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FGFs: neurodevelopment's Jack-of-all-trades – how do they do it?

Jean M. Hébert [1,2] *

[1] Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, USA
[2] Department of Genetics, Albert Einstein College of Medicine, Bronx, NY, USA

Edited by:
Nicholas Gaiano, Johns Hopkins School of Medicine, USA

Reviewed by:
Maria J. Donoghue, Georgetown University, USA
Umberto Di Porzio, Institute of Genetics and Biophysics, Italy

***Correspondence:**
Jean M. Hébert, Department of Neuroscience, Albert Einstein College of Medicine, Kennedy Building, 1410 Pelham Parkway South, Bronx, NY 10461, USA.
e-mail: jean.hebert@einstein.yu.edu

From neurulation to postnatal processes, the requirements for FGF signaling in many aspects of neural precursor cell biology have been well documented. However, identifying a requirement for FGFs in a particular neurogenic process provides only an initial and superficial understanding of what FGF signaling is doing. How FGFs specify cell types in one instance, yet promote cell survival, proliferation, migration, or differentiation in other instances remains largely unknown and is key to understanding how they function. This review describes what we have learned primarily from *in vivo* vertebrate studies about the roles of FGF signaling in neurulation, anterior–posterior patterning of the neural plate, brain patterning from local signaling centers, and finally neocortex development as an example of continued roles for FGFs within the same brain area. The potential explanations for the diverse functions of FGFs through differential interactions with cell intrinsic and extrinsic factors is then discussed with an emphasis on how little we know about the modulation of FGF signaling *in vivo*. A clearer picture of the mechanisms involved is nevertheless essential to understand the behavior of neural precursor cells and to potentially guide their fates for therapeutic purposes.

Keywords: FGF, neural patterning, cell survival, neurogenesis, telencephalon, neocortex

INTRODUCTION

FGFs were first identified as factors derived from bovine pituitary and brain that were mitogenic for fibroblasts (Armelin, 1973; Gospodarowicz, 1974, 1975). The first two FGFs that were purified, cloned, and sequenced were acidic and basic FGF (aFGF, bFGF, now FGF1, and FGF2; Abraham et al., 1986a,b). FGFs can be found throughout metazoan species and the number of genes encoding them significantly expanded in early vertebrate evolution (Itoh and Ornitz, 2004, 2011; Popovici et al., 2005). In mammals there are 22 genes that encode FGFs. Since their identification as mitogenic factors for fibroblasts, the list of biological processes in which they are known to play crucial roles has grown to a surprising length – and continues to grow (Beenken and Mohammadi, 2009; Dorey and Amaya, 2010; Itoh and Ornitz, 2011). Nowhere is this more obvious than in the regulation of neural development where FGFs are found to be required for an increasing number of processes.

FGF genes can be divided into subfamilies based on their sequence and the mode of action of their respective peptides (Itoh and Ornitz, 2011). FGFs, except those from two subfamilies, are thought to act in a paracrine fashion. The hormone-like FGFs (FGF15/19, 21, 23) instead act in an endocrine manner (Beenken and Mohammadi, 2009), while the intracellular FGFs (FGF11–14) are thought to function in an FGF receptor-independent manner (Goldfarb, 2005). Although some members of all the subfamilies are likely to influence CNS development and/or function (see below; Mason, 2007; Iwata and Hevner, 2009; Umemori, 2009; Vaccarino et al., 2009; Guillemot and Zimmer, 2011), many of their roles may still remain unknown. This is in part because although almost all FGF genes have been knocked out individually (Itoh and Ornitz, 2011), those with overlapping expression patterns may functionally compensate for each other and mask the other's role at different developmental times and in different tissues.

In contrast to the large number of genes encoding ligands, only four genes, *Fgfr1–4*, encode FGF receptors. This is a more manageable number of genes to work with in order to overcome compensation when disrupting FGF signaling. The extracellular portion of FGF receptors is comprised of three immunoglobulin-like domains and an acid box while the intracellular portion contains a split tyrosine kinase domain. A fifth receptor gene, *Fgfrl1*, also exists, but does not encode an intracellular domain and is not yet known to have a function in the CNS. Alternative splicing of *Fgfr1–4* transcripts leads to receptors with differing extracellular domains, but most alternatively spliced forms contain the intracellular kinase domain (Johnson and Williams, 1993). Upon binding FGF ligand, receptors dimerize, autophosphorylate, and phosphorylate one or more of several immediate intracellular mediators described in sections below.

FGFs play essential roles in the induction and anterior–posterior (A–P) patterning of the neural plate, in the local patterning of several developing brain regions, in several steps in neurogenesis, and in establishing functional neural networks. Moreover, at the level of the cell, FGFs within the developing CNS are in some cases required for cell survival, fate specification, proliferation, migration, differentiation, or axon pathfinding. What can account for such diverse functions? Here, rather than providing a comprehensive review of FGFs in neurodevelopment, select examples of the different functions of FGFs in the developing neural plate and neocortex are provided to illustrate the broad spectrum of FGF

functions. In addition, the differences in FGF ligands, receptors, intracellular and extracellular modulators, and signal transduction pathways are discussed as potential explanations for the wide range of FGF effects (**Figure 1**).

FGFs ARE REQUIRED FOR EARLY PATTERNING PROCESSES IN CNS DEVELOPMENT

FGFs play roles in the earliest steps of CNS development (**Table 1**). To start with, FGF signaling participates in neural induction, although there is still some controversy as to the extent of its involvement in each species. In zebrafish, chick, and ascidian embryos FGF signaling is necessary and sufficient to initiate the acquisition of a neural fate (Rodriguez-Gallardo et al., 1997; Inazawa et al., 1998; Streit et al., 2000; Wilson et al., 2000; Hudson and Lemaire, 2001; Bertrand et al., 2003; Sheng et al., 2003; Kudoh et al., 2004), with perhaps a greater role in inducing posterior neural fates (Alvarez et al., 1998; Storey et al., 1998; Rentzsch et al., 2004; Londin et al., 2005; Takemoto et al., 2006). In *Xenopus*, even though some studies suggest no role for FGFs in neural induction (Kroll and Amaya, 1996; Wills et al., 2010), other studies indicate that it plays either a role in establishing posterior fates or in inducing anterior versus posterior fates in a time-dependent manner (Kengaku and Okamoto, 1995; Lamb and Harland, 1995; Launay et al., 1996; Sasai et al., 1996; Pera et al., 2003; Delaune et al., 2005; Marchal et al., 2009). A role for FGFs in neural induction in mammals remains to be clearly demonstrated.

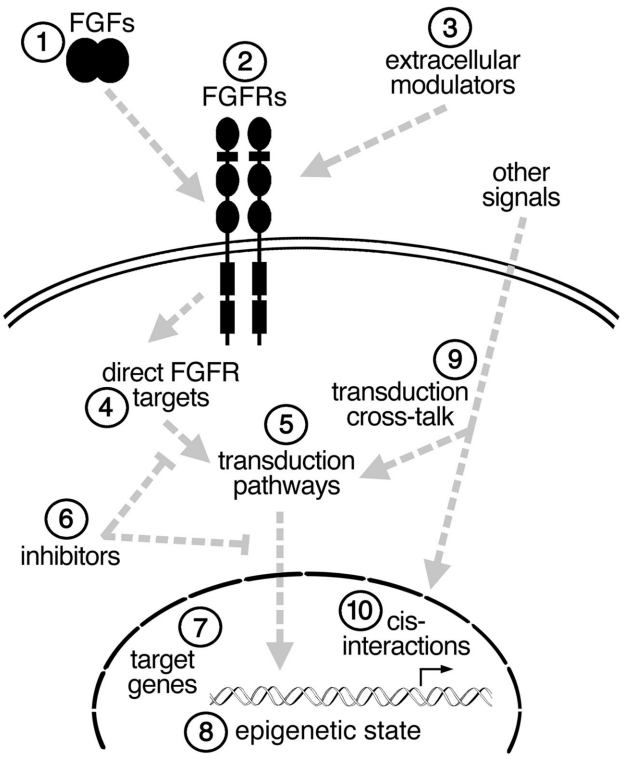

FIGURE 1 | Simplified schema illustrating some of the possible steps (1–10) at which an FGF signal could be modulated in different cell types to affect cell fate. See text for details.

Perhaps as an extension of its role in neural induction, FGF signaling is also essential for patterning the neural plate along its A–P axis as part of the overall A–P patterning of the embryo (Amaya et al., 1991; Isaacs et al., 1992; Griffin et al., 1995; Draper et al., 2003). Studies using chick, zebrafish, and *Xenopus* embryos show that graded FGF signaling, with high posterior and low anterior levels, patterns the neural plate at least in part by regulating the expression of Hox genes, which in turn determine the positional identities of neurons along the developing spinal cord (Isaacs et al., 1994; Cox and Hemmati-Brivanlou, 1995; Kengaku and Okamoto, 1995; Lamb and Harland, 1995; Pownall et al., 1998; Holowacz and Sokol, 1999; Ribisi et al., 2000; Liu et al., 2001; Bel-Vialar et al., 2002; Kudoh et al., 2002; Dasen et al., 2003). In mammals, FGFs are also likely required in A–P patterning of the neural plate given that FGFs (in particular *Fgf8*) are expressed in a high posterior to low anterior gradient in the neurulating embryo, ectopic FGF4 can suppress anterior development, and certain mutations in *Fgfr1* cause general A–P patterning defects (Partanen et al., 1998; Davidson et al., 2000). Of course other factors, WNTs, retinoic acid, BMPs, and BMP antagonists, are likely to participate with FGFs in patterning the neural plate (Dorey and Amaya, 2010).

As development proceeds, signaling centers that express FGFs emerge in discrete areas of the developing brain. At least three signaling centers have been characterized. One is rhombomere 4 (zebrafish) or 5 and 6 (mouse or chick) in the hindbrain. In zebrafish, FGF3 and FGF8 emanating from rhombomere 4 are necessary and sufficient to promote development of adjacent rhombomeres 5 and 6 by regulating the expression of transcription factors including Krox20 (Maves et al., 2002; Walshe et al., 2002; Waskiewicz et al., 2002; Wiellette and Sive, 2003; Hernandez et al., 2004; Labalette et al., 2011). Similar FGF-dependent patterning mechanisms are likely to operate in the developing hindbrain of other vertebrates since FGFs also regulate *Krox20* expression in chicks (Aragon et al., 2005). Moreover, FGF signaling also plays a role later in rhombomere development: FGF20a in zebrafish is

Table 1 | Examples of functions for FGF signaling in the nascent central nervous system and developing neocortex.

Early CNS	Neural induction
	Anterior–posterior patterning
	Rhombomere patterning
	Cerebellar and midbrain induction and patterning
	Telencephalon induction and patterning
Neocortex	Areal patterning
	Expansion of neuroepithelial progenitors
	Initiation of neurogenesis
	Maintenance of undifferentiated neurogenic precursors
	Gliogenesis
	Timing of oligodendrogenesis
	Axon pathfinding
	Synaptogenesis
	Adult functions?

See text for references.

essential during neurogenesis for maintaining precursor cells in segment centers in an undifferentiated state (Gonzalez-Quevedo et al., 2010).

A second signaling center that expresses FGFs is the isthmus at the mid–hindbrain boundary. Here FGF8, and to some extent FGF17 and 18, mediate the isthmus' organizing activity for inducing and patterning the midbrain and cerebellum. An ectopic source of FGF8 in the caudal diencephalon is sufficient to induce the formation of a normally organized, ectopic, mirror-image midbrain whereas deletion of *Fgf8* results in the loss of most or all midbrain and cerebellar structures due to cell death of the early precursors (Crossley et al., 1996; Martinez et al., 1999; Chi et al., 2003; Liu et al., 2003; Trokovic et al., 2003; Basson et al., 2008). FGF signaling is required concurrently and in a dose-dependent manner for both survival and patterning of cerebellar and midbrain precursors (Chi et al., 2003; Basson et al., 2008; Chen et al., 2009). As for rhombomere development, FGFs in the cerebellum play other roles later in development, for example as attractants for trochlear axons and in synaptogenesis (Irving et al., 2002; Umemori, 2004; Partanen, 2007; Yaguchi et al., 2009).

Finally, a third signaling center in which FGFs are required is the anterior neural ridge (ANR) at the anterior-most tip of the embryo between the neuroectoderm and underlying ectoderm. At least five FGFs, FGF3, 8, 15, 17, and 18, are expressed in the ANR or its early derivatives and three receptors FGFR1, FGFR2, and FGFR3 are expressed broadly in the anterior neuroectoderm. Similar to their function in mid–hindbrain development, FGFs emanate from the ANR to induce broad telencephalic cell types in a dose-dependent manner and to maintain the survival of telencephalic precursor cells (Shimamura and Rubenstein, 1997; Shanmugalingam et al., 2000; Shinya et al., 2001; Gunhaga et al., 2003; Walshe and Mason, 2003; Gutin et al., 2006; Storm et al., 2006; Theil et al., 2008; Paek et al., 2009). FGFs are also critical for several later steps of telencephalon development. The known requirements for FGFs in the developing neocortex, which comprises the dorsal part of the telencephalon, are described below as an example of the continued and varied functions for FGFs within one part of the brain.

REQUIREMENTS FOR FGFs IN THE DEVELOPING NEOCORTEX

In addition to inducing cell fates and maintaining cell survival in the early telencephalon, FGFs play key roles in the developing neocortex (**Table 1**; Iwata and Hevner, 2009). Early on, FGFs pattern and expand the neocortex. FGF8 acts as a morphogen and is necessary and sufficient to assign positional identities to cortical precursors along the anterior–lateral to posterior–medial axis in a dose-dependent manner (Fukuchi-Shimogori and Grove, 2001; Garel et al., 2003; Storm et al., 2006; Toyoda et al., 2010). FGF17, meanwhile, is required for patterning the frontal neocortex (Cholfin and Rubenstein, 2007). In addition to patterning, FGFs are required for expanding the pool of neuroepithelial precursor cells by extending the number of precursor cell divisions prior to generating neurons. For example, in the absence of FGF2, there are fewer precursor cells resulting in fewer neurons, especially in the anterior neocortex (Vaccarino et al., 1999; Raballo et al., 2000; Korada et al., 2002).

FGFs are also essential for the onset of cortical neurogenesis: FGF10 is required in rostral areas to promote the transition of neuroepithelial cells to radial glial cells, which in turn generate intermediate progenitors and neurons, marking the start of neurogenesis (Sahara and O'Leary, 2009). FGF8, meanwhile, is required to generate rostral Cajal–Retzius cells, one of the earliest born type of cortical neuron (Zimmer et al., 2010). During neurogenesis itself, if FGF signaling is disrupted by deleting one or more Fgfr genes, then the radial glial precursors fail to maintain their undifferentiated state and prematurely differentiate (Kang et al., 2009; Stevens et al., 2010). In this case, FGF18, which is expressed in neurons, is likely one of the ligands that feeds back to radial glia to maintain their precursor state (Hasegawa et al., 2004).

In addition to its roles in cortical patterning and neurogenesis, FGF signaling regulates the production of the other major classes of neural cell types, astrocytes, and oligodendrocytes. Toward the end of neurogenesis, FGFR1 and FGFR2, possibly responding to FGF9, are required for radial glia to transition from generating neurons to generating astrocytes (Smith et al., 2006; Tole et al., 2006; Seuntjens et al., 2009). And postnatally, FGFR3 is required for the timely onset of oligodendrocyte production (Oh et al., 2003). Hence FGF signaling plays continuous, yet distinct, roles throughout cortical development.

Not surprisingly, disruption of FGF signaling during cortical patterning, neurogenesis, and gliogenesis are associated with defects in axon pathfinding and behavioral anomalies in adult mice. The loss of midline glial cell types that result from disruption of *Fgfr1* leads to a failure of callosal and other axons to cross the midline and connect the neocortex of both hemispheres (Shanmugalingam et al., 2000; Walshe and Mason, 2003; Smith et al., 2006; Tole et al., 2006). Connections within each hemisphere of the cortex can also be disrupted, as shown in *Fgf8* hypomorphs (Huffman et al., 2004). Moreover, early ectopic sources of FGF8 can cause misrouting of thalamocortical axons (Shimogori and Grove, 2005). Imbalances in early cortical cell fate specification due to disruption of FGF signaling can also lead to behavioral anomalies such as abnormal social behaviors or hyperactivity, although the mechanism for the latter, whether due to a reduction in glutamatergic or a reduction in GABAergic neurons in the cortex, remains unclear (Shin et al., 2004; Muller-Smith et al., 2008; Scearce-Levie et al., 2008). Interestingly, FGF22 and FGF7 are required for the formation of glutamatergic and GABAergic synapses, respectively, in hippocampal CA3 neurons (Terauchi et al., 2010).

Finally, the roles for FGFs in adult neurogenesis, physiology, and homeostasis are largely unexplored. One or more of the intracellular FGFs (the FGFR-independent FGFs11–14) are likely to directly regulate the excitability of neocortical neurons as they do in the hippocampus and cerebellum (Goldfarb et al., 2007; Xiao et al., 2007; Shakkottai et al., 2009). The secreted FGFs are also likely to have functions in the adult cortex as diverse as during development, but these functions have yet to be determined in detail *in vivo*.

FGF–FGFR SIGNALING, DIFFERING LEVELS VERSUS DIFFERENT MECHANISMS

The genetic disruption of individual FGF ligand and receptor genes can clearly result in distinct phenotypes in the developing CNS and embryo (e.g., above; Beenken and Mohammadi, 2009).

Much of these phenotypic differences are likely due to the individual patterns and levels of expression for each gene, which does not explain how FGF signaling promotes cell survival in one case, or proliferation, differentiation, or the adoption of one of many cell identities in other cases.

Two broad, non-mutually exclusive possibilities exist to explain the varied effects of FGFs on cells: the first is that the individual ligands and/or receptors in fact transmit different signals to cells (for example, some FGF–FGFR combinations activate one transduction pathway whereas another combination induces a different pathway); and the second is that individual target cell types and their environments modulate and interpret an FGF signal differently (for example, one cell is predisposed to respond to FGFs by activating one intracellular pathway whereas another cell type responds by activating a different pathway). Although both of these possibilities will undoubtedly be found to affect FGF function *in vivo*, the little evidence that exists to date suggests that mechanistic differences in ligand–receptor signaling will be less substantial than the inherent modulation of the signal by the target cell type and its environment.

Although alternatively spliced forms of both ligands and receptors exist and these can affect binding specificities and levels of signaling as measured in cultured cells, binding of the FGF ligands to their receptors remains rather promiscuous (Ornitz et al., 1996; Zhang et al., 2006). Moreover, there is little evidence that distinct FGFs binding to the same receptors illicit distinct cellular responses. For example, the different effects of FGF8a and FGF8b on midbrain and cerebellar cell fates appear to simply reflect their different potencies (i.e., levels of activity; Sato and Nakamura, 2004).

Moreover, the existing evidence suggests that the receptors themselves transmit signal via the same intracellular pathways for a given cell type. For example, activation of FGFR1 promotes proliferation in some cell types, but activation of the intracellular domain of this receptor in chondrocytes leads to suppression of proliferation in a manner similar to FGFR3, the receptor that is normally expressed in these cells (Wang et al., 2001). Similarly, in zebrafish, constitutively active forms of several FGFRs each caused dorsalization, brain caudalization, and secondary axis formation, suggesting that signal transduction is similar among FGFRs for several embryonic cell types (Ota et al., 2009).

In addition, when the three *Fgfr* genes, *Fgfr1*, *Fgfr2*, and *Fgfr3*, that are expressed in the embryonic neuroepithelium are deleted in the early mid–hindbrain region, the telencephalon, or the neocortex, the cell death, patterning, and differentiation phenotypes obtained are dramatically more severe than loss of one or two receptors alone (Saarimaki-Vire et al., 2007; Kang et al., 2009; Paek et al., 2009). Hence the receptors can largely compensate for each other indicating that they likely signal through the same intracellular pathways for a given cell type.

This does not mean the receptors are equivalent and interchangeable since the efficiencies with which they activate downstream mediators may differ, leading to quantitative or qualitative differences in a cell's response. There might even be cases in which individual FGF ligands, which have different receptor binding preferences, illicit different responses on the same cells. For example, *Fgf15* and *Fgf8* appear to have opposite effects on telencephalic precursors (Borello et al., 2008; Danjo et al., 2011). In cases in which phenotypic differences are associated with different ligands, it becomes of interest to decipher the underlying mechanism, whether it is the activation of different receptors, the duration or strength of receptor activation, and/or the recruitment of different intracellular signal transduction components.

EXTRACELLULAR MODULATORS OF FGF SIGNALING

Extracellular molecules that interact directly with FGFs or their receptors may affect both the levels of signaling and the cellular responses. Perhaps the best characterized molecule that interacts with FGFs is heparan sulfate (HS) as part of heparan sulfate proteoglycans. HS is widely believed to be a required component of FGF signaling (Dailey et al., 2005; Mason, 2007; Beenken and Mohammadi, 2009; Krejci et al., 2009; Umemori, 2009; Itoh and Ornitz, 2011). For example, disruption of the *Ndst1* gene, which encodes an HS modifying enzyme, results in cerebral hyperplasia and mimics aspects of the forebrain phenotypes of FGF and SHH mutants (Grobe et al., 2005).

However, a strict requirement for heparan sulfate for FGF signaling has yet to be demonstrated *in vivo*. Expression of the *Exostoses 1* (*Ext1*) gene is essential for heparan sulfate biosynthesis in mice and without it no heparan sulfate can be detected (Lin et al., 2000). Yet, the *Ext1* null mutant survives later than the earliest FGF-related lethal phenotype, the *Fgf4* null phenotype (Feldman et al., 1995; Lin et al., 2000). Similarly, the phenotype of a CNS specific deletion of *Ext1* using a Nestin-Cre driver only recapitulates defects obtained with *Fgf8* hypomorphs or partial loss of Fgfr expression (Inatani et al., 2003). These results cast doubt on a strict requirement for heparan sulfate, although they do not rule it out due to other potential explanations for the discrepancies between *Ext1* associated phenotypes and the most severe FGF-associated phenotypes (such as strain differences, timing of recombination, heparan sulfate perdurance, or simultaneous loss in the *Ext1* mutants of other signals that act antagonistically to FGFs and therefore partially rescue loss of FGF signaling). The protein moieties of the heparan sulfate proteoglycans involved in FGF signaling within the developing CNS are largely uncharacterized, although Glypican-1 plays an important role during neurogenesis (Jen et al., 2009). Nevertheless, it remains likely that the association of heparan sulfates with FGF ligands and receptors promotes higher levels of signaling rather than affecting the nature of the intracellular response.

FGF ligands and receptors can also interact with a variety of other extracellular molecules, including NCAM, cadherins, integrins, fibronectin, Klotho, anosmin-1, EphA4, and others (Polanska et al., 2009). These could potentially regulate levels of signaling and cellular responses to FGFs. However, the importance of these proteins to FGF signaling and neurodevelopment remains unclear.

INTRACELLULAR FGF SIGNAL TRANSDUCTION

Proteins that can interact directly with the intracellular domain of FGF receptors and that may mediate signal transduction have been identified. Potential mediators include FGF receptor substrate (FRS) 2 and 3, Phospholipase-Cγ (PLCγ), CRK, growth factor receptor bound (GRB) 14, Src homology domain-2 containing protein B (SHB), and possibly a complex comprised of

GRB2, SH2-containing transforming protein C (SHC), and son of sevenless (SOS; Mohammadi et al., 1991; Wang et al., 1996; Kanai et al., 1997; Kouhara et al., 1997; Curto et al., 1998; Xu et al., 1998; Larrson et al., 1999; Ong et al., 2000; Reilly et al., 2000; Cross et al., 2002). FGF receptors can also translocate to the nucleus and interact directly with nuclear components (Wiedlocha and Sorensen, 2004; Bryant and Stow, 2005; Stachowiak et al., 2007). Importantly, the role for each protein that potentially interacts physically with the FGF receptors in mediating signaling remains unclear for any neurodevelopmental process *in vivo*.

The FRS proteins, in particular FRS2, are generally accepted as key mediators of FGF signaling (Wang et al., 1996; Kouhara et al., 1997; Xu et al., 1998; Ong et al., 2000; Hadari et al., 2001; Mason, 2007; Turner and Grose, 2010). FRS2 is a docking protein that appears constitutively bound to the juxtamembrane region of FGF receptors and becomes phosphorylated in the presence of FGFs. Upon phosphorylation, FRS2 is thought to recruit Grb2 and SHP2 leading to activation of the PI3K → AKT and Sos → Ras → Raf → MEK → MAPK pathways. These findings are based mainly on biochemical and cell culture data. Few studies have addressed the functional requirement for the interaction between FGF receptors and FRS proteins directly during neurodevelopment.

An *Fgfr1* mutant that specifically lacks the ability to bind FRS2 and FRS3 was directly compared to an *Fgfr1* null mutant in the same strain background. Whereas the *Fgfr1* null mutant exhibits failures in mesoderm migration during gastrulation, somitogenesis, and neural tube closure, leading to small, truncated embryos that die shortly after gastrulation, the *Fgfr1* mutant that cannot bind FRS undergoes normal gastrulation and somitogenesis, but exhibits neural tube, tail bud, and pharyngeal arch deficits (Deng et al., 1994; Yamaguchi et al., 1994; Hoch and Soriano, 2006). This suggests at the very least that FRS adaptor proteins are not the exclusive effectors of FGFR1 signal transduction *in vivo*. Likewise, an *Fgfr2* mutant that lacks the binding site for FRS2 and FRS3, can rescue the effects of a gain-of-function *cis* mutation in *Fgfr2* (Eswarakumar et al., 2006). However, no phenotype was reported for the FRS-binding mutation itself, yielding little insight on the normal requirement for the interaction between FGFR2 and FRS.

The phenotype of *Frs2* null mice themselves does not clarify the role of this molecule in mediating FGF signaling. *Frs2* null embryos lack normal extraembryonic tissue and die at ∼E8 (Gotoh et al., 2005), a phenotype that may overlap but does not recapitulate any FGF-associated phenotype. The interpretation of this result is confounded by the possibilities that there is some compensation by FRS3 and that FRS2 signaling is not specific to the FGF pathway (e.g., FRS2 can mediate neurotrophin signaling as well). *Frs2* mutants that lack the binding residues for the tyrosine phosphatase SHP2 fail to maintain intermediate progenitor cells during cortical neurogenesis (Yamamoto et al., 2005). However, intermediate progenitors do not express detectable levels of Fgfr genes and mutants in which FGF signaling is abolished during cortical neurogenesis fail to maintain the radial glial stem cells rather than the intermediate progenitors, which are unaffected (Kang et al., 2009), suggesting that FRS2 may be acting downstream of neurotrophins rather than FGFs in this process. Note that no knockout or knockdown studies for *Frs3* have been reported. Interestingly, the function of FRS-like proteins as direct targets of FGF receptors is not conserved in flies and worms (Wilson et al., 2004; Lo et al., 2010). Hence, in mammals there is still uncertainty as to where, when, and whether FRS is required *in vivo* for FGF signaling and how it might differentially affect cellular responses.

Similarly, PLCγ is postulated to be an important immediate target of FGFR phosphorylation (Mason, 2007; Turner and Grose, 2010), and regulation of this interaction could influence a cell's response. However, *in vivo* evidence is still sparse. PLCγ activates the IP3 → Ca^{++} and DAG → PKC pathways. A direct comparison of *Fgfr1* hypomorphic embryos to ones carrying an *Fgfr1* point mutation that abolishes the interaction with PLCγ revealed that both exhibit homeotic vertebral transformations, but in some cases in opposite directions along the A–P axis, leading to the suggestion that signaling through PLCγ may negatively feedback on FGF function (Partanen et al., 1998). However, the overall requirement for the FGFR–PLCγ interaction *in vivo* remains largely obscure. In addition, the requirements for potential immediate targets of FGFRs other than PLCγ and FRS2, for example CRK, SHB, and GRB, are also not understood and need to be explored. Nevertheless, the use of different FGFR targets is likely to account, in part, for different cellular responses.

The immediate targets of activated FGF receptors will in turn activate one or more downstream effectors that include components of the Src, STAT, Shc, PI3K, and MAPK pathways (Mason, 2007; Beenken and Mohammadi, 2009; Turner and Grose, 2010; Guillemot and Zimmer, 2011). There is evidence that some of these pathways are differentially activated in different neural cell types in response to FGF signals, providing part of the explanation for how FGFs induce a variety of cellular responses. Activation of the Ras–Erk pathway has been examined most closely and has been implicated in mediating FGF signals, for example, in neural induction and patterning in *Xenopus* (Ribisi et al., 2000; Delaune et al., 2005), in patterning rhombomeres and promoting ventral forebrain development (Shinya et al., 2001; Hernandez et al., 2004; Aragon and Pujades, 2009), and in generating cerebellar, but not midbrain, cell fates at the mid–hindbrain boundary in the chick (Sato and Nakamura, 2004). On the other hand, conditional deletion of *Erk2* during cortical neurogenesis appears to affect primarily the proliferation of intermediate progenitors (Samuels et al., 2008), a cell type in which FGF signaling appears not to play a significant role (Kang et al., 2009). The roles of the other intracellular pathways that are potentially activated by FGFs remain unclear.

In addition to mediators of FGF signaling, there are a number of important inhibitors. The functions of some of these have begun to be characterized in CNS development and include members of the Sprouty (Spry) family, inhibitors of the Ras–ERK pathway (Mason et al., 2006). Spry genes are typically induced by FGF signals and negatively feedback to restrict the amount of signaling. For example, *Spry2* misexpression reduces FGF signaling and disrupts mid–hindbrain development in mice (Basson et al., 2008) and *spry4* constrains FGF activity in patterning the hindbrain and expanding the telencephalon in zebrafish (Furthauer et al., 2001; Labalette et al., 2011). There are also negative feedback regulators of FGF signaling other than the Spry proteins, including Sef, MapK phosphatases (MKPs, also know as Dusps), and factors

promoting receptor turnover (e.g., Furthauer et al., 2002; Tsang and Dawid, 2004; Echevarria et al., 2005; Ron et al., 2008). These are likely important in regulating neurogenic processes. However, their functions in the CNS have just begun to be explored.

In different parts of the CNS and at different stages of development, FGF signaling promotes and inhibits different sets of target genes. Target genes induced by FGFs usually include genes that encode feedback inhibitors (e.g., Spry) and members of the Ets family of transcription factors (including *Pea3*, *Erm*, *Er81*, and others) suggesting that these are immediate targets. The transcription complexes downstream of FGF signaling that regulate expression of these genes are largely uncharacterized. Cell type specific activation of transcription factors and target genes is likely due in part to the use of different intracellular signal transducers and inhibitors. Although little characterized, the epigenetic states of the target cell types will also be instrumental in determining which genes are activated by FGFs and what cell fates are adopted.

INTEGRATION OF MULTIPLE EXTRACELLULAR SIGNALS

In addition to intracellular modulators of FGF signaling affecting cellular responses, the presence of other secreted factors in the environment of a cell is bound to affect its response to FGFs as it tries to integrate the multiple signals. How a cell integrates multiple concurrent signals to adopt an appropriate response remains a fundamental question in developmental biology. Integration of multiple signals can potentially occur at several levels. For instance, cross-talk can occur between the different transduction pathways activated by different extracellular factors. In addition, the regulatory sequences of target genes can act as sites at which transduction pathways converge and integrate to affect gene expression and ultimately a cell's fate.

Although few to date, there are some studies that demonstrate such interactions between FGFs and other signals that affect a cell's response and its fate in the developing nervous system. For example, at the level of cross-talk between transduction pathways, BMP, WNT, FGF, and/or IGF signals during neural induction can be integrated via phosphorylation of alternate sites on SMAD1 (Pera et al., 2003; Fuentealba et al., 2007). Also, in patterning the posterior neural tube in *Xenopus*, FGF, WNT, and antagonistic BMP signals converge on regulatory elements of the *Xcad* gene (Haremaki et al., 2003). Finally, at the earliest stages of telencephalon development in the mouse, loss of either FGF or WNT signaling leads to the death of the neuroectoderm, whereas loss of *Smad4* can rescue this phenotype (Paek et al., 2009, 2011). In this case, integration of FGF, WNT, and TGFβ signals occurs at several levels including the regulation of *Cdkn1a* expression via direct binding of SMAD/FOX and MYC complexes to its *cis* regulatory elements (Seoane et al., 2004; Paek et al., 2011). However, the few examples to date provide only limited mechanistic insights into the interactions of FGFs with other signals in regulating neural cell fates.

SUMMARY AND PERSPECTIVE

In humans, there are at least 70 nucleotide substitutions that affect the amino acid sequences of the FGFR genes (Wilkie, 2005; Beenken and Mohammadi, 2009). Mutations in ligands also exist and some of these are strongly associated with disease. Before we can devise effective treatments to remedy or cure neural or FGF-related disorders, it might be useful, if not essential, to know what intracellular pathways transduce FGF signaling in each target cell type and how signaling is affected by intracellular and extracellular modulators. Despite our progress in identifying the many requirements for FGFs in neurodevelopment and neurogenesis, our understanding of how FGFs fulfill so many functions remains preliminary and superficial. This is because we do not yet have a firm grasp of the mechanisms for how an FGF signal at the cell surface is transduced and how combined with other signals it leads to changes in gene expression that ultimately affect a cell's fate.

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