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Minireview

The high molecular weight isoforms of basic fibroblast growth factor (FGF-2): an insight into an intracrine mechanism

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Abstract Basic fibroblast growth factor (FGF-2) is an important modulator of cell growth and differentiation under both physiological and pathological conditions. Until recently, most investigations into the FGF-2 signalling pathway were concerned with its interaction with specific membrane receptors. Nevertheless, while a 18 kDa protein of FGF-2 is cytosolic, there are also co-translated high molecular weight (HMW) isoforms that are predominantly located in the cell nucleus. An increasing amount of data strongly argue in favour of distinct biological functions depending on the subcellular location of the FGF-2 species. This review describes the evidence concerning the strictly intracellular mode of action of the HMW isoforms of FGF-2.

Key words: Basic fibroblast growth factor; High molecular weight isoform; Intracrine activity; Gene regulation

1. Introduction

Basic fibroblast growth factor (bFGF or FGF-2) was first characterised in 1974 as having proliferative activity for fibroblastic cells, and belongs to the 18 member family of fibroblast growth factors. FGF-2 is a multifunctional cytokine, involved in the proliferation and differentiation of a broad spectrum of mesodermal and neuro-ectodermal cell types. The findings describing the pleiotropic functions exerted by this single molecule in various physiological systems and during the developmental process (reviewed in [1]) strongly suggest that its biological activities arise from multiple signal transduction pathways.

The biological activity of FGF-2 is highly modulated, resulting from regulatory events occurring at each step of its synthesis. Different molecular isoforms of FGF-2 have been characterised, representing alternative translation products from a single mRNA. While the 18 kDa protein is cytosolic and efficiently secreted, the high molecular weight isoforms of FGF-2 (HMW FGF-2) contain nuclear localisation sequence (NLS)-like signals responsible for their nuclear targetting. Most studies to date concern the 18 kDa low molecular weight (LMW) form, acting via its specific transmembrane receptor (fibroblast growth factor receptor: FGFR) and activating the subsequent intracellular second messenger cascades. Until recently, little was known about the FGFR-independent activities of the HMW isoforms. The purpose of this review is to give a synopsis of the last 10 years' research on the biological significance and mode of action of the intracellular forms of FGF-2.

2. FGF-2: from gene to proteins

FGF-2 is encoded by a single-copy gene which includes two introns and large 5′ and 3′ untranslated regions (UTR), suggesting important regulation of its expression. The functional characterisation of the *fgf-2* gene promoter identified multiple regulatory elements [2,3]. A bidirectional transcription of the gene gives rise to multiple polyadenylated mRNAs from a single transcription start site, as well as a 1.5 kb antisense transcript (*gfg*) which is complementary to the 3′ untranslated region of the FGF-2 mRNA. This antisense RNA has been implicated in the transcriptional and post-transcriptional regulation of FGF-2 expression [4], and contains a long open reading frame encoding a functional nuclear protein with anti-mutator nucleotide hydrolase enzymatic activity [5].

In addition, higher molecular weight isoforms of FGF-2 have been described in the brain [6], or in *ras*-transformed cells [7]. In 1989, sequencing of the gene showed that an alternative initiation of translation at CUG codons, located 5′ to the AUG codon, accounts for the 24, 22.5 and 22 kDa proteins in humans, whereas the AUG codon is used to generate a 18 kDa species (Fig. 1) [8,9]. Recently, Arnaud et al. [10] described a new 34 kDa isoform of FGF-2, resulting from the use of a fourth CUG codon on the gene. Hence, the HMW isoforms are colinear amino-terminal extensions of the 18 kDa-FGF-2 protein.

3. FGF-2 subcellular localisation and the known subsequent signalling pathways

It is very likely that a differential subcellular location of the HMW and 18 kDa FGF-2 (Fig. 1) mediates distinct effects on cell phenotype. Despite the fact that the protein lacks a conventional secretory signal peptide, 18 kDa FGF-2 is found in vivo in biological fluids, in plasma and the extracellular matrix. A mechanism for FGF-2 exocytosis via an endoplasmic reticulum (ER)–Golgi-independent pathway has been described [11], involving the catalytic α subunit of Na^+,K^+-ATPase. Once on the cell surface (Fig. 2), FGF-2 can bind to the low and high affinity receptors: heparan sulphate proteoglycans (HSPG) and FGFR, respectively (for reviews, see [12,13]). The consensual binding model suggests that the formation of a specific side by side heparin-induced FGF-2 dimer

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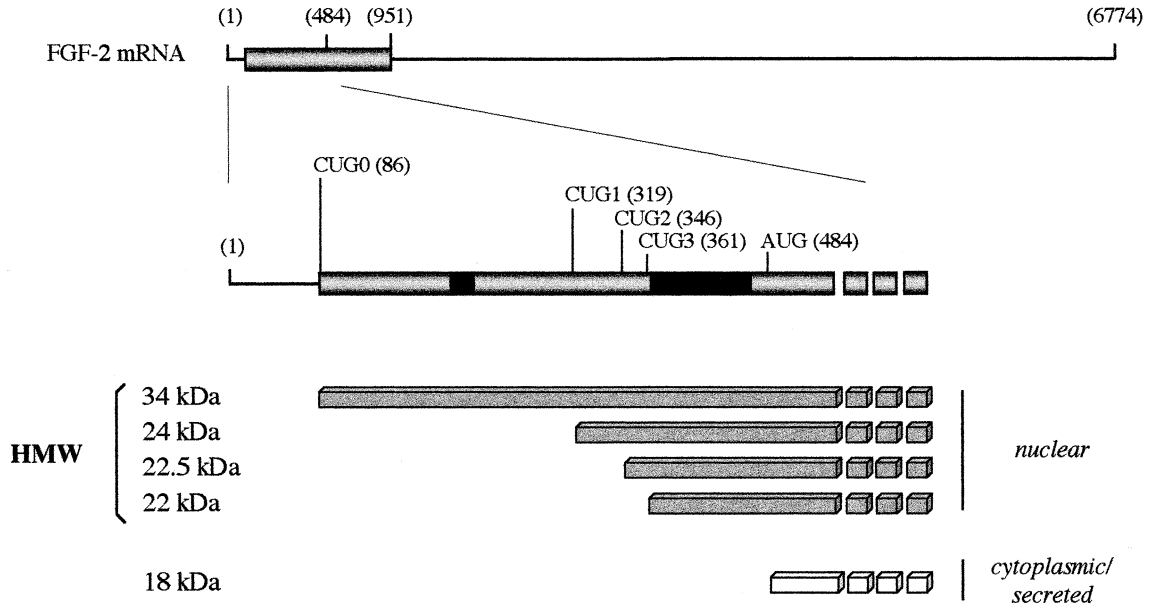

Fig. 1. Human FGF-2, from messenger RNA to proteins. Upper panel: the 6774 nucleotide FGF-2 single mRNA contains the 288 bp open reading frame region (open box) and the 5′ and large 3′ untranslated regions (black lines). Nucleotide positions relative to the transcription start site (1) are indicated in brackets. Middle panel: 5′ end of the FGF-2 mRNA with the AUG and the non-canonical CUG start codons accounting for the various FGF-2 isoforms. The NLS-like signals are shown (black boxes). The first one is a PRRRPRR motif similar to the arginine-rich NLS of the human immunodeficiency virus type 1 (HIV-1) Rev protein. The second one, located between the CUG3 and the AUG, is contained with a 37 amino acid sequence which encompasses three GRGR$(X)_5$R motifs. Lower panel: the HMW isoforms initiated from the CUG codons and the AUG-initiated protein, showing their respective molecular mass and localisation.

is required for dimerisation and activation of the FGF receptor tyrosine kinase, and consequently for the subsequent initiation of biological responses [14].

In the early 1990s, immunofluorescence studies with antibodies against FGF-2 showed intense nuclear staining in various endothelial FGF-2-producing cells and FGF-2-transfected BHK-21 cells [15], as well as in astrocytes and oligodendrocytes. Different mechanisms can explain these observations: the internalisation of the extracellular 18 kDa FGF-2 proteins, and/or the preferential nuclear location of the HMW isoforms of the growth factor.

Bouche et al. [16] showed that exogenously added FGF-2 can indeed translocate to and accumulate in the nucleolus of adult bovine aortic endothelial (ABAE) cells during G0/G1 transition. In coronary venular endothelial cells, up to 50% of total internalised FGF-2 is also rapidly targeted to the nucleus [17], suggesting that some biological activities of the growth factor may be mediated by nuclear FGF-2, subsequent to its binding to the cell surface receptors. The nucleolar localisation of 18 kDa FGF-2 is indeed correlated with the stimulation of ribosomal gene transcription, whose activation is mediated via the direct interaction of nuclear FGF-2 with the regulatory subunit of the protein kinase CKII [18]. Stachowiak and colleagues studied the roles and subcellular location of FGF-2 and its high affinity receptor FGFR-1 in the nervous system (reviewed in [19]). They showed that following the transition of cells to a subconfluent proliferating state, FGFR-1 translocates in parallel with FGF-2 to the nucleus, where they both accumulate and act to stimulate transition from the G0/G1 to the S phase of the cell cycle [20].

Apart from the internalisation process of extracellular 18 kDa FGF-2, the HMW isoforms also account for the nuclear location of the growth factor. In transfected NIH-3T3 fibroblasts, SK-Hep-1 or COS cells, the 18 kDa FGF-2 protein is cytosolic or exported at the cell surface, whereas the HMW species are preferentially nuclear [21,22]. Using COS cells transfected with cDNA encoding fusion protein of FGF-2 and chloramphenicol acetyltransferase (CAT), Bugler et al. [23] demonstrated that the nuclear targeting of HMW FGF-2 is governed by a 37 amino acid sequence between the second CUG and the AUG start codons (Fig. 1). Similar results were

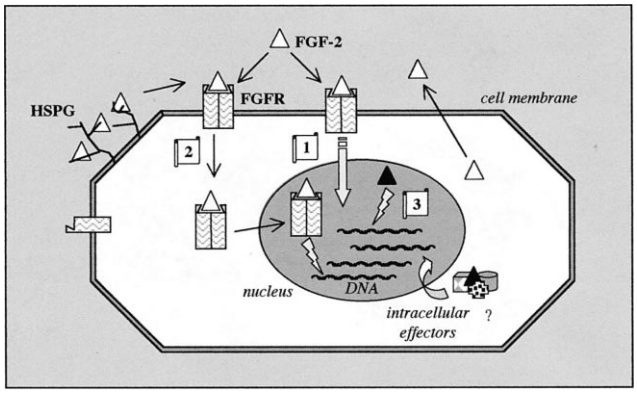

Fig. 2. FGF-2 signalling pathways. When secreted at the cell surface, the 18 kDa FGF-2 (white triangle) can bind to the heparan sulfate proteoglycan (HSPG) receptors and the high affinity receptor FGFR to act in an autocrine/paracrine manner. Two pathways are distinguishable, both of which are responsible for subsequent specific genes activation: the tyrosine kinase FGFR signal transduction pathway (1), or internalisation leading to the colocalisation of both ligand and active receptor in the cell nucleus (2). The nucleus-targeted HMW isoforms of FGF-2 (black triangle) have an intracrine mode of action, probably interacting with intracellular partners in the cytoplasm and/or the nucleus, and also regulating the expression of specific target genes (3).

obtained when using proteins containing the amino-terminal extension of HMW FGF-2 fused to β-galactosidase [24]. Arginine methylation has been shown to be probably relevant to the intracellular distribution of these isoforms [25]. Moreover, the newly discovered 34 kDa protein of FGF-2 contains an additional functional arginine-rich NLS sequence, similar to the NLS of human immunodeficiency virus type 1 Rev protein [10].

4. FGF-2 isoforms display differential patterns of expression

The different isoforms of FGF-2 display specific patterns of expression depending on tissue, species, developmental stage or cellular stress conditions. When comparing normal and *H-ras*-transformed Rat-1 fibroblasts [7], a preferential increase in the HMW FGF-2 protein level is observed as a consequence of cell transformation. In the rat central nervous system, the HMW 24 kDa isoform is developmentally regulated [26], appearing only after birth and reaching maximum levels in the adult. In contrast, in the development of the rat heart, HMW FGF-2 progressively disappears during the progression from immature to differentiated cardiac phenotype, and this occurs predominantly for the synthesis of the 18 kDa isoform [27]. Moreover, expression of the HMW but not of the 18 kDa isoform is selectively increased by cytokines such as interleukin 1β (IL-1β) or tumour necrosis factor α in rat hippocampal astrocyte cultures [28]. Specific translation of the CUG-initiated FGF-2 protein is activated in transformed cells, as well as in stressed primary skin fibroblasts in response to heat shock and oxidative stress [29]. This differential regulation of FGF-2 isoform expression occurs via both a cap-dependent and cap-independent initiation of translation, involving at least one internal ribosomal entry site (IRES) in the FGF-2 mRNA [30]. Alternative translation mechanisms involving *trans*-acting factors specific to transformed and stressed cells are responsible for the differential expression of the HMW proteins [29].

5. Specific effects of HMW FGF-2 on cell phenotype

On the basis of the latest studies, it has been suggested that 18 kDa and HMW proteins may serve distinct physiological functions. Several strategies have been used to address this possibility, involving the use of antisense RNA molecules for FGF-2 or selective expression of the different isoforms (Table 1).

Couderc et al. [31] observed that the constitutive overexpression of recombinant HMW FGF-2 leads to ABAE cell immortalisation, whereas cells transfected with the 18 kDa coding vector form colonies in soft agar. In addition, the tumorigenic potential is reached when all isoforms are constitutively expressed. In NIH-3T3 fibroblasts, contrary to the effect of 18 kDa FGF-2, the HMW proteins do not modify cell migration or FGF receptor number, but allow proliferation in low serum and cell growth to a high saturation density [32]. Moreover, when these same cells are cotransfected with a cDNA encoding FGF receptor lacking the COOH-terminal domain (dominant negative FGFR-2), only the phenotypes allocated to the 18 kDa FGF-2 can be reversed, strongly suggesting a dissociated intracrine activity of the HMW isoforms versus the extracellular mode of action of FGF-2. Estival and colleagues performed studies in the rat pancreatic acinar cancer cell line AR4-2J, which expresses FGF-2 receptors but not FGF-2 proteins. Only the cells transfected with

Table 1
Specific effects of the various FGF-2 isoforms on cell phenotype

Cell type	Source of FGF-2 synthesis	FGF-2 isoform (kDa)	Cell phenotype	Effects of inhibitors	References
ABAE	selective expression (a)	21/22.5 18 HMW+LMW	immortalisation transformation tumorigenic potential		[31]
NIH-3T3	selective overexpression (b,c)	21/22.5/24	growth in low serum medium to a high saturation density	⊢✕ FGFR-2$^-$	[32,46]
		18	increased cell migration	⊢ FGFR-2$^-$	
AR4-2J	selective expression (a)	22.5 HMW+LMW	proliferation in serum-free medium		[33]
Schwann cell precursors	TPA-induced expression	HMW+LMW	*trans*-differentiation into melanocytes	⊢ antisense FGF-2 RNA, ⊢✕ Ab α-FGF-2, InsP6	[35]
SK-Hep1	endogenous expression	HMW+LMW	transformation/tumorigenicity	⊢ antisense FGF-2 RNA	[36]
rat cardiac myocytes	selective overexpression (c)	21.5/22 (rat) 18	cell binucleation proliferation	⊢✕ Ab α-FGF-2 ⊢ Ab α-FGF-2	[37]
HeLa	selective expression (a)	24	radioresistance (γ-rays)		[38]
Glioma cells	endogenous expression selective overexpression (c)	HMW+LMW HMW+LMW	proliferation increased proliferation	⊢ antisense FGF-2 RNA ⊢✕ InsP6	[19,39]
PC-12	selective overexpression (c)	21/23	stabilisation of the endocrine phenotype		[40]
		18	differentiation towards the neuronal phenotype		

Expression vectors: (a) retroviral; (b) adenoviral; (c) plasmidic. FGFR-2$^-$: dominant negative FGF receptor-2; InsP6: antagonist of FGFR binding; α-FGF-2: neutralising antibody. ⊢: blocking action; ⊢✕: no blocking action.

the HMW FGF-2 were able to grow in serum-free medium and revealed a strong increase in both high and low affinity receptors, hence enhancing cell responses to exogenous FGF-2 [33,34]. The use of neutralising anti-FGF-2 antibodies and suramin did not reverse these effects.

In the central nervous system, FGF-2 or 12-*O*-tetradecanoyl phorbol 13-acetate (TPA) can stimulate the *trans*-differentiation of avian neural crest-derived Schwann cell precursors into melanocytes. The TPA-induced differentiation process is blocked with antisense RNA targeted against FGF-2 mRNA [35]. In this same study, an antagonist of FGFR binding and activity (inositol-hexakisphosphate: InsP6), or FGF-2-neutralising antibodies, had no effect on TPA-induced differentiation, thus indicating the crucial involvement of intracellular FGF-2 proteins in melanogenesis.

The antisense methodology also allowed the elucidation of the intracrine effect of FGF-2 on transformation and tumorigenesis of the SK-Hep1 hepatoma cell line, which naturally produces all the FGF-2 isoforms. Inhibition of FGF-2 synthesis in these cells led to a loss of anchorage independence in soft agar, and this effect was not reversed by the addition of exogenous FGF-2 [36].

In the development of the rat heart, the question of a putative distinct role of the high and low molecular weight isoforms of FGF-2 has also been addressed. Neonatal rat cardiac myocytes were transfected with cDNA of both isoforms [37]. Both the 18 kDa and HMW FGF-2 affected proliferation via a paracrine mechanism, but overexpression of the HMW isoforms only led to a significant increase in cell binucleation, which was not affected by neutralising antibodies against FGF-2. Here again, the preferential synthesis of the nuclear isoforms of FGF-2 versus the 18 kDa protein correlates with differential effects on cell phenotype.

A selective overexpression of HMW FGF-2 has also been frequently characterised in human tumour cells surviving irradiation treatment. As such, the distinct behaviour of the FGF-2 species has been studied in a model of cell radioresistance acquisition. Transfecting HeLa cells with FGF-2-coding vectors, Cohen-Jonathan et al. [38] observed that cells overexpressing the 24 kDa FGF-2 become radioprotected compared to the wild type or 18 kDa FGF-2-transfected cells. This radioresistance was associated with an increased G2 delay after irradiation and the hyperphosphorylation of p34cdc2 kinase.

Finally, it has also been shown that while the glioma cells do not respond to extracellular FGF-2 stimulus, their proliferation rate strongly increases when transfected with FGF-2-expressing vectors. This effect is unaffected by the InsP6 antagonist that disrupts FGF-2 binding to plasma membrane receptors, and is correlated with nuclear accumulation of FGF-2 [39]. Moreover, in the PC12 cell line, overexpression of HMW FGF-2 stabilises the endocrine phenotype, while the 18 kDa protein led these cells to differentiate towards the neuronal phenotype [40].

6. Intracellular FGF-2 can direct gene regulation

As increasing evidence for the differential activity of HMW FGF-2 has accumulated, an investigation into the intracellular targets of these proteins has been addressed. In 1992, Nakanishi et al. [41] first demonstrated a direct modulation of gene activity by FGF-2 in a cell-free system. Using nuclear extracts of Ehrlich ascites tumour cells, they analysed the effect of the recombinant 18 kDa FGF-2 isoform on the expression of the mouse phosphoglycerate kinase 1 and 2 (Pgk-1 and Pgk-2) isozyme genes. These proteins are involved in the transcriptional switch occurring during spermatogenesis and evolve from the somatic-type Pgk-1 to the sperm-specific Pgk-2. The authors showed that FGF-2 modulates transcription of *Pgk-1* and *Pgk-2* genes in a dose-dependent and promoter-specific manner, stimulating *Pgk-2* while inhibiting *Pgk-1* transcription.

More recently, Delrieu and colleagues investigated whether or not nuclear FGF-2 could be involved in the regulation of another multifunctional cytokine expression: IL-6. Part of this work, using cotransfection systems in NIH-3T3 fibroblasts [42], showed that while exogenously added 18 kDa FGF-2 results in a down-regulation of IL-6 expression, the nuclear 24 kDa isoform leads to accumulation of the IL-6 mRNA. This was shown to occur via activation of the IL-6 promoter. However, the overexpression of 24 kDa FGF-2 in HeLa human cells led to an inhibition of the IL-6 promoter activity, hence revealing a cell-specific effect of this nuclear isoform on IL-6 transcriptional regulation [43]. When investigating further this down-modulation, it appeared that neither the AP-1, NF-κB nor NF-IL-6 elements on the IL-6 promoter were involved. On the contrary, the deletion of a short region, containing a retinoblastoma control element (RCE) consensus sequence, abolished the effect of the 24 kDa protein, indicating that RCE could be a direct or indirect nucleic target for the nuclear activities of the HMW FGF-2 molecules.

7. Conclusion

Taken together, these findings emphasise the complexity of the mechanisms accounting for the biological activities of FGF-2. As for another member of the FGF family, FGF-1 [44], intracellular proteins of FGF-2 are responsible for some of its important biological activities, e.g. growth in low serum conditions and survival phenotype acquisition. Nevertheless, apart from the internalisation process of extracellular growth factor molecules, de novo synthesis of the nuclear HMW isoforms accounts for the nuclear localisation of FGF-2. As a result, HMW FGF-2 appears to play a role in the regulation of gene expression in the mediation of these specific effects. It is very likely that the differential signalling pathway between the 18 kDa and HMW FGF-2 depends more on their distinct subcellular location than on their respective biochemical features, e.g. amino-terminal extensions. Indeed, both purified species compete for the same high affinity membrane receptors when administered to endothelial cells, and hence are similarly capable of inducing plasminogen activator production as well as proliferation and migration [45]. In addition, both 18 kDa FGF-2 and HMW FGF-2 are capable of binding non-specifically and with high affinity to nuclear chromatin, suggesting that sequences within the 18 kDa protein, but not the amino-terminal extension, are necessary for this binding. This hypothesis has been recently confirmed by Arese et al. [46] using artificially nucleus-targeted 18 kDa FGF-2. When overexpressing these constructs in NIH-3T3 cells, the authors showed that the 'core' 18 kDa molecule of FGF-2 is the biological messenger for the mitogenic activity under serum starvation conditions. In addition, the LMW and HMW FGF-2

isoforms have been shown to be involved in different molecular protein complexes in the cytosol and nucleus [47].

Hence, FGF-2 is capable of controlling several distinct activities via different signal transduction pathways, depending on its specific cellular localisation which itself relies on tightly regulated alternative translation mechanisms. Intracellular FGF-2 molecules can be targeted to the nucleus via NLS-independent (internalised 18 kDa), or NLS-dependent (HMW isoforms or artificial NLS 18 kDa recombinant proteins) pathways. Depending on the pathway involved, they might be addressed to distinct subcellular/subnuclear compartments where they may associate with distinct effectors, hence resulting in distinct biological responses.

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