Differential Intracellular Localization of Fibroblast Growth Factor-2 Isoforms and Specific Interaction with the Survival of Motoneuron Protein*

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Fibroblast growth factor 2 (FGF-2) is an important modulator of cell growth and differentiation and a neurotrophic factor. FGF-2 occurs in isoforms, at a low molecular weight of 18,000 and at least two high molecular weight forms (21,000 and 23,000), representing alternative translation products from a single mRNA. In addition to its role as an extracellular ligand, FGF-2 localizes to the nuclei of cells. Here we show differential localization of the 18- and 23-kDa isoforms in the nuclei of rat Schwann cells. Whereas the 18-kDa isoform was found in the nuclei, nucleolus, nucleoplasm, and Cajal bodies, the 23-kDa isoform localized in a punctuate pattern and associates with mitotic chromosomes suggesting different functional roles of the isoforms. Moreover, we show here that the 23-kDa FGF-2 isoform co-immunoprecipitates specifically with the survival of motor neuron protein (SMN). SMN is an assembly and recycling factor of the splicing machinery and locates to the cytoplasm, the nucleoplasm, and nuclear gems, where it co-localizes with 23-kDa FGF-2. Patients with spinal muscular atrophy suffer from fatal degeneration of motoneurons because of mutations and deletions of the gene for the SMN protein.

A number of mitogenic growth factors, growth-regulatory proteins, and growth factor receptors have been reported to be localized in the cell nucleus and its substructures; e.g. platelet-derived growth factor, fibroblast growth factor-1 (FGF-1), FGF-2, and ciliary neurotrophic factor (1, 2). The data show that nuclear localization is a general phenomenon for some growth factors, suggesting nuclear functions independent of the function as extracellular factors.

FGF-2 is a member of the FGF family, which has been shown to mediate a variety of biological processes during development and in the adult organism, including mitogenesis, angiogenesis, chemotaxis, mesoderm induction, and differentiation of various mesoderm- and neuroepithelial-derived cells. FGF-2 as an extracellular ligand is able to bind to high affinity tyrosine transmembrane receptors (FGF receptors, FGFR). FGF-2 has been shown to bind to all four known FGFR, however, with distinct affinities (3).

FGF-2 exists in protein isoforms translated from a common messenger RNA by alternative use of AUG (18,000 isoform) and CUG (high molecular weight isoforms 21,000 and 23,000) start codons. The isoforms exert different biological effects when overexpressed in different cell types. Specific effects seen by the 23-kDa isoform but not the 18-kDa isoform after overexpression are reduced spreading of pancreatic cancer cells (4), the ability of NIH 3T3 cells to grow in low serum medium (5), increased radioresistance in HeLa cells (6), growing in serum-free medium of rat AR4–2D cells (7), and differential effects on binucleation and nuclear morphology of neonatal rat cardiac myocytes (8). We have previously shown that in PC12 cells and rat immortalized Schwann cells, cell growth and morphology are altered after transfection with constructs coding for 18- and 23-kDa FGF-2, respectively (9, 10). In this study we extend our previous data by analyses of subcellular localization and interaction of FGF-2 in immortalized rat Schwann cells.

The FGF-2 isoforms are known to localize to the nucleus, however, the 18-kDa isoform has been found also in the cytoplasm (8, 10–14). The N terminus of the 23-kDa isoform exhibits a nuclear localization signal (NLS) (15). However, because the 18-kDa isoform localizes also to the nucleus, a second NLS in the 18-kDa “core” sequence can be expected. The individual isoforms were reported to localize to the nuclei (18, 16). The aim of the present study was to analyze the localization of FGF-2 isoforms in more detail in other nuclear substructures by means of tagging with fluorescent proteins (EGFP and DsRed) and to elucidate the molecular mechanisms responsible for the nuclear localization of FGF-2 isoforms. Our results revealed a differential localization of the isoforms in nuclear substructures of rat immortalized Schwann cells and, in addition, identified two nuclear localization sequences in the 23-kDa isoform. A further important and interesting result in our study is the first presentation of a co-immunoprecipitation and co-localization of the 23-kDa FGF-2 high molecular weight isoform with the survival of motor neuron protein (SMN), which is mutated in patients with spinal muscular atrophy. This study provides new insights into the physiological functions of FGF-2 in the nucleus.

EXPERIMENTAL PROCEDURES

Plasmid Constructs and Subcloning—The FGF-2 isoforms were cloned by PCR using the vector RSVpΔmetFGF comprising the full-length 23-kDa isoform as a template. In this vector the ATG start codon of the 18-kDa isoform is mutated and replaced by a HindIII linker (17).
PCR was used for cloning of the respective isoforms. Because the 5' region of the 23-kDa FGF-2 coding sequence is very GC-rich, a PCR optimized for GC-rich sequences was employed using 40 μM of each dNTP, 20 pmol of each primer, PCR buffer containing 1.5 mM MgCl₂ (Qiagen), 1× Q-Solution (Qiagen), and 2 units of KlenTaq Platinum Taq polymerase (Generica). The forward primers introduced an ATG construct and I for the 23-kDa isoform.

Site-directed mutageneses of FGF-2 were performed by using the Gene-editing site-directed mutagenesis kit (Clontech) comprising the complete coding sequence was digested with Smal/HindIII and cloned into pEGFP-N1.

RESULTS

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In this study, FGF-2 isoforms and N-terminal constructs were fused to DsRed, respectively, with ATG start codons from the 18-kDa core sequence deleted in the 23-kDa FGF-2 and NT(I-16) constructs. The primary structure of the N terminus of the 23-kDa isoform comprises RGR motifs with hydrophobic spacer sequences.

The available antibodies did not allow distinction between localization patterns of single FGF-2 isoforms or certain deletion and single-point mutations. In the approach applied here, we cloned the isoforms (Fig. 1a) in-frame into red fluorescent protein vector (pDsRed), transfected immortalized rat Schwann cells with the constructs, and observed directly the in vivo localization of the proteins by fluorescence microscopy. Cell lines stably expressing the 18- and 23-kDa isoforms, respectively, were selected and the localization patterns were studied.

The isoforms were cloned by means of PCR with reverse primers deleting the stop codons for in-frame ligations into pD-Red1-N1. In the 23-kDa construct the natural ATG start codon of the 18-kDa core sequence (Fig. 1a) was replaced by an HindIII linker sequence (14, 17) and an ATG codon introduced at the 5' end replacing the alternative start codon CTG in the cDNA. Because it is known that DsRed can aggregate resulting in artificial spots in the cell, we performed controls by using a new mutagenized version of the vector coding for DsRed2 (Clontech) and molecularly cloned the cDNAs of the 18- and 23-kDa isoforms into it. This DsRed2 carries the mutations R2A, K5E, K9T, V105A, I161T, and S197A, preventing the protein from nonspecific aggregating and resulting in a faster developing fluorescence. However, no changes of the localization patterns of FGF-2 in the nuclei could be observed (data not shown). In other controls, Schwann cells were co-transfected with 18-kDa GFP/18-kDa DsRed and 23-kDa GFP/23-kDa DsRed to determine localization changes dependent on the nature of the fluorescent tag. The localizations were nearly identical, but for EGFP with a stronger nucleoplasmic labeling in relation to e.g. nuclear label. Although cytoplasmic labeling could be observed in a number of cells according to biochemical data (Fig. 1c), many cells displayed low staining of the cytoplasm arguing for a dynamic and regulated distribution in the cell.

The 18- and 23-kDa FGF-2 isoforms displayed distinct localizations. The 18-kDa isoform was clearly enriched in the nuclei of Schwann cells.
of Schwann cells where it localized to the nucleoli and nucleoplasm (Fig. 2, a and b). This demonstrates that the 18-kDa FGF-2 isoform core sequence possesses a previously not described nuclear localization signal (see below). Cytoplasmic staining could be observed to some extent. The nucleolar localization was verified by phase-contrast microscopy (Fig. 2 e) showing prominent nucleoli of the Schwann cells. In addition, cells displayed red-labeled nucleated bodies in a dynamic pattern, probably dependent on the physiological state (Fig. 3, a–c). In the transfected Schwann cell line about 35% of the cells displayed a pattern of distinct nuclear bodies visible. These nuclear bodies were in spatial relationship to the nucleoli (Fig. 3a), sometimes demonstrating continuous staining from the nucleolar body to the nucleoli (Fig. 3b) or no nuclear bodies (Fig. 3c). The observed continuous staining pattern is in agreement with a transport phenomenon between these nuclear structures. This has been observed previously for proteins traveling between Cajal bodies (formerly coiled bodies; Ref. 20) and nucleoli as in the case of Nopp140 (21). To verify that the 18-kDa isoform of FGF-2 is indeed enriched in Cajal bodies we performed double labeling experiments with Coilin-p80 (20) fused to green fluorescent protein (GFP) as a marker protein for this nuclear structure. The 18-kDa isoform and Coilin-p80 partially co-localize in Cajal bodies (Fig. 3, d–f). The co-transfection analysis also revealed Coilin-p80 enriched in nucleoli.

In contrast, the 23-kDa FGF-2 isoform was distributed in a punctuate pattern, in the periphery of nucleoli and in the nucleoplasm (Fig. 2, c–f) with significantly less red-labeled 23-kDa FGF-2 in the nucleoli than it was the case for the 18-kDa isoform. This pattern was observed in almost all cells not undergoing mitosis in the stably transfected Schwann cell line. With regard to nucleoli, confocal microscopy revealed localization of the 23-kDa isoform with the nucleolar periphery (Fig. 2e). Most of the fusion protein also localized close to the nuclear membrane (Fig. 2f) suggesting a chromatin-associated pattern. This was verified by labeling cells with Hoechst 33258 (Fig. 2g and h), which stained AT-rich DNA, demonstrating a co-localization of both 23-kDa FGF-2 and DNA patterns. In cells undergoing mitosis the 23-kDa isoform displayed a redistribution and associated with mitotic chromosomes (Fig. 1, k and l). In strong contrast, association of the 18-kDa isoform with mitotic chromosomes could not be observed (Fig. 2, i and j). The observed putative chromatin or DNA-associated distribution pattern of the 23-kDa isoform is probably because of its N-terminal extension including several arginine-glycine-arginine (RGR) motifs in comparison to the 18-kDa core sequence (Fig. 1b).

The N Terminus of the 23-kDa FGF-2 Isoform Confers Nuclear Localization—The difference between both FGF-2 isoforms is the N-terminal extension of the 23-kDa isoform. This N-terminal region has been shown to contain a nuclear localization signal (15), however, the localization pattern had to be determined. Using the same approach as above we cloned this N-terminal fragment comprising the 34-amino acid residues of the 23-kDa FGF-2 isoform. This N-terminal extension contains several arginine-glycine-arginine (RGR) motifs, surrounded by mainly hydrophobic residues (Fig. 1b). This structure constitutes a positively charged N terminus of the 23-kDa FGF-2 isoform.
a NLS in agreement with previously published data (15). In addition, we could demonstrate that the transfected cells revealed a nuclear localization pattern of the N terminus (Fig. 2, g and h) like after transfection with the complete 23-kDa isoform, but with no clear labeling in the nucleolar periphery. This suggests a nuclear localization signal located in the 18-kDa core sequence. Additionally, the N terminus is able to associate with mitotic chromosomes similar to the 23-kDa isoform (data not shown).

**The 18-kDa FGF-2 Isoform Contains an Additional Nuclear Localization Signal**—Both 18- and 23-kDa FGF-2 isoforms localized to the nuclei of Schwann cells. The 18 kDa lacks the N-terminal extension of the 23-kDa isoform, which we demonstrated to serve as the nuclear localization signal, and does not display any canonical NLS. To identify sequences responsible for nuclear localization in the 18-kDa core isoform, we performed site-directed mutageneses of clusters of basic residues that could serve as putative NLS (Fig. 4a). Two amino acid residues in each cluster were mutated together to nonpositively charged amino acid residues, cloned into pDsRed, and the localization was analyzed after transfection of Schwann cells (Fig. 4b). A Western blot analysis after transfection of Schwann cells with the 23-kDa DsRed isoform revealed a 5–10-fold higher expression of the tagged protein compared with the total amount of endogenous FGF-2 isoforms (Fig. 4d). No changes in the nuclear localization pattern for the mutants K63G/R64G and R86G/K88E could be observed. However, the more C-terminal mutant R149G/R151G displayed a cytoplasmic localization (Fig. 4b). Both the 18- and 23-kDa FGF-2 isoforms completely failed to localize to the nuclei when carrying this mutation (Fig. 4b, shown for the 23-kDa isoform). The observed localization pattern is not the result of partial proteolysis of the DsRed-tagged protein as shown by the Western blot in Fig. 4c. The results demonstrate an important role for residues Arg149/Arg151 for nuclear localization of both isoforms. These residues are surrounded by putative phosphorylation sites at residues Thr147 and Ser150 for protein kinase C and Ser154 for cAMP or cGMP-dependent protein kinase (Fig. 4a). The residues are putative targets for regulated localization by introducing negatively charged phosphate groups in close proximity to the positively charged guanidino groups of the arginine residues and therefore neutralizing charges.

**The 23-kDa Isoform, but Not the 18-kDa Isoform of FGF-2 Co-immunoprecipitates with the SMN and Co-locates with SMN in Nuclear Gems**—The N-terminal extension of high molecular weight FGF-2 contains arginine residues reported to be dimethylated (23, 24). The biological function of arginine methylation in FGF-2 still remains unclear. The SMN has been reported to bind to methylarginine sequences in proteins (25) while dimethylated (23, 24). The biological function of arginine methylation in FGF-2 still remains unclear. The SMN has been reported to bind to methylarginine sequences in proteins (25) while dimethylated structures as the putative interaction sites with 23-kDa FGF-2. To elucidate a possible co-localization of 23-kDa FGF-2 and SMN in nuclear gems we performed co-transfections (Fig. 3, g–i). Superposition of the images reveals a partial co-localization in nuclear gems.

**DISCUSSION**

Immunolocalization studies and Western blotting after cell fractionation have previously demonstrated the existence of FGF-2 in the nucleus (10–13, 27). In this study we labeled FGF-2 isoforms by fusion constructs with the red fluorescent protein DsRed. Because no specific antibodies against the in-
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Fig. 5. Co-immunoprecipitation analyses of FGF-2 isoforms with survival of motor neuron protein. a, the fractionated antiserum (α-FGF-2 pol.; polyclonal anti-FGF-2 antibody; reactive with human, bovine, and rat FGF-2) was tested on Western blots of extracts from a human hepatocellular carcinoma cell line (HepG2) provided by Transduction Laboratories as a positive control for SMN and rat Schwann cells transfected with the 23-kDa FGF-2/DsRed plasmid. The position of the respective proteins, 23-kDa FGF-2/DsRed (23 tag), SMN, and the endogenous FGF-2 isoforms (18, 21, and 23 kDa) are indicated. The fractionated antiserum showed no cross-reactivity with SMN (lanes 1 and 3 and 4 and 6) in both extracts and was used in subsequent immunoprecipitation analyses as well as the anti-SMN monoclonal antibody (αSMN). αFGF-2 mon., monoclonal FGF-2 antibody used as a detection antibody for Western blots of immunoprecipitated proteins. b, immunoprecipitation analyses in Schwann cells (SC; lane 1) and with the 23-kDa FGF-2/DsRed-tagged isoform-transfected Schwann cells (SC-transf.; lane 2) show immunoprecipitation of 40-kDa SMN with anti-FGF-2 antibody, but not with rabbit IgG as a control (lane 3). Total protein content was not normalized between individual extracts, which accounts for the differences seen between signal strengths. Lanes 4 and 5 show input controls. Lanes 6 and 7 show no change in expression of endogenous FGF-2 in untransfected (SC) and transfected (SC-transf.; 23 tag) Schwann cells after immunoprecipitation with anti-FGF-2 antibody. Note that this separation was on 10% SDS-polyacrylamide gels and therefore no separation of the individual isoforms could be observed. c, in Schwann cells transfected with DsRed-tagged 23- and 18-kDa constructs, the 23-kDa but not the 18-kDa isoform can be immunoprecipitated by anti-SMN antibody (lanes 3 and 4). Controls show the individual isoforms in the input material (lanes 1 and 2) and immunoprecipitated tagged FGF-2 isoforms (lanes 5 and 6). Lanes 7-12 demonstrate SMN in the input (lanes 7 and 8), as control in the immunoprecipitation with anti-SMN antibody (lanes 9 and 10) and immunoprecipitated with anti-FGF-2 antibody (lanes 11 and 12). Co-immunoprecipitated SMN in lane 12 is probably because of the presence of endogenous 23-kDa FGF-2 in the 18-kDa FGF-2 overexpressing cell line. HC, IgG heavy chain; 23 tag, 18 tag, 18- and 23-kDa FGF-2 isoforms tagged with DsRed, d, model of FGF-2 18- and 23-kDa isoforms demonstrating the N terminus of the 23-kDa isoform with RGR motifs as a putative interaction domain with SMN (SMN-Int) and the determined NLS.

Many growth factors display sequences required for nuclear localization (1). Removal of the NLS from FGF-1β leads to decreased mitogenic activity, whereas receptor binding and activation is not influenced. Addition of a heterologous NLS from histone H2 is able to restore the mitogenic function (41). We show in this study that both FGF-2 isoforms localize to the nucleus, with the 18-kDa isoform possessing one and the 23-kDa displaying a second NLS: the N-terminal extension exclusively in the 23-kDa isoform and a common C-terminal sequence element in the 23-kDa core primary structure. This is in agreement with data showing that the N-terminal extension is able to target β-galactosidase to the nucleus (15). Interestingly, mutations of the second NLS in the 23-kDa sequence (R149G/R151G) override the effect of the N-terminal extension NLS, suggesting an effect on the overall structure of this isoform. It is possible, of course, that the other mutants also had an influence on FGF-2 structure, but they retained nuclear localization. Our data indicate that the 18-kDa FGF-2 core sequence is able to confer nuclear localization, because the N-terminal constructs displayed no clear enrichment in the nucleoli. For FGF-3 it has been shown recently that a nucleolar binding partner NoBP is essential for its nuclear localization (42).

different isofrom are available, we used this approach, although the possibility of artificial localization patterns because of overexpression of the tagged proteins cannot be completely excluded. One previous study shows a 18-kDa FGF-2/DsRed fusion protein localizing to the nuclei in corneal endothelial cells, however, the nuclear substructures enriched in this isoform have not been described explicitly (28). Here we demonstrate differential localization of FGF-2 isoforms in the nucleus, located in nuclear bodies, and a specific protein-protein interaction of 23-kDa FGF-2. For several growth factors, apart from FGF-2, localization in the cell nucleus is well known including platelet-derived growth factor (29), FGF-1 (30), FGF-3 (31), and EGF (32, 33). However, only limited information about their specific nuclear roles exists. Additionally, nuclear localization of the respective receptors has been described as in the case of FGFR-1 (34, 35), which is part of a transcription complex in the nucleus (36). Nuclear EGF receptor acts as a putative transcription factor and binds to the promoter region of cyclin D1 in vivo (37).

In this study, the 23-kDa FGF-2 isoform has been found to be putatively chromatin-associated. At present, it is unclear if specific chromatin components can be bound by FGF-2 in vivo, however, an association with histone H1 and an influence on chromatin compaction of the FGF-2 high molecular weight isoforms has been reported previously (12, 38). For the 18-kDa FGF-2 isoform we demonstrate in this study for the first time the localization in Cajal bodies. Recent data suggest a role of Cajal bodies in the maturation and transport of small nuclear ribonucleoprotein particles (39). Sm proteins are transported in the nucleus, where they localize first to Cajal bodies, before they are transported through the nucleolus to splicing factor compartments (40).

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The localization of the nucleolar localization sequence in FGF-2 has to be determined in further studies.

With regard to putative functions distinct effects of the isoforms have been shown, e.g., on neurite formation and survival of dopaminergic neurons after exogenous application of the isoforms (43). Examination of cell death rates and proliferation in Schwann cells stably overexpressing either the 18- or 21/23-kDa isoforms resulted in differential effects of both isoforms: the 18-kDa cells exhibited a significant increase of cell death but no higher proliferation rate in contrast to the high molecular weight isoforms (14).

For the understanding of nuclear functions of FGF-2, identification of interacting proteins is a crucial step. A previously unknown protein, called FIF (FGF-2-interacting factor), has been found in a two-hybrid assay and the exclusive interaction with high molecular weight FGF-2 was determined in a co-immunoprecipitation analysis (44). Recently, it was shown that the N terminus of the 23-kDa high molecular weight isoform of FGF-2 contains arginine residues that are post-translationally dimethylated (24). The RG repeats of the N-terminal extension are substrates for protein-arginine methyltransferases (23, 45). The product of the spinal muscular atrophy gene SMN is able specifically transported by motoneurons (55). In a recent study inhibition of small nuclear ribonucleoprotein assembly, splicing and abolishes assembly of small nuclear ribonucleoprotein. nuclear ribonucleoprotein particle core factors (Sm proteins) gene. Blocking of the central interaction do-

SMN2 correlated with the amount of functional SMN protein from the

but no higher proliferation rate in contrast to the high molecular weight isoforms (14).

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