Fibroblast Growth Factor 13 Is Essential for Neural Differentiation in Xenopus Early Embryonic Development*

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In Xenopus embryonic development, the MEK5-ERK5 pathway, one of the MAPK pathways, lies downstream of SoxD and upstream of Xngnr1 in a signaling pathway regulating neural differentiation. It remains unclear, however, how the MEK5-ERK5 pathway is regulated in Xenopus neural development. As SoxD is a transcription factor, we hypothesized that some growth factor should be induced by SoxD and activate the MEK5-ERK5 pathway. As the expression level of fibroblast growth factor 13 (FGF13) is increased by SoxD, we analyzed the function of FGF13 in neural development. Knockdown of FGF13 with antisense morpholino-oligonucleotides (MOs) results in the reduced head structure and inhibition of neural differentiation. FGF13 MOs inhibit the activation of the MEK5-ERK5 pathway by dominant-negative bone morphogenetic protein receptor, a mimicker of neural inducers, indicating that FGF13 is involved in the activation of the MEK5-ERK5 pathway. Together, these results identify a role of FGF13 in Xenopus neural differentiation.

In Xenopus, cells in ectoderm are committed to neural fate by neural inducers, such as Noggin, Chordin, and Follistatin, all of which are inhibitors of BMP signaling (1–5). Thus, attenuation of BMP signaling induces the expression of early neural marker genes, such as soxD and sox2 (6, 7). After their expression, progenitor cells with the capacity of neural differentiation are induced. We have previously shown that the MEK5-ERK5 pathway, one of the MAPK pathways, lies downstream of SoxD and upstream of Xngnr1 in a signaling pathway regulating neural differentiation (10). However, the regulatory mechanism of the MEK5-ERK5 pathway has not been understood. As SoxD is a transcription factor, it is likely that SoxD directly regulates the MEK5-ERK5 pathway. It has been reported in other systems that the MEK5-ERK5 pathway is activated by a number of growth factors (11–14). Therefore, we speculated that SoxD should induce enhanced expression of a growth factor that could activate the MEK5-ERK5 pathway. Our preliminary screening identified FGF13 as a possible candidate; an expression level of FGF13 could be increased by SoxD (10).

FGF13 was initially termed fibroblast growth factor homologous factor 2 (FHF-2) and constitutes an FGF subfamily with FGF11, FGF12, and FGF14 (15–17). FGF13 is conserved among vertebrates and is shown to be abundant in neural tissues in chick and mouse embryos (17–19). Overexpression experiments suggested that FGF13 is involved in chick limb development (19). However, neither knock-out nor knockdown experiments have been reported. Thus, the role of FGF13 in embryonic development has been unknown.

In this study, we have shown that Xenopus FGF13 (xFGF13) regulates neural differentiation. FGF13 MOs inhibit SoxD-induced Xngnr1 expression, indicating that xFGF13 lies downstream of SoxD and upstream of Xngnr1 in a signaling pathway regulating neural differentiation. xFGF13 is shown to be involved in the activation of the MEK5-ERK5 pathway, which also lies downstream of SoxD and upstream of Xngnr1. We further show that FGF13 MOs inhibit expression of neural marker genes induced by Xngnr1.

**EXPERIMENTAL PROCEDURES**

Molecular Cloning and Plasmid Construction—One of the isoforms of Xenopus FGF13 (xFGF13-VY) was already isolated (DDBJ/EMBL/GenBank™ accession number BC076721). Therefore, we designed primers based on the sequence. We performed PCR with cDNAs isolated from embryos at stage 25 and obtained a novel isoform of xFGF13, xFGF13-V. We also found a sequence in Xenopus laevis EST data base (DDBJ/EMBL/GenBank™ accession number BI314017) that is homologous to another isoform of FGF13 in Xenopus tropicalis. We designed primers based on the sequence of BI314017 and isolated xFGF13-S. Expression plasmids were constructed as described (10).

Embryonic Manipulation, LacZ Staining, Whole-mount in Situ Hybridization, and RT-PCR—In vitro fertilization, injection, LacZ staining, whole-mount in situ hybridization, and RT-PCR were performed as described (10). Embryos subjected to whole-mount in situ hybridization were sectioned on a cryostat Microm (Zeiss). The sequences of primer pairs used in semiquan-
Role of FGF13 in Neural Development

SoxD induces expression of xFGF13. A, SoxD mRNA was injected at the indicated dose, and animal caps from the embryos were cultured to stage 14. An expression level of xFGF13 mRNA was analyzed by real time quantitative RT-PCR. B, SoxD mRNA was injected, and animal caps were cultured to the indicated stages. xFGF13 expression was analyzed.

FIGURE 2. Cloning of Xenopus FGF13 (xFGF13). One of the isoforms of xFGF13 was already isolated (xFGF13-VY, DDBJ/EMBL/GenBank accession number AF230862), and we isolated two novel isoforms (xFGF13-S, DDBJ/EMBL/GenBank accession number AB830862, and xFGF13-S, DDBJ/EMBL/GenBank accession number AB840863, respectively). xFGF13-V, xFGF13-V, and xFGF13-S consist of 225, 199, and 245 amino acids, respectively. Each exon is represented by a box. xFGF13-V contains exons 1V and 1Y, and xFGF13-S contains an exon 1S. The sequences downstream of exon 1 are invariant among isoforms.

Morpholino-oligonucleotides—Antisense morpholino-oligonucleotides were obtained from Gene Tools Inc. The morpholino-oligonucleotide sequences were as follows: FGF13 MO1, 5'-TAGGCTTGACCTCTTTCCACTCAT-3', FGF13 MO2, 5'-AGAGAGCTCGCAATGGCGGCAGGCA-3', and XeODC MO, 5'-CGGAGGCGGCGGAAATA-3'. A standard control oligo (control MO), 5'-CGGAGCCCTGGAAGGAAATAGCG-3', and r, 5'-CCGGGGTGAGGCGGATTA-3', and r, 5'-GGGAATCAAGGCGGAGTTC-3'. NeurO: 5'-CCGGGGTGAGGCGGATTA-3', and r, 5'-TCCGGTGAAGCTCTTACC-3'.

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Immunoblotting—Animal caps were lysed in a buffer consisting of 20 mM HEPES (pH 7.2), 0.25 mM sucrose, 0.1 mM NaCl, 2.5 mM MgCl₂, 10 mM NaF, 10 mM EGTA, 10 mM β-glycerophosphate, 1 mM vanadate, 1 mM phenylmethylsulfonyl fluoride, 0.5% aprotinin, and 1 mM dithiothreitol and then centrifuged. The supernatant was used for immunoblotting with anti-Myc antibody.

Kinase Assays—Animal caps were crushed in a buffer containing 20 mM HEPES (pH 7.5), 25 mM β-glycerophosphate, 150 mM NaCl, 10% glycerol, 0.5% Triton X-100, 1.5 mM MgCl₂, 2 mM EGTA, 50 mM NaF, 1 mM vanadate, 1 mM phenylmethylsulfonyl fluoride, 1% aprotinin, and 2 mM dithiothreitol. Myc-tagged xERK5 was immunoprecipitated and incubated for 15 min at 37 °C with 20 μg of myelin basic protein in 2mM dithiothreitol. Myc-tagged xERK5 was immunoprecipitated and incubated for 15 min at 37 °C with 20 μg of myelin basic protein in 2mM dithiothreitol. Myc-tagged xERK5 was immunoprecipitated and incubated for 15 min at 37 °C with 20 μg of myelin basic protein in 2mM dithiothreitol. Myc-tagged xERK5 was immunoprecipitated and incubated for 15 min at 37 °C with 20 μg of myelin basic protein in 2mM dithiothreitol. Myc-tagged xERK5 was immunoprecipitated and incubated for 15 min at 37 °C with 20 μg of myelin basic protein in 2mM dithiothreitol. Myc-tagged xERK5 was immunoprecipitated and incubated for 15 min at 37 °C with 20 μg of myelin basic protein in 2mM dithiothreitol.
RESULTS

Cloning and Expression of xFGF13—We analyzed the effect of SoxD on FGF13 expression in detail. Forced expression of SoxD in animal caps increased an expression level of FGF13 mRNA in a dose-dependent manner (Fig. 1A). Induction of FGF13 by SoxD was not observed at stage 10, but was first observed at stage 13, and maximally at stage 16 (Fig. 1B). These results demonstrate that FGF13 expression is up-regulated by SoxD.

We then isolated complementary DNAs encoding *Xenopus* FGF13 (xFGF13), and named xFGF13 isoforms after the names in murine FGF13 isoforms (20). One of the isoforms of xFGF13 was already isolated (xFGF13-VY), and we isolated two novel isoforms (xFGF13-V and xFGF13-S) (Fig. 2). The temporal and special expression pattern of xFGF13 was analyzed by RT-PCR (Fig. 3, A and B) and whole-mount *in situ* hybridization (Fig. 3C). By using a sequence conserved among all isoforms, we analyzed the temporal expression pattern of xFGF13 by real time RT-PCR (Fig. 3A). xFGF13 was expressed maternally, and zygotic expression was observed at neurula and tailbud stages. The expression patterns of each isoform were then analyzed by semiquantitative RT-PCR (Fig. 3B). Although maternal expression of xFGF13-VY was weak, its strong expression was observed at the tailbud stage. Strong expression of xFGF13-V was observed both maternally and at the tailbud stage. xFGF13-S expression was observed weakly at neurula stages and strongly at the tailbud stage. The analysis with a primer pair that recognizes all of the three isoforms gave a result similar to that obtained with real time PCR. Whole-mount *in situ* hybridization using a sequence conserved among all isoforms revealed that xFGF was expressed widely in the presumptive ectoderm during blastula, and in the dorsal structures during neurula and tailbud stages (Fig. 3C). At tailbud stages, strong expression was observed in the ventral region of neural tube (Fig. 3C, bottom).

**FGF13 Is Necessary for Head Development**—We examined the possibility that xFGF13 is involved in neural development. To determine the loss-of-function phenotypes, we designed two antisense morpholino-oligonucleotides (MOs) against xFGF13 as follows: FGF13 MO1 for xFGF-VY and xFGF13-V and FGF13 MO2 for xFGF13-S. We also designed five-base mismatched MOs as follows: FGF13 MO1 mis5 for FGF13 MO1 and FGF13 MO2 mis5 for FGF13 MO2. Injection of FGF13 MOs with Myc-tagged xFGF13 mRNAs showed that FGF13 MO1 dramatically reduced the protein level of xFGF13-VY and xFGF13-V, but not xFGF13-S; FGF13 MO2 dramatically reduced the protein level of xFGF13-S, but not xFGF13-VY or xFGF13-V; and control MO, MO1 mis5, and MO2 mis5 did not reduce corresponding xFGF13 proteins (Fig. 4A and data not shown). In addition, any MOs did not affect the protein level of xERK2 (Fig. 4A). These results indicate the specificity of FGF13 MOs. We then injected control MO, FGF13 MO1 plus MO2 (FGF13 MO), or FGF13 MO1 mis5 plus MO2 mis5 (FGF13 mis-MO) into the dorsal animal blastomere on the right side. Although embryos injected with control MO or FGF13 mis-MO were normal, embryos injected with FGF13 MO on the right side showed the reduced head structure and the loss of eyes on the right side but not on the left side (Fig. 4B). These defects observed in xFGF13 morphants were very similar to those observed in xERK5 or xMEK5 morphants (10).

Embryos injected with FGF13 MOs and other MOs were classified into four groups according to the eye size as follows: class

A buffer (15 μl) containing 20 mM Tris-Cl (pH 7.5), 17 mM MgCl₂ and 50 μM ATP (3 μCi of [γ-32P]ATP).

FIGURE 3. Expression pattern of xFGF13. A, total RNA was isolated from embryos at the indicated stages, and expression of xFGF13 was analyzed by real time PCR. B, expression of each isoform of xFGF13 was analyzed by semiquantitative RT-PCR. XeODC was used as an RNA loading control. Xbra was also examined. C, whole-mount *in situ* hybridization against xFGF13 at the indicated stages.
Role of FGF13 in Neural Development

A, indicated sets of morpholino-oligonucleotides (30 ng) and mRNA (0.8 ng) were injected, and the protein level was examined by immunoblotting with anti-Myc antibody. We used xERK2 as a loading control. B, control MO (30 ng), FGF13 MO1 (15 ng) plus MO2 (15 ng), or FGF13 MO1 mis5 (15 ng) plus MO2 mis5 (15 ng) were injected into the dorsal animal hemisphere on the right side at the four-cell stage. C, embryos injected with MOs were classified into four groups according to the eye size: class 1, normal or only slightly smaller; class 2, smaller; class 3, much smaller; class 4, none. About 80% of embryos injected with FGF13 MO1 plus MO2 (n = 108) showed definite defects in eyes, whereas only 20% of embryos injected with control MO (n = 101) and 6% of embryos injected with FGF13 MO1 mis5 plus MO2 mis5 (n = 118) showed defects. D, xFGF13-S (rMO) mRNA (3.2 ng) was co-injected with FGF13 MO1 plus MO2 for the rescue experiment. 58% of embryos co-injected with xFGF13-S (rMO) mRNA showed defects (n = 102), whereas 79% of embryos injected with FGF13 MO1 plus MO2 showed defects (n = 170) (p < 0.001 by Mann-Whitney test).

FIGURE 4. FGF13 is required for head development. A, indicated sets of morpholino-oligonucleotides (30 ng) and mRNA (0.8 ng) were injected, and the protein level was examined by immunoblotting with anti-Myc antibody. We used xERK2 as a loading control. B, control MO (30 ng), FGF13 MO1 (15 ng) plus MO2 (15 ng), or FGF13 MO1 mis5 (15 ng) plus MO2 mis5 (15 ng) were injected into the dorsal animal hemisphere on the right side at the four-cell stage. C, embryos injected with MOs were classified into four groups according to the eye size: class 1, normal or only slightly smaller; class 2, smaller; class 3, much smaller; class 4, none (Fig. 4C, left). About 80% of embryos injected with FGF13 MO showed definite defects and were classified into class 2, 3, or 4, whereas only 20 and 6% of the embryos injected with control MO and FGF13 mis-MO, respectively, showed defects (Fig. 4C, right). To further confirm the specific-
role of FGF13 in neural development.

In Xenopus neural development, following neural induction, transcription factors such as SoxD and Sox2 are induced (6, 7). The proneural genes such as xngnr1 and neuroD are induced in this order (8, 9). As N-tubulin is a terminal neural marker gene, we next examined whether FGF13 MO affects early steps of neural development, such as neural induction. FGF13 MO had no effect on the expression of soxD and sox2 (Fig. 5A), indicating that xFGF13 is not required for neural induction. We further examined the effect of FGF13 MO on neural induction by animal cap assay. We used a dominant-negative form of BMP receptor (dnBMPR), whose expression mimics the activity of neural inducers. Animal caps injected with dnBMPR mRNA expressed early neural marker genes, such as soxD, zic2, zic3, zicr1, and sox2 (Fig. 5B). FGF13 MO did not suppress the dnBMPR-induced expression of soxD, zic2, zic3, and zicr1 but weakly suppressed the sox2 expression (Fig. 5B), confirming that xFGF13 is not involved in neural induction.

As an expression level of xFGF13 was significantly increased by SoxD (Fig. 1, A and B), we next examined whether xFGF13 functions downstream of SoxD. As reported previously (7), forced expression of SoxD resulted in the induction of neural markers, such as xngnr1, neuroD, N-tubulin, and NCAM (Fig. 6A). FGF13 MO as well as ERK5 MO suppressed the induction of these marker genes by SoxD (Fig. 6A). Therefore, it is likely that xFGF13 functions downstream of SoxD and upstream of Xngnr1.

As the MEK5-ERK5 pathway also lies downstream of SoxD and upstream of Xngnr1 (10), it is possible that xFGF13 is the regulator of the MEK5-ERK5 pathway in neural differentiation. Therefore, we tested whether xFGF13 is involved in the activation of the MEK5-ERK5 pathway. As we have shown before, the ERK5 activity was activated in the presence of dnBMPR (Fig. 6B). When FGF13 MO was injected, the dnBMPR-induced activation of ERK5 was inhibited (Fig. 6B), suggesting that xFGF13 functions as an activator of the MEK5-ERK5 pathway during neural development.

**FIGURE 5. FGF13 is required for neural differentiation.** A, control MO (60 ng) or FGF13 MO1 (30 ng) plus MO2 (30 ng) (FGF13 MO) were injected into the right blastomeres of four-cell stage embryos. The expression pattern of soxD, sox2, N-tubulin, and MyoD were analyzed by whole-mount in situ hybridization. Nuclear localization signal sequence-fused β-galactosidase mRNA was co-injected and used as a tracer (red staining). Dorsal views of embryos are shown with the anterior side at the top. B, dominant-negative BMP receptor (dnBMPR) mRNA (0.4 ng) was injected with control MO (60 ng) or FGF13 MO1 (30 ng) plus MO2 (30 ng), and animal caps were cultured to stage 14. Expression levels of marker genes were analyzed by real time RT-PCR.

**FGF13 Regulates Neural Differentiation**—To investigate the role of xFGF13 in neural development in more detail, we examined the expression of marker genes. FGF13 MO was injected into right blastomeres, and the embryos were analyzed by whole-mount in situ hybridization. Although N-tubulin, a terminal neural marker gene, was expressed normally on the uninjected left side, its expression on the right side was suppressed (Fig. 5A). Nuclear localization signal sequence-fused β-galactosidase was used as a tracer. Expression of myoD, a mesodermal marker gene, was unchanged in the presence of FGF13 MO (Fig. 5A). These results indicate that xFGF13 is required for neural development.
Xngnr1 promotes neuralization that is marked by expression of NCAM (9). We thought that FGF13 MO would not inhibit Xngnr1-induced promotion of neural differentiation, as the results described so far indicated that xFGF13 functions upstream of Xngnr1 in a pathway regulating neural differentiation. Unexpectedly, however, FGF13 MO suppressed the Xngnr1-induced expression of these marker genes in animal caps (Fig. 7A) and in embryos (Fig. 7B). These results suggest that xFGF13 is necessary for Xngnr1-promoted neuronal differentiation and neuralization. As we have previously shown that ERK5 MO does not inhibit Xngnr1-induced expression of neural marker genes (10), the function of xFGF13 downstream of Xngnr1 may not be mediated through the MEK5-ERK5 pathway. We then tested the possibility that xFGF13 is regulated by Xngnr1. In animal caps, ectopic expression of Xngnr1 induced a large increase in the expression level of xFGF13 mRNA (Fig. 7C), indicating that Xngnr1 is able to induce xFGF13 expression.

DISCUSSION

Our results show the essential role of FGF13 in Xenopus neural differentiation. FGF13 MOs inhibited both the SoxD-induced Xngnr1 expression and the Xngnr1-induced NeuroD expression. The simplest model to understand these results is that xFGF13 may function at two points during neural differentiation, upstream of Xngnr1 and downstream of Xngnr1 in a signaling pathway regulating neural differentiation. In contrast, the MEK5-ERK5 pathway regulates the neural differentiation upstream of Xngnr1 but not downstream of Xngnr1 (10). As xFGF13 is involved in the activation of the MEK5-ERK5 pathway, it is likely that xFGF13 functions upstream of Xngnr1 by regulating the MEK5-ERK5 pathway and functions downstream of Xngnr1 independently of the MEK5-ERK5 pathway. It is also possible that other growth factors are also involved in the activation of the MEK5-ERK5 pathway upstream of Xngnr1, as ERK5 MO suppressed neural differentiation more effectively than FGF13 MO (Fig. 6A).

So far, it is still unclear how the MEK5-ERK5 pathway is activated by xFGF13. As some of MAPKKks, such as MEK2 and MEKK3, have been shown to activate the MEK5-ERK5 pathway (21, 22), it is possible that these kinases are also regulated by xFGF13. A signaling pathway from xFGF13 to MEK5 should be elucidated in future studies. It also remains to be determined whether SoxD and Xngnr1 induce expression of xFGF13 mRNA directly or indirectly.
FGF13 constitutes an FGF subfamily with FGF11, FGF12, and FGF14 (17). Although many studies have been reported for the biological functions of FGFs, little is known about the function of this subfamily (15). So far, FGF12-deficient mice, FGF14-deficient mice, and mice lacking both genes have been generated (15, 23, 24). Although these mice show behavioral anomalies, no histological abnormalities have been reported (15, 23). Therefore, the importance of this FGF subfamily in embryonic development has not been understood, and our study is the first to demonstrate its essential role in neural development. As FGF13 is abundant in neural tissues in mice and chick embryos (17–19), it is possible that the essential role of FGF13 in neural development is conserved in vertebrates. The function of FGF13 in other species should be elucidated in future studies.

Acknowledgment—We thank members of our laboratory for helpful discussions.

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