., 2010). Presynaptic specializations are regions of cell terminals with neurotransmitters-filled synaptic vesicles, which can be released at the presynaptic active zones upon stimulation. Meanwhile, postsynaptic densities are enriched with neurotransmitter receptors, channels and downstream signaling molecules to sense the released neurotransmitters in the synaptic cleft (Kaizuka and Takumi, 2018). Importantly, synaptic transport is a crucial process that ensures a continuous supply of synaptic proteins and organelles to synapses while preventing build-up of defective synaptic components at the terminals in order to maintain synaptic homeostasis (Guedes-Dias and Holzbaur, 2019; Vasudevan and Koushika, 2020).

As previously mentioned, FEZ1 is an important adapter for Kinesin-1-mediated anterograde transport in axons. Synaptic proteins constitute major cargoes transported by the FEZ1/Kinesin-1 transport complex in neurons. These include...
presynaptic active zone scaffold proteins Bassoon, Piccolo and Liprin-α, synaptic vesicle proteins VAMP/Synaptobrevin and postsynaptic proteins, including the postsynaptic density-95 family of membrane-associated guanylate kinases and members of the ionotropic glutamate receptor family (Butkevich et al., 2016).

Confirming its role in synaptic protein transport, axonal cargo aggregates are observed in neurons of C. elegans unc-76/FEZ1 mutants, which are indicative of defective axonal transport (Chua et al., 2012). Similarly, deletion of FEZ1 in developing human motor neurons significantly delayed axonal delivery of the active zone protein Piccolo (Gunaseelan et al., 2021). While Piccolo was already present in both proximal and distal neurites in 86% of control motor neurons as early as DIV9, less than 6% of FEZ1-deficient motor neurons showed proximal presence of the protein at the same timepoint. The defects in synaptic protein transport have a strong negative impact on synapse formation and function. In C. elegans, unc-76 mutants show a dramatic loss and disorganization of presynaptic specializations (Butkevich et al., 2016). In the latter instance, this could arise from disrupted interaction with UNC-69/SCOCO as both proteins are required to maintain normal presynaptic organization (Su et al., 2006). Post-synaptically, FEZ1 over-expression rescued spine density reductions in neurons with abnormal levels of ZNF804A (Dong et al., 2021). Synaptic loss caused by perturbation of FEZ1 function is also recapitulated in the peripheral nervous system. In Drosophila, motor neuron specific knockdown of UNC-76 expression resulted in a significant decrease in the number of synaptic boutons in these animals as compared to control flies (Gunaseelan et al., 2021). The abnormalities corroborated strongly with locomotion defects observed in these mutant flies and is accompanied by a significantly shortened lifespan. Importantly, synaptic and locomotion defects (but not lifespan) were rescued with pharmacological activation (using rapamycin and metformin) of ATG1, one of the two known FEZ1/UNC-76 activating kinases. Notably, the locomotion and survival defects observed in motor neuron specific unc-76 knockdown flies were also observed in unc-76 null Drosophila mutants (Gindhart et al., 2003). Taken together, the recent evidence highlights the critical importance of FEZ1 in the proper development of neurons and their synapses and, thus, in the establishment of functional neural circuits during the development of the brain and peripheral nervous system.

### Perturbation of Fasciculation and Elongation Protein Zeta-1 Function as a Contributing Factor in Causing Neurodevelopmental Disorders

Given its importance in the formation of neural circuits, it is not surprising that FEZ1 alterations have been linked to various brain disorders. FEZ1 gene polymorphisms and reduced mRNA expression have been reported in patients affected by schizophrenia (SCZ) (Yamada et al., 2004; Lipska et al., 2006; Rampino et al., 2014; Vachev et al., 2015; Tang et al., 2017). Despite its complex etiology and pathophysiology, schizophrenia is now widely regarded as a neurodevelopmental disorder with origins rooted in perturbations affecting the establishment and optimization of neural circuits over the course of brain development (Birnbaum and Weinberger, 2017; McCutcheon et al., 2020). In particular, abnormalities in neural circuits involving the dorsolateral prefrontal cortex and hippocampal formation and their associated networks have been implicated. Magnetic resonance imaging studies of brains of schizophrenic patients revealed that significant volume loss, particularly in the temporal and prefrontal cortices, associated with the progressive loss of grey and white matter are already detectable upon the onset of psychosis that further deteriorates with progression of the disorder (Schwarz et al., 2019; Cetin-Karayumak et al., 2020). At the cellular level, observations of reductions in dendritic length, complexity and spine density together with lower presynaptic specializations and defective activity-induced release of synaptic vesicles further support the existence of altered or loss of synaptic connectivity between neurons in the affected areas (Hunt et al., 2017; Kahn, 2020).

As discussed previously, loss of FEZ1 alone is sufficient to disrupt the development of neurons and the networks they form. In addition, FEZ1 is known to either physically interact with SCZ-related risk genes or be involved in SCZ-implicated pathways. For instance, interactions at the protein, as well as, epistatic level have been reported between FEZ1 and disrupted in schizophrenia 1 (DISC1) or ZNF804A. Interestingly, the effect of perturbing these interactions is synergistic and affects neurite development (Miyoshi et al., 2003; Kang et al., 2011; Zhou et al., 2018; Dong et al., 2021). Deletion of histone deacetylase 11 (HDAC11), another SCZ-associated gene, leads to decreased expression of FEZ1 in the hippocampus (Bryant et al., 2017). Moreover, perturbed synaptic function has been identified as common denominator in a broad range of neuropsychiatric disorders (Gandal et al., 2018; Koopmans et al., 2019). Reduced synapse number and disrupted synapses observed in the absence of FEZ1 strongly argues for its involvement not only in SCZ, but also in other neuropsychiatric disorders.

Apart from polymorphisms, the FEZ1 gene is frequently deleted in patients suffering from Jacobsen syndrome (JS) (Grossfeld et al., 2004). The gene is located at the long arm of chromosome 11 (11q). Deletions ranging from 7 to 16 Mb in size of the 11q terminal region lead to heterozygous loss of a number of genes, of which only some have been functionally characterized. Amongst other clinical symptoms, intellectual disability exists in JS patients and the extent of chromosomal deletion is known to positively correlate with increasing disability. A significant proportion of patients also manifest attention deficit hyperactivity disorder, autism spectrum disorder and, less frequently, schizophrenia or bipolar disorders (Mattina et al., 2009). Psychomotor impairments, including gross and fine motor delays are also commonly identified. Importantly, the locomotion defects were recapitulated in a Drosophila motor neuron specific knockdown model, indicating that partial loss of FEZ1 at least contributes to such impairments (Gunaseelan et al., 2021). Given FEZ1’s importance in neuronal development and formation of neuronal networks, it would not be surprising if partial loss of the protein also contributes to the behavioral and cognitive impairments observed in JS patients.

Studies using mouse models have at least partially confirmed that perturbation of FEZ1 function can cause behavioral phenotypes relevant to neuropsychiatric disorders. FEZ1-knockout mice exhibited a hyperactive phenotype caused by increased dopaminergic signaling in the nucleus accumbens, which is reminiscent of observations in schizophrenia patients (Sakae et al., 2008). The expression of FEZ1 in inhibitory neurons further suggest that the alterations in dopaminergic transmission could have arisen from impaired GABAergic transmission in FEZ1-deficient inhibitory neurons. This finding is significant given that perturbations of the dopaminergic, glutamatergic and GABAergic neurotransmitter systems have all been implicated in causing schizophrenia (Canitano and Pallagrosi, 2017; Egerton et al., 2020). A follow up study by the same group further reported hyperactivity and impulsivity phenotypes in these animals that could be treated using methylphenidate or guanfacine, which have been used for the treatment of attention deficit hyperactivity disorder (Sumitomo et al., 2018).
Loss of Fasciculation and Elongation Protein Zeta-1 Function at Later in Life Is Associated with Neurodegeneration

Expression of FEZ1 persists late into adulthood (Whitehouse et al., 2002). While perturbing FEZ1 function early in life is linked to neurodevelopmental disorders, loss of its function at later stages contributes to neurodegenerative disorders (Figure 2). Axonal transport defects in the form of aggregates and synapse loss are observed in neurons missing FEZ1 (Gindhart et al., 2003; Toda et al., 2008; Chua et al., 2012).

Moreover, progressive aggregation of FEZ1 is observed in brains of the triple-transgenic mouse model of AD (3xTg-AD). These features are frequently found in neurodegenerative diseases such as Alzheimer’s disease (Bitetto and Di Fonzo, 2020). Importantly, FEZ1 is phosphorylated by microtubule affinity regulating kinases, which also phosphorylate Tau and are implicated in the formation of neurofibrillary tangles and disruption of axonal transport (Butkevich et al., 2016; Combs et al., 2019). Loss of FEZ1 phosphorylation either via substituting the targeted serine with an alanine residue or by using microtubule affinity regulating kinases/PAR-1 mutants also causes axonal transport effects.

In addition to stranded cargoes, loss of FEZ1 in neurons causes the abnormal appearance of axonal autophagosomes (Chua et al., 2012). In agreement with these observations, FEZ1 inhibits autophagy but formation of a FEZ1-UNC-51-like kinase-short coiled coil protein (SCOC) complex allows autophagy to proceed (McKnight et al., 2012). Alternatively, release of ultraviolet radiation resistance associated gene (UVRAG) from a complex with FEZ1 and SCOC is thought to allow it to initiate autophagy via associating with the vacuolar protein sorting 34 complex. Loss of FEZ1 could prevent the formation of this complex and allow UVRAG to constitutively activate autophagy. Increased autophagy to remove damaged cellular components has been implicated as a protective mechanism in neurodegeneration (Menzies et al., 2017). This could indicate an attempt by affected neurons to clear up axonal aggregates. As such, it would be interesting to investigate if autophagic abnormalities associated with loss of FEZ1 is linked to susceptibility to neurodegeneration and its onset.

FEZ1 may be implicated in other neurodegenerative disorders as well. Axonal aggregates have not been observed in motor neurons lacking FEZ1 (Gunaseelan et al., 2021). However, given the identification of Kinesin-1 mutations in ALS patients, it will be relevant to determine if FEZ1 malfunctions could also contribute to motor neurone disorders. Moreover, given the involvement of dysfunctional mitochondrial dynamics in neurodegenerative diseases it would also be important to determine if abnormalities in mitochondrial trafficking arising from perturbed FEZ1 function could also contribute to neuronal degeneration. Finally, while FEZ1 also binds Huntingtin, its role in Huntington’s disease remains uncharacterized (Goeehler et al., 2004).

Conclusion

Accumulating evidence has highlighted the importance of FEZ1 in the development, formation and maintenance of neuronal networks in the brain as well as peripheral nervous system. Notably, altered FEZ1 function causes abnormalities in the development and maintenance of neuronal networks that are associated with neurodevelopmental as well as neurodegenerative disorders involving cognitive and motor deficits. Further elucidation of the protein and its functions will provide important insights into our understanding of how neurons are wired together for the proper functioning of the brain and its associated neuronal networks.

Author contributions: All authors contributed to data collection and writing. The final version of the manuscript was approved by all authors.

Conflicts of interest: The authors declare no conflicts of interest.

Financial support: This work was supported by funding from the Singapore Ministry of Education (T1-2015 April-G3), the National University of Singapore, and from Institute for Health Innovation and Technology to JIEC.

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Plagiarism check: Checked twice by iThenticate.
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