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FGF binding proteins (FGFBPs): Modulators of FGF signaling in the developing, adult, and stressed nervous system

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Abstract

Members of the fibroblast growth factor (FGF) family are involved in a variety of cellular processes. In the nervous system, they affect the differentiation and migration of neurons, the formation and maturation of synapses, and the repair of neuronal circuits following insults. Because of the varied yet critical functions of FGF ligands, their availability and activity must be tightly regulated for the nervous system, as well as other tissues, to properly develop and function in adulthood. In this regard, FGF binding proteins (FGFBPs) have emerged as strong candidates for modulating the actions of secreted FGFs in neural and non-neural tissues. Here, we will review the roles of FGFBPs in the peripheral and central nervous systems.

Keywords

FGFBP; Synapse; Neuromuscular junction; Aging; Diseases; Injury

1. Introduction

Fibroblast growth factor binding proteins (FGFBPs) affect a plethora of biological processes by modulating the actions of FGF ligands. Three genes encoding FGFBPs (FGFBP1, FGFBP2 and FGFBP3) are present in humans and other species. Rodents, however, are an exception to this as they lack an FGFBP2 gene locus [1]. Additionally, FGFBP2 is produced in lymphoid tissues, where it appears to modulate immune responses [2–6]. Hence, FGFBP2 is not discussed further in this review. Despite the evolutionary divergence of these three genes, FGFBPs are highly homologous across species (Fig. 1). Each contains a signal sequence for secretion as well as binding sites for heparin and FGF ligands. These structural features allow FGFBPs to reversibly bind and increase the bioavailability of FGF ligands.

FGFs are expressed in most tissues and play essential functions at all stages of development and in adulthood. In humans and rodents, 22 genes encode for 18 secreted and 4 intracellular

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FGFs [20]. While intracellular FGFs interact with voltage-gated sodium channels and other intracellular proteins to modulate biological processes, secreted FGFs function by activating FGF receptors (FGFRs) in an autocrine or paracrine fashion [21]. Secreted FGFs can be further segregated into subfamilies based on interacting cofactors, binding and activation of one of the four FGFRs and splice variants, as well as sequence and evolutionary similarities [21]. To date, FGFBP1 and FGFBP3 have been found to bind and enhance the biological actions of the FGF1 and FGF7 subfamilies. While FGFBP1 interacts with and augments the activity of FGF-1, -2, -7, -10 and -22 [14,22,23], FGFBP3 has been shown to bind and affect the actions of FGF2 [19,24]. Through these and potentially other FGF ligands, FGFBPs have been found to play important roles in various types of cancer, modulating vascular function, and accelerating repair of damaged skin and kidneys [23,25–32]. Additionally and the focus of this review, FGFBPs have been implicated in the development, maintenance, and repair of neural circuits.

2. Mode of action of FGFBPs

Although it is clear that FGFBPs act through FGF ligands, there are outstanding questions regarding the mode of action of FGFBPs. In particular, it remains unknown when FGFBPs interact with FGFs in vivo. It is also unclear how the interaction between FGFBPs and FGFs affect FGF signaling. Based on published data and the domains present within FGFBPs, several models can be constructed to explain the mode of action of FGFBPs (Fig. 2). In one model, FGFBPs bind and release FGFs associated with heparan sulfate proteoglycans (HSPGs) in the extracellular matrix (ECM) (Fig. 2a). This model is particularly intriguing in light of the fact that FGFBP1 was found to bind near the FGF7 binding site of perlecan, a HSPG with important roles at synapses [33–35]. However, FGFBPs appear to displace rather than pluck away FGF7 from perlecan. Biochemical studies have also shown that FGFBPs, heparin and heparan sulfates do not simultaneously bind to FGFs [22,36]. Thus, there is no evidence that FGFBPs bind and release FGFs associated with HSPGs. In a second model, FGFBPs instead bind to FGFs following their release into the ECM from HSPGs by heparanases, sulfatases, and proteinases (Fig. 2b). In this case, it is plausible that chaperoning FGFBPs serve to protect FGFs from proteolysis during their migration to FGF receptors (FGFRs). In a third model, FGFBPs bind to FGFs immediately after being secreted from cells and, thus, prior to interacting with HSPGs (Fig. 2c). Each of these models is possible when considering the evidence that FGFBPs compete with heparin for FGF binding [22,33], as well as the literature suggesting that HSPGs serve as a reservoir for FGFs [20,21,37].

FGFBPs may modulate FGF-signaling through additional mechanisms. For example, the heparin- and FGF-binding domains may allow FGFBPs to participate in the secretion of FGFs together with other proteins. FGF1 and FGF2 lack a signal peptide and are not secreted through the endoplasmic reticulum/Golgi pathway and, therefore, require unique assistance by cell surface proteins for secretion [21]. FGF1 secretion occurs following its interaction with a heparin-binding complex composed of synaptotagmin 1 and S100A13 [38]. FGF2 requires direct interaction with cell-surface HSPGs, such as perlecan, for secretion into the ECM [33,39–41]. In either case, it is possible that FGFBPs could interact with these protein complexes via its heparin-binding domain and with FGF1/2 through its

FGF-binding domain to assist in their secretion. Additionally, FGFBPs may alter the relationship between FGFs and FGFRs, and thereby impact varied biological processes. FGF1/2 bind and activate all FGFRs and their splice variants. FGF7/10/22 only bind and activate the 2b splice variant of FGFR1 and FGFR2 [23,42]. To date, it remains unknown whether FGFBP1 affects the affinity of FGF1/2 for the b-isoforms of FGFRs, or possibly allows FGF7/10/22 to bind and activate additional FGFR isoforms, such as the c-isoform. Lastly, FGFBPs may cooperate with HSPGs to augment FGFs availability at sites populated by preferred and non-preferred FGFRs. During development, cells expressing FGFR2b tend to express FGF ligands with specificity to FGFR2c, while cells expressing the c-isoform express FGF ligands specific to the b-isoform [43,44]. This pattern of expression makes it possible for neighboring cells to coordinate their differentiation. If present, FGFBPs may be utilized to adjust levels of FGF-signaling necessary for the differentiation of each cell type. In adulthood, FGFBPs may function to alter the bioavailability and binding of FGF ligands to different FGFRs, and thereby allow FGF-secreting cells to affect several different cell types. Through these potential modes of action, FGFBPs may modulate FGF-signaling to ensure the proper formation, stability, and repair of neuronal tissues.

3. FGFBPs actions in the peripheral nervous system (PNS)

Recent studies have examined the expression and function of FGFBP1 at neuromuscular junctions (NMJs), the synapse formed between α -motor neurons and extrafusal muscle fibers. These studies uncovered important functions for FGFBP1 in the development, maintenance, and repair of NMJs. In addition, FGF ligands known to interact with FGFBPs are known to play diverse and critical roles in the PNS. The known and potential additional functions of FGFBPs in the PNS are discussed in this section.

3.1. FGFBPs at developing NMJs

The formation and stability of the NMJ requires instructive molecular signals secreted by muscle fibers and innervating motor axons. FGF7/10/22, the ligands shown to bind FGFBP1 [23], are among muscle-derived soluble signaling factors proposed to act to ensure the timely maturation of the presynaptic region (motor axon nerve ending responsible for secreting neurotransmitters) at the NMJ during development [45–47]. These ligands act through FGFR2, located on the presynaptic membrane, to promote the clustering of synaptic vesicles. Demonstrating the importance of this signaling module in the development of NMJs, deletion of FGFR2 has been shown to delay the timely clustering of synaptic vesicles in developing NMJs [48].

FGF2, a ligand through which both rodent FGFBPs are known to act, has also been found to play important roles at developing NMJs by activating FGFR1 following its release from muscles and motor neurons. Recombinant FGF2 increases the clustering of synaptic vesicles, an early cellular change at developing NMJs, when added to cultured motor neurons [49]. Additionally, FGF2 is important for the timely elimination of supernumerary axons innervating a single muscle fiber, a term often referred to as “synaptic elimination” [50–52]. In mice and rats, synaptic elimination ends around nine postnatal days (P9), but injection of FGF2 into rat gastrocnemius muscles at P2 slows the rate of synaptic

elimination, and muscle fibers remain innervated by multiple motor axons until P14 [51]. However, another study found a contrary phenotype. Seitz and colleagues [53] showed that deleting FGF2 in mice slows the rate of synaptic elimination. While these published data appear to contradict each other, it is worth noting that the first study injected FGF2 during synapse elimination whereas FGF2 was deleted in the germ line, and thus globally and permanently, in the second study. It is therefore plausible that the levels of FGF2 at specific stages of development and secreted from unique cell types have different effects on the formation of the NMJ. In this regard, FGF2 levels have been found to correlate with different cellular changes associated with synaptic elimination [52], such as the arrival of the growing motor axon, the differentiation of the motor axon growth cone into a presynaptic site, and the reduction of nerve sprouts that migrate beyond the post-synaptic site. In addition to affecting the presynaptic region of the NMJ, FGF2 also affects the development of the postsynaptic region. Specifically, FGF2 was found to induce the aggregation of nicotinic acetylcholine receptors (nAChRs), which are responsible for receiving and decoding cholinergic transmission derived from innervating α -motor axons [54]. Although the impact of FGF2 on NMJ development and maturation is broad and somewhat contradictory, it is clear that FGF2 function must be tightly regulated. Thus, it is plausible that FGFBPs may play a key role in regulating the actions of FGF2 at developing NMJs.

Among FGFBPs, there is growing evidence to suggest that FGFBP1 promotes presynaptic maturation of developing NMJs, possibly through its interaction with FGF7/10/22. FGFBP1 enhances the ability of FGF10 to induce aggregation of synaptic vesicles along neurites of cultured motor neurons [55]. In vivo, decreasing FGFBP1 using interfering RNA delays the aggregation of synaptic vesicles at presynaptic sites and reduces the size of the postsynaptic region at developing NMJs [47]. Additionally, we recently demonstrated that deletion of FGFBP1 delays the aggregation of synaptic vesicles at the presynapse and slows synaptic competition at the developing NMJ in mice [56]. In light of previous findings characterizing the role of FGF7/10/22 in orchestrating presynaptic maturation [45,48], we propose that FGFBP1 may work in concert with these ligands at developing NMJs. Interestingly, FGFBP1 expression is relatively low in developing compared to adult skeletal muscles. In stark contrast, FGF7/10/22 are expressed at high levels early in development, but decrease as skeletal muscles and their NMJs mature [55,57]. This anti-correlated expression pattern suggests that FGFBP1 may not have a major effect on FGF-signaling in the early stages of NMJ maturation, but may become increasingly important for regulating FGF activity during the later stages of NMJ maturation.

In addition to the high levels of FGF ligands during the earlier stages of NMJ development, the presynaptic and postsynaptic regions are in very close proximity during this time [58]. We propose that this architectural design could make it more feasible for FGFs to reach and activate FGFRs located in opposite membranes without the aid of FGFBPs (Fig. 3). Additionally, the short distance between the presynaptic and postsynaptic regions at developing NMJs may be sufficient for FGFs bound to HSPGs to directly activate FGFRs (Fig. 3). The extracellular space separating the NMJ is referred to as the synaptic cleft, which is relatively small early in development but increases to become approximately 50 nm wide [58] in adulthood (Fig. 3). The synaptic cleft is populated by a myriad of molecules including HSPGs known to play active roles in the formation and maturation of presynaptic

and post-synaptic sites. In particular, neuronal-agrin (z-agrin) and perlecan are critical for the formation, maturation, and stability of the NMJ [34,35,59–62]. Thus, it is possible that HSPGs, such as z-agrin and perlecan, are utilized by FGF2 and FGF7/10/22 to activate FGFRs in developing skeletal muscles and their NMJs. Supporting this notion, FGF2 has been demonstrated to bind z-agrin [63]. Furthermore, in cultured motor neurons, z-agrin enhances the ability of FGF2 to stimulate neurite formation [64]. Additionally, FGF7 has been found to bind to perlecan, an interaction that may aid in its synaptogenic activity [40,65]. Based on these data, we propose that FGFBPs may be less important for FGFs to promote the initial maturation of the NMJ (Fig. 3a). However, as levels of FGFs decrease and the synaptic cleft widens during the later stages of NMJ maturation (Fig. 3b–), appropriate levels of FGF-signaling may be bolstered by a concomitant increase in FGFBP1 expression in skeletal muscles [56].

3.2. FGFBPs at adult NMJs

In skeletal muscles, FGFBP1 was initially discovered as a factor utilized by a microRNA, miR-206, to promote reinnervation of previously vacated postsynaptic sites following injury and in amyotrophic lateral sclerosis (ALS) [47,66]. Recently, we demonstrated important roles for FGFBP1 at NMJs during normal aging and in the SOD1^{G93A} mouse model for ALS [56]. Similar to miR-206, FGFBP1 is enriched at the endplate region of skeletal muscles, where NMJs are located, in healthy adult mice. However, FGFBP1 expression decreases at the endplate region and elsewhere in skeletal muscles with advancing age. FGFBP1 expression also decreases in skeletal muscles of SOD1^{G93A} mice prior to obvious morphological changes at NMJs and outward ALS-related pathological symptoms. While FGFBP1 expression decreases, the synaptic cleft likely further widens in part due to excess deposition of ECM proteins in aged and ALS-affected skeletal muscles [67,68]. In light of this, we hypothesize that a combination of decreased expression of FGFBP1 and changes in the ECM results in diminished FGF-signaling, which may be a contributing factor to the pathophysiological features that accrue with advancing age and progression of ALS in skeletal muscles. In support of this hypothesis, we recently showed that deletion of FGFBP1 accelerates age-related degeneration of NMJs and alters expression of genes critical for the function of the NMJ and involved in muscle atrophy. We also found that FGFBP1 is required to slow the degeneration of ALS-affected NMJs [56]. Loss of FGFBP1 accelerates the degeneration of NMJs in SOD1^{G93A} mice, and shortens their lifespan. These published findings demonstrate that FGFBP1 plays important roles in the timely development and maintenance of adult NMJs.

4. Regulation of FGFBP1 expression in skeletal muscles and NMJs

Since FGFBP1 is important for slowing the degeneration of NMJs, it is critical to understand the molecular mechanisms that inhibit FGFBP1 expression in aged and ALS-affected skeletal muscles. The transforming growth factor beta (TGF- β) is a prime candidate for inhibiting FGFBP1 expression in skeletal muscles. TGF- β has been shown to repress FGFBP1 expression in mesenchymal and neural crest cells as they differentiate into smooth muscles [69]. In addition, TGF- β inhibits expression of the Krüppel-like factor 15 (KLF15) transcription factor, which promotes FGFBP1 expression in skeletal muscles [70]. The TGF-

β pathway is also known to drive muscle atrophy with advancing age and in ALS [71], two conditions in which FGFBP1 expression decreases. It is therefore not surprising that TGF- β and FGFBP1 levels are anti-correlated in skeletal muscles of developing, healthy young adult, ALS-affected, and aged mice [56]. Demonstrating a direct relationship between TGF- β and FGFBP1 in skeletal muscles, TGF- β inhibits FGFBP1 expression when added to cultured myotubes. Supporting the notion of a direct effect, SB-431542, a small pharmacological agent that blocks the activity of the TGF- β type I receptor, prevents TGF- β from inhibiting FGFBP1 expression in cultured myotubes. TGF- β was also found to accumulate at the synaptic cleft of NMJs in degenerating skeletal muscles. This finding suggests that TGF- β inhibits FGFBP1 in the synaptic region of stressed skeletal muscles possibly by inhibiting the miR-206/HDAC4 signaling axis, which concentrates at the NMJ and modulates FGFBP1 expression [47,69,72,73].

5. Unanswered questions regarding FGFBPs in the PNS

The role of FGFBP1 in repairing NMJs remains unexplored in healthy adult skeletal muscles. This is despite the fact that FGFBP1 was discovered as a factor that miR-206, a synaptically-enriched microRNA, utilizes to promote reinnervation of muscle fibers, and thus reconstitution of whole NMJs [47]. It also remains unknown if FGFBPs augment the ability of FGF1 and FGF2 to induce the growth of peripheral nerves during both development and following injury [74–76]. Although not a focus of this review, FGFBPs may also play important functions in myogenesis during development, aging and progression of diseases. Among FGFBP ligands, FGF1 and FGF2 have been shown to affect the proliferation and differentiation of muscle satellite cells [77–86]. However, these FGF ligands do not appear to be very effective at promoting myogenesis in aged animals [77], and this may be due in part to the development of age-related changes in ECM composition [87]. The ECM has also been shown to change in diseases that affect skeletal muscles, such as the spectrum of muscular dystrophies [88]. These are conditions where FGFBPs would presumably be most beneficial for myogenesis as well as for the NMJ given their ability to release FGFs from the ECM, and thus promote FGF-signaling. However, the expression of FGFBPs in aged and muscular dystrophy-affected skeletal muscles remains largely unexplored. While we recently showed that FGFBP1 decreases in skeletal muscles with advancing age [56], FGFBP1 expression in skeletal muscles afflicted with muscular dystrophy has yet to be determined. There is even less known regarding levels and function of FGFBP3 in healthy, aged and disease-affected skeletal muscles and their NMJs. If decreased, the loss of FGFBPs could impair the ability of FGFs to traverse the ECM, and thus induce myogenesis. Additionally, it is imperative to determine if FGFBPs bind to additional secreted FGF ligands, such as FGF6, that are known to play key roles in skeletal muscles [21,89,90] and elsewhere in the PNS. These questions will need to be addressed to better understand the roles of FGFBPs in developing, adult and stressed skeletal muscles, NMJs, and peripheral nerves.

6. Role of FGFBPs and their binding partners in the central nervous system (CNS)

To date, there is little information regarding the expression and function of FGFBPs in the CNS. In one study, FGFBP3 was found expressed at high levels in the brain during development but decreased in the brain of adult mice. This study also showed that FGFBP3 is primarily expressed by neurons [24]. Importantly, it demonstrated that deletion of FGFBP3 reduces neuronal activity in the orbitofrontal cortex, causing anxiety-like behaviors. Recently, Schmidt et al. revealed that FGFBP1 may also play important roles in the CNS [91]. The authors performed a comprehensive analysis of mice lacking FGFBP1, detailed in the supplementary material of the publication, including behavioral and electrophysiological tests. They discovered that mice lacking FGFBP1 have altered auditory brain stem response, a measure of hearing sensitivity in mice, and increased likelihood of falling off a rotarod before completion of the test even though the time spent on the rotarod was not significantly different. In an open field test, mice lacking FGFBP1 were less likely to enter, spent less time, and covered less distance within the center of the field. These mice also exhibited a lower frequency of rearing compared to wild-type mice. Interestingly, several of these behavioral alterations were more severe in female mice lacking FGFBP1. These studies thus indicate that FGFBPs play important functions in the CNS, and their loss contributes to neurological deficits.

The published findings described above suggest that FGFBPs are important for modulating the actions of FGFs involved in the wiring of neural circuits in the CNS. Consequently, there is a rich literature on the role of FGF1/2 and FGF7/10/22, FGFBP ligands, in synapse development, plasticity, and repair in the CNS [92–94]. Based on this, some inferences can be made about the potential roles of FGFBPs in the CNS due to their modulatory activity of FGF ligands. For example, FGF7/10/22 are intimately involved in promoting the formation and maturation of synapses in the CNS [46,55,94]. Neurons in the hippocampus, dorsal lateral geniculate nucleus (dLGN), cerebellum, and spinal cord release FGF22 to promote the formation of excitatory synaptic inputs [46,95,96]. In the dLGN, neurons secrete FGF22 to ensure the timely development of retinogeniculate synapses [95]. In the cerebellum, conditionally deleting FGFR2b, the main receptor for FGF7/10/22, at P0 reduces the size, number, and intensity of synapsin-positive vesicles during development [94]. In the spinal cord, relay neurons secrete FGF22 to promote the reformation of corticospinal inputs following injury [97]. FGF7, on the other hand, is critical for the formation of inhibitory synapses in the CNS. In the hippocampus, pyramidal neurons release FGF7 to promote the formation of inhibitory synaptic inputs while also secreting FGF22 to promote the formation of excitatory synaptic inputs [46,94,98,99]. These studies have established FGF7/10/22 as target-derived synaptic organizing molecules secreted by post-synaptic neurons to direct the formation and maturation of presynaptic sites [55]. They have also shown that FGF7 and FGF22 are necessary for establishing the correct ratio of excitatory to inhibitory synapses in the hippocampus. Consequently, it is possible that FGFBPs may be involved in fine-tuning the excitatory-inhibitory balance during development. However, the spatial and temporal expression pattern of FGFBPs, and particularly FGFBP1, in the developing brain remains unknown.

FGF2 has also been shown to promote the maturation of excitatory synapses in the developing hippocampus. FGF2 expression is widespread throughout the CNS, including the hippocampus, and it is present as early as embryonic day 9 in mice [100–102]. In the CNS, expression of FGF2 is found in both neuronal and non-neuronal cell types, including astrocytes. Its specific role in synaptic maturation was first demonstrated in vitro by Li and colleagues [103], where treatment of cultured rat hippocampal neurons with recombinant FGF2 resulted in an overall increased number of presynaptic-like sites marked by increased aggregation of synaptophysin and synapsin I. FGF2 also increased the number of postsynaptic-like sites marked by increased aggregation of PSD95 and GluR1. These FGF2-induced changes resulted in a net increase in the number of synapses in cultured hippocampal neurons. Additionally, electrophysiological analysis using potassium stimulation showed that FGF2 leads to the formation of functional synapses since no differences in the percent of active synapses were observed between FGF2 treated and control groups. Subsequent in vivo work added support for the role of FGF2 in synapse formation [104]. Using transgenic mice that overexpress FGF2, increased VGluT1, but not VGAT or GABA levels were observed in the hippocampus by immunohistochemistry. This was accompanied by observations of elevated glutamate release following single cell stimulation of Schaffer collaterals in the hippocampus of FGF2 transgenic mice as well as increased susceptibility to kainate-induced seizures [57]. Together, these results demonstrate a clear role for FGF2 in promoting the formation of glutamatergic synapses and may have important implications for FGFBPs in the developing hippocampus.

Although there are no reports that FGF1 plays roles in synapse formation in the brain directly, it should be noted that FGF1 is present throughout the developing rodent brain and spinal cord, and has been implicated in synaptic plasticity [102,105]. In addition, FGF1 is primarily expressed by specific neuronal cell types in the CNS [106]. Within neurons, FGF1 is localized to the cytoplasmic side of the extracellular membrane [107]. The presence of FGF1 at the extracellular membrane of neurons in the developing brain suggests an unexplored role of FGF1 in neuronal development or the establishment of neural circuits, which includes the formation of synapses. These discoveries along with findings that various HSPGs, such as perlecan, play important functions in the CNS suggest that secretion of FGFBPs is important for modulating the synaptogenic actions of FGF ligands.

7. FGFBPs role in CNS pathology

As central modulators of FGF signaling with known roles at the NMJ, it is reasonable to posit that FGFBPs play important functions in the CNS affected by diseases, the normal aging process, and following injury. Accordingly, Bachis et al. [108] found that both FGF2 and FGFBP1 levels increase in the brains of rats treated with antidepressants. Specifically, they found that FGFBP1 remains increased in the cortex and hippocampus two weeks following treatment with desipramine or fluoxetine, which are norepinephrine and serotonin reuptake inhibitors, respectively. The sustained increase in FGFBP1 suggests that it may be involved in modifying the structure and function of neural circuits following noradrenergic and serotonergic treatments, potentially by modulating FGF2-initiated signaling. More recently, Yamanaka et al. showed that FGFBP3 is necessary to prevent changes in neural circuits that cause anxiety-like behaviors [24], and loss of FGFBP1 results in behavioral and

electrophysiological alterations in mice [91]. Supporting these and other roles for FGFBPs in the CNS, FGF7 and FGF22 are critical for establishing the correct ratio of excitatory to inhibitory synapses, and disrupting their function alters the threshold for neuronal activity associated with epileptogenic seizures [46,98,109]. Moreover, a wealth of evidence has accumulated demonstrating the importance of FGF1/2, FGF7/10/22 and HSPGs in long-term potentiation, neurogenesis, and neuronal migration in the developing and adult brain [110–125] as well as in CNS disorders and injury [57,117,126–132]. In the spinal cord, Tassi et al. [133] demonstrated that FGFBP1 is upregulated at the lesion site of injured rat spinal cords. Their study also provides evidence that FGFBP1 works in concert with FGFs to promote the regeneration of axons in the injured spinal cord. Together, these published findings indicate that FGFBPs likely mediate a variety of cellular processes critical for preventing and repairing damages that occur in the CNS.

8. Conclusion and final remarks

Over the last three decades, data have accrued indicating important functions of FGFBPs in the nervous system. FGFBP1 has been shown to play important roles at NMJs during development, normal aging and in ALS. It has also been found to be important for repairing neural circuits in the spinal cord. There is also evidence suggesting roles for both FGFBP1 and FGFBP3 in the formation and function of neural circuits in the brain. However, there is still much to be learned about the function of FGFBPs in the PNS and CNS. In the PNS, it remains unknown if FGFBPs augment the ability of FGF ligands to promote nerve growth during development and following injury. The role of FGFBPs at the synaptic cleft of regenerating synapses has also not been established. In the CNS, there are even more outstanding questions regarding the function of FGFBPs. The role of FGFBPs in synaptogenesis, maintaining the stability of synapses and repairing damaged neural circuits has yet to be determined in the brain and spinal cord. To fully answer these questions, it will be necessary to determine if each FGFBP acts alone or synergizes with others to optimally impact FGF-signaling. At a more basic level, there is limited information concerning the cellular source, location and mode of action of FGFBPs in the CNS. For example, are FGFBPs co-expressed with their ligands in neurons or other CNS resident cells? Where do FGFBPs concentrate once released? Are FGFBPs required to release FGFs that become stuck in HSPG-rich regions that accumulate in the CNS during aging, in diseases such as Alzheimer's disease, and following traumatic brain and spinal cord injuries? Answers to these questions are necessary for understanding the function and potential of FGFBPs as therapeutic agents to prevent and reverse damages in the nervous system caused by diseases and injuries.

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Fig. 1.

Evolutionary relationship between FGF binding proteins. (A) Phylogenetic tree of FGFBP proteins. Nucleotide sequences for FGFBP1, -2, and -3 in select species were aligned with MUSCLE alignment and were built by the Phylogeny.fr platform using the neighbor joining method [7–13]. GenBank accession numbers for this analysis: humBP1 (NM_005130.4), msBP1 (NM_001271616.1), ratBP1 (NM_022603.1), chickBP1 (XM_420773.4), chimpBP1 (XM_009447384.2), rhesBP1 (NM_001194145.2), humBP2 (NM_031950.3), chickBP2 (NM_204447.1), chimpBP2 (XM_526532.6), rhesBP2 (NM_001194149.1), rabbBP2 (XM_002709363.2), humBP3 (NM_152429.4), msBP3 (NM_028263.1), ratBP3 (NM_001109165.1), chickBP3 (XM_015288868.1), chimpBP3 (XM_016918851.1), rhesBP3 (XM_001088750.3), rabbBP3 (XM_017348416.1). Numbers denote branch support values. Scale bar indicates branch length. (B) Domains present in human FGFBP proteins. The schematic depicts the primary heparin-binding domain and partially conserved heparin-binding domains of FGFBP1 [14–18]. Heparin-binding sites for FGFBP2 and FGF binding sites for FGFBP2 and FGFBP3 are predicted based on sequence homology [19]. Disulfide bonds for all FGFBPs are predicted by UniProt database. Numbers above domains indicate amino acids.

Fig. 2.

Proposed modes of action of FGFBPs in the ECM. FGFBPs presumably augment signaling by chaperoning FGFs through the ECM to FGFRs. While FGFs are known to interact with HSPGs following release into the ECM, the exact mechanism by which FGFBPs chaperone FGFs is not known. FGFBPs may assist FGF movement through the ECM by (A) displacing FGFs from HSPGs located distally from FGF receptors, (B) binding and chaperoning FGFs following degradation of HSPGs by heparanases, sulfatases, MMPs and other proteases, or (C) directly binding FGFs soon after secretion into the ECM, and prior to interacting with HSPGs.

Fig. 3.

Models for FGFs actions at the NMJ. (A) Elevated levels of FGFs assist in early NMJ formation by promoting formation of the motor axon terminal and clustering of synaptic vesicles. The synaptic cleft is relatively narrow during development, which introduces the possibility that muscle-secreted FGFs are capable of binding FGFRs on the presynapse either through direct interaction or with the assistance of HSPGs involved in synapse formation, such as perlecan and laminin. Levels of FGFBP1 are low during this period of NMJ development, making it an unlikely candidate for mediating FGF activity. (B) As the NMJ matures, the synaptic cleft widens, FGF levels begin to taper, and FGFBP1 levels increase. While it is possible that much FGF-signaling occurs independently of FGFBPs, the increased thickness and complexity of the ECM may cause FGFs to require assistance of FGFBPs to bind and activate FGFRs. (C) Adult NMJs are characterized by a relatively wide synaptic cleft with a complex ECM makeup. In adult skeletal muscles, FGF levels are lower and FGFBP1 levels are much higher than in developing muscles. FGF signaling is necessary for the maintenance of the NMJ and may rely entirely on the chaperone activity of FGFBPs to traverse the increased distance from the postsynaptic to the presynaptic site.