Published in final edited form as:

Curr Signal Transduct Ther. 2012 January ; 7(1): 81–86. doi:10.2174/157436212799278205.

Role of fibroblast growth factor receptors in astrocytic stem cells

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Abstract

There are two well-defined neurogenic regions in the adult brain, the subventricular zone (SVZ) lining the lateral wall of the lateral ventricles and, the subgranular zone (SGZ) in the dentate gyrus at the hippocampus. Within these neurogenic regions, there are neural stem cells with astrocytic characteristics, which actively respond to the basic fibroblast growth factor (**bFGF**, **FGF2** or **FGF-β**) by increasing their proliferation, survival and differentiation, both *in vivo* and *in vitro*. FGF2 binds to fibroblast growth factor receptors 1 to 4 (**FGFR1**, **FGFR2**, **FGFR3**, **FGFR4**). Interestingly, these receptors are differentially expressed in neurogenic progenitors. During development, FGFR-1 and FGFR-2 drive oligodendrocytes and motor neuron specification. In particular, FGFR-1 determines oligodendroglial and neuronal cell fate, whereas FGFR-2 is related to oligodendrocyte specification. In the adult SVZ, FGF-2 promotes oligodendroglialogenesis and myelination. FGF-2 deficient mice show a reduction in the number of new neurons in the SGZ, which suggests that FGFR-1 is important for neuronal cell fate in the adult hippocampus. In human brain, FGF-2 appears to be an important component in the anti-depressive effect of drugs. In summary, FGF2 is an important modulator of the cell fate of neural precursor and, promotes oligodendrogenesis. In this review, we describe the expression pattern of FGFR2 and its role in neural precursors derived from the SVZ and the SGZ.

Keywords

Neural stem cells; basic fibroblast growth factor; fibroblast growth factor receptor; subventricular zone; subgranular zone; astrocyte; glia

Introduction

In the adult mammalian brain discrete proliferative regions exist that throughout life produce new neurons. These cerebral areas are commonly known as neurogenic niches, which provide a microenvironment and a very particular cytoarchitecture to preserve the cell proliferation and survival of neural stem cells [1]. The most well-accepted neurogenic niches in the adult brain are the subventricular zone (SVZ), lining the lateral wall of the lateral ventricle [2], and the subgranular zone (SGZ) located in the dentate gyrus in the hippocampus [3]. Remarkably, the neural stem cells in the SVZ and the SGZ are a subpopulation of astrocytes, which derived from the embryonic radial glia [4, 5]. During

development, radial glia generates neurons and glia [6, 7]. In the adult human brain, neural stem cells have been successfully isolated [8], but the precise role of these progenitors and their progeny has not been elucidated, yet [9].

During embryonic development of CNS, FGF2 promotes differentiation of neural cells in different brain regions [10]. In adulthood, astrocytic neural stem cells, located in the SVZ and the SGZ also produces neurons and glial cells in response to a number of cytokines, including the basic fibroblast growth factor (bFGF, FGF-2 or FGF- β) [11, 12]. In the central nervous system (CNS), FGF2 is produced by glial cells [13] and binds to four different types of receptors: FGFR-1, FGFR-2, FGFR-3 y FGFR-4 [14]. Interestingly, FGFRs are differentially expressed in the neural progenitors of the SGZ and the SVZ [15]. The role of FGFR subtypes in these neurogenic regions and adult progenitor cells is still unclear [16]. However, it is known that FGF2 induces high proliferation rate in cell cultures and, depending on cell culture conditions, promotes neuronal [17] or glial differentiation [18]. These differential effects may be due to different FGFR-subtype expression, as well as regional properties of neural progenitors in the SVZ and SGZ. In this review, we summarize the role of FGF-2 on neural stem cells resident in the SVZ and the SGZ and, its potential role in regenerative processes.

Neurogenic regions in the adult brain

The SVZ is adjacent to the lateral wall of the lateral ventricles [2]. Neural stem cells in this region are a subpopulation of SVZ astrocytes, also known as type-B1 cells [19]. Type-B1 astrocytes produce 'transit amplifying progenitor cells' (type-C cells). Cell differentiation of type-C cells give origin to neuroblasts referred to as type-A cells, which migrate tangentially through the 'rostral migratory stream' (RMS) [19]. Upon reaching the rodent olfactory bulb, migrating neuroblasts spread and populate the granular and periglomerular layers [20]. The function of these novel interneurons is unclear, but it seems they are implicated in odor discriminating tasks [21].

The SGZ is located in the dentate gyrus of adult hippocampus. In this region, radial astrocytes, also known as type-B cells or type-1 progenitors, function as neuronal progenitors *in vivo* [22]. SGZ radial astrocytes divide and give rise to "dark" cells referred to as type-D1 cells. Subsequent progeny of type-D1 cells are type-D2 and type-D3 cells [3]. Type-D3 cells display morphology of immature granular neurons and express several neuronal markers [12]. Further differentiation of type-D3 cells give origin to mature granular neurons, which incorporate into local neuronal circuits within the hippocampus [3, 23]. Interestingly, new-born neurons in the dentate gyrus appear to play a role in learning-memory processes [24] and depression syndrome [25].

Basic fibroblast growth factor (FGF-2)

The family of FGF comprises twenty three peptides. Member of this family play important roles during neural development by modulating proliferation, migration, angiogenesis and chemoattractant activity [26]. In the adult brain, FGF promotes wound recovery, increases proliferation and enhances development and progression of brain tumors [27, 28]. FGF-2 has a molecular weight of 18 kDa, but a 24-kDa FGF-2 isoform has also been described [27]. The 18-kDa FGF-2 isoform is located in the cytosol, whereas 24-kDa isoform is found into the nucleus [27]. It is thought that FGF-2 is one of the first mitogen factors expressed during neural development, but other member of this family, such as FGF-1, FGF-5 and FGF-8 also participate in embryonic brain development [29]. In the whole body, the main endogenous sources of FGF-2 are endothelium, smooth muscle and fibroblasts [30]. In the brain, the main source of FGF2 is glial cells, in particular mature astrocytes [13]. FGF-2 can signal through paracrine and autocrine mechanisms [13, 30]. This growth factor also

modulates pituitary functioning by regulating prolactin synthesis [31] and, promotes angiogenesis and tumor development. These effects appear to be mediated by inducing endothelium to produce vascular endothelial growth factor (VEGF) or by promoting synthesis of chemokines and cytokines, such as, interleukin-1 (IL-1) interleukin-8 (IL-8) and tumor neural factor alpha (TNF- α), which activates Ras/Raf/MAPK1 pathways [26]. After a brain injury, FGF-2 increases the levels of glial fibrillary acidic protein (GFAP) [32] and enhances astrocyte reactivity [13]. In turn, reactive astrocytes appear to promote neurogenesis in the adult brain [33].

FGFR expression in neural stem cell

Neurogenic glia are the primary source of FGF-2 that binds to four different receptors (FGFR-1, FGFR-2, FGFR-3 y FGFR-4) [34] with two transmembrane domains (Figure 1). FGFR is constituted by: 1) an extracellular domain with two or three immunoglobulin-like peptides plus a hydrophilic heparine-binding domain, 2) a transmembrane region and, 3) an intracellular tyrosine-kinase-like domain [28]. Following ligand binding and FGFR dimerization, the kinase domains phosphorylate each other, leading to the docking of adaptor proteins and the activation of RAS-RAF-MAPK and PI3K-AKT downstream pathways [35](Figure 1).

Heparan sulphate epitopes are important for binding FGFR ligands and appear to control neural differentiation of embryonic stem cells [36]. FGF-2 strongly regulates the function of neural stem cells in both the embryo and adult brain.

During development, FGFRs begin to be expressed at E12.5 in the CNS. FGFR-1, FGFR-2 and FGFR-3 are initially expressed in ventral regions of the ventricular zone [18]. Inhibition of FGF in neuroectodermal stem cells blocks ERK_{1/2} and reduces Pax-6 transcription factor [37]. Pax-6 is associated with neuronal differentiation during embryonic development and adult neurogenesis in the SVZ and the SGZ [38]. Therefore, FGF-2-induced neuronal differentiation appears to be mediated through ERK1/2 pathway. Mice lacking FGFR-1 and FGFR-2 show an important reduction in oligodendrocytes and motor neurons in the developing spinal cord [18]. FGFR-1 drives both oligodendroglial and neuronal cell fate and is also involved in axonal growth of sensorial neurons [39]. Mutant mice lacking FGFR-1 show a decrease in radial glia and oligodendroglial progenitors [40]. On the other hand, FGFR-2 is essential for oligodendrocyte specification, but not for neuronal production [18]. Mutations on FGFR-3 expression have none of these effects [18].

In neuronal-glial cocultures from the embryonic rat ventral midbrain, FGF-2 helps maintain proliferation and differentiation of neural stem cell into dopaminergic neurons. [13]. Administration of FGF-2 *in vivo* drives neural progenitors into the oligodendroglial lineage. A short exposure to FGF-2 in cell cultures of cortical glutamatergic neurons (Pax6+/Mash1+/Ngn2+) induces a GABAergic phenotype and oligodendroglial lineage [41]. This cellular specification in ventral brain regions is mediated by Olig-2 and Mash-1 transcription factors, which is associated with an increase in bone morphogenetic protein-4 levels (BMP-4) and a reduction in noggin [41]. On this regard, the phosphorylation of Ngn2 at serine residues S231 and S234 promotes the interaction of Ngn2 with LIM homeodomain transcription factors to specify motor neuron identity [42]. Therefore, high levels of phospho-GSK-3 β activated through FGFRs are important cell components to promote the neuronal lineage [43]. In summary, the higher expression of PI3K/Akt, the lesser GSK-3 β level and neuronal differentiation.

In the adult brain, FGFR and phosphorylated FGFR (phospho-FGFR) are highly expressed in neurogenic niches. In fact, phospho-FGFRs are strongly expressed by dividing neural progenitors in both the SVZ and the SGZ (Figure 2). FGFR-1, FGFR-2 and FGFR-3 are

initially expressed in ventral regions of the ventricular zone [18]. By *in situ* hybridization and immunohistochemistry, FGFR-1 and FGFR-2 were described in dividing SVZ neural progenitors, whereas FGFR-3 was only found by non-proliferative SVZ cells [15]. Similar findings have been described in along the RMS in migratory neuronal precursors [44]. Axonal growth mediated by FGF-2 signaling appears to be regulated via receptor degradation. Upon FGFR-1 is activated by its ligand, it is endocytosed and degraded by lysozymes, which controls axonal growth [39]. Sprouty (Spry 1 y 2) and Mkp/Dusp transcription factors regulate the mitogen activated protein kinase (MAPK) by proteasome ubiquitination upon interaction between FRS2 and E3 proteins [26]. Therefore, these proteins might regulate the FGFR signaling pathway in adult neural stem cells. FGF-2 has a synergistic effect with insulin-like growth factor-1 (IGF-1) producing an important increase in oligodendrogenesis mediated by mitogenic effects of cyclin D1 [45]. In this case, FGF-2 induces ERK₁ (p44) and ERK₂ (p42) phosphorylation, allowing cyclin D1 to enter in the S-phase of cell cycle, whereas IGF-1 stabilizes cyclin D1 by activating Akt/PI3k pathway [45]. Phosphorylated Akt overexpression is associated with myelination in white matter tracts, but not with proliferation or cell survival [46]. Activation of EGFR and FGFR can activate PI3K/Akt signal transduction pathway that, in turn, negatively regulates glycogen synthase kinase 3 β (GSK-3 β). EGFR stimulation induces SVZ multipotential astrocytes to produce oligodendrocyte progenitors and decreases the neurogenesis rate [47–49].

In contrast, SGZ progenitors in dentate gyrus seem to express FGFR-1 only [15]. The precise role of FGF2 in dentate gyrus is still not well-understood. Radial astrocytes in the SGZ express FGFR-1 [15]. FGF-2 deficient mice do not show obvious changes in the number of neuronal precursor in the SGZ, but a reduction in the number of new neurons, which suggests that FGFR-1 is important for neuronal cell fate [16]. These changes may be due to down-regulation of Pax-6, a transcriptional factor expressed by stem cells in this region and associated with neuronal differentiation [38].

Increasing evidence indicates that the immune system can regulate the proliferation, differentiation and migration of adult neural stem cells [50, 51]. Thus, it has been proposed that a number of trophic and morphogenic factors control the function of human neural stem cells [52]. FGF-2 induces proliferation and differentiation of neural stem cells isolated from the adult SVZ [8]. The function of FGF-2 *in vivo* has not been elucidated in the human brain, but some evidence indicates that several members of FGF family might be implicated in the pathogenesis of major depression and Alzheimer's disease [53–55]. Thus, FGF2 gene transfer has recently been found to restore hippocampal functions in a model of Alzheimer's disease, partly as a result of enhanced neurogenesis [56]. FGF-2 levels are increased by antidepressant treatment. In fact, FGF-2 treatment increases neurogenesis in the dentate gyrus and reduces depressive-like behavior induced by bulbectomy in rodents [53]. This suggests that FGF-2 is an important component in the antidepressive effect of drugs and in the SGZ neurogenesis.

Conclusion

FGF-2 it is one of the most important growth factor that regulates cell activity in neurogenic niches by acting through FGFRs (1, 2, 3 and 4). These four receptors are expressed in different cells within the SVZ and SGZ and, probably, activate different intracellular signaling pathways. Understanding cellular mechanisms activated by FGFR on astrocytic neural stem cells and their intracellular signaling pathways will contribute to the design of stem-cell- or gene-transfer-based therapies against neurodegenerative disorders [55, 57–60].

Acknowledgments

This work was supported by grants from the Consejo Nacional de Ciencia y Tecnologia (CONACyT; CB-2008-101476) and The National Institute of Health and the National Institute of Neurological Disorders and Stroke (NIH/NINDS; R01 NS070024).

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Figure 1.

Signaling pathways of the fibroblast growth factor receptor in neural stem cells. In the MAPK (also known as ERK) pathway, activated receptors lead to activation of RAS and signal through RAF, MEK (also known as MAP2K) and MAPK.

Figure 2.

Expression of phosphorylated FGFR (phospho-FGFR) in the subventricular zone (SVZ) and the subgranular zone (SGZ). Note that most of the proliferative cells (BrdU+ cells) co-express phospho-FGFR. V: Ventricle; st: Striatum; DG: Dentate gyrus. Scale bar = 100 μ m.