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Mini-review

NF90 isoforms, a new family of cellular proteins involved in viral replication?

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ABSTRACT

The Nuclear Factor 90 (NF90) and its isoforms constitute a family of proteins that can interact with double-stranded (ds) RNA, through its dsRNA binding motifs. Due to various potential translational events such as alternative splicing, the human Interleukin enhancer binding factor 3 (*ilf3*) gene codes for multifunctional proteins that are NF90 and its isoforms, involved in transcription, translation, mRNA export and microRNA biogenesis. These proteins can act as cellular partners affecting viral replication and they are also implicated in host defense. As a result of these numerous functions, these protein isoforms have been given various names over the years, leading to confusion in determining their specific functions. In this review we focus on the role of the human NF90 protein isoforms in DNA and RNA virus replication.

1. Introduction

The human Interleukin enhancer binding factor 3 (*ilf3*) gene which encompasses 21 exons, is at the heart of the synthesis of many proteins that operate at specific levels in cell development. Moreover, it is now widely accepted that all the isoforms of Nuclear Factor 90 (NF90) are encoded by the *ilf3* gene. Thanks to two possible splicing and two possible frameshift events, and to three possible polyadenylation signals, several isoforms can be generated: ILF3 (also frequently referred to as NFAR110, NFAR-2, TCP110 or NF110a), DRBP76 (also frequently referred to as NFAR-1, NFAR90 or NF90a), NF110b (also designated as MPP4 110), NF90b (also designated MPP4 90), TCP80, and NF90 (also frequently referred to as NF90a, NF90c and NF90ctv; Fig. 1). The most important differences between these proteins result from the two possible splicing events, one in exon 14 leading to the insertion of the NVKQ tetrapeptide in the resulting protein between the two double-stranded (ds) RNA-binding motifs (dsRBMs), and another in exon 17 resulting in the most important difference in the C-terminal region [1]. NVKQ is present in the proteins designated NF110b, NF90b and NF90 [2–4]; Fig. 1]. In addition, Reichman et al., described the NF110a protein, which does not have the NVKQ insertion [4]. Furthermore, these authors described NF90c, but also mention that this isoform corresponds to the NF90 described by Kao et al. [5]; Fig. 1]. The cDNA coding for this protein contains a 2 bp insertion resulting in a protein with a different, slightly shortened C-terminus. However NF90 is also designated NF90ctv whose C-terminal 70 amino acids (aa) contain an arg/gly-rich (RGG-rich) motif that is replaced by acidic residues resulting from a CT insertion in exon 15 and altering the reading frame [6]. A second possible splicing event between exons 17 and 19 skipping exon 18, generates the isoforms designated NFAR-2, TCP110, ILF3, NFAR110 and NF110a producing a 894 aa-long protein [1–4,7,8]; Fig. 1). While NFAR-1 contains exon 18 generating a protein of 702 aa, NFAR-2 lacks exon 18 but comprises the additional coding exons 19, 20 and 21 [4,9,10]. Another NF90 isoform described is DRBP76 (*ilf3-b*), which is now known to be identical to NFAR-1 [1,11] (also designated as NF90a [4]), that has a termination codon and a polyadenylation signal in exon 18. Since DRBP76 shares 99% homology with the cDNA clone of NFAR-1 [9], NFAR-1, NF90a and DRBP76 are considered identical proteins. Moreover, NF90 and DRBP76 are similar; these proteins do not contain the tetrapeptide NVKQ (Fig. 1).

Frameshift events are responsible for the divergence in the predicted aa sequence of TCP80, which is likely identical to MPP4 110 over the first 670 aa and to NF90 up to aa 599 [12]. Furthermore, TCP80 (Fig. 1) has the same sequence as ILF3 up to aa 687, beyond which the C-terminus of 77 aa is completely different from that of the other isoforms. However, TCP80 does not contain the NVKQ peptide [12]. NF90 results from two splicing and two frameshift events, creating two regions very different from those of the other

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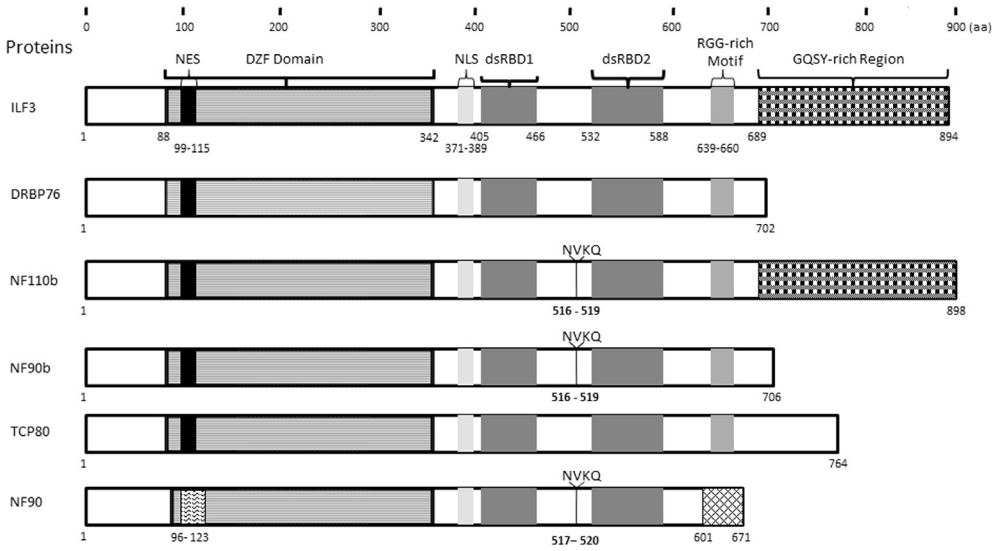

Fig. 1. Schematic representation of the NF90 and ILF3 isoforms. The proteins predicted from the cDNA corresponding to ILF3 also frequently referred to as NFAR110, NFAR-2, TCP110 or NF110a), DRBP76 (also frequently referred to as NFAR-1, NFAR90 or NF90a), NF110b (also designated as MPP4 110), NF90b (also frequently referred to as MPP4 90), TCP80, and NF90 (also frequently referred to as NF90a, NF90c and NF90ctv), are shown. The various domains discussed in the text (NES, DZF, NLS, dsRBDs, RGG-rich and GQSY-rich), as well as the position of the tetrapeptide NVKQ are highlighted.

isoforms, the first one between aa 96 and 123 causing the loss of the Nuclear Export Signal (NES), and the second one between aa 601 and 671 leading the loss of RGG-rich motif (Fig. 1), but containing the NVKQ peptide [2,5,6,13]. NF90 and its isoforms, possess many biological functions and interact with a vast number of cellular mRNAs and proteins, viral RNAs and proteins, non-coding RNAs and dsRNAs.

Several reviews [14,15] have recently aimed at clarifying the many interactions that these isoforms can perform with proteins and nucleic acids, and the variety of functions they play such as in transcription and/or translation, and in microRNA biogenesis. Moreover, since NF90 and its isoforms are frequently involved in controlling virus life-cycles, they are acquiring increased attention in virology. The aim of this minireview is to focus on the role of NF90 and its isoforms in viral infections, promoting or reducing viral replication, or acting as antiviral proteins. To avoid confusion with the names of the different isoforms, the names used in this minireview correspond to the name used by the authors in the respective publications.

1.1. NF90 isoforms and their domains

Members of the NF90 family of proteins possess a domain associated with zinc fingers (DZF) in their N-terminal region, through which they form heterodimers with the NF45 protein produced by the *ilf2* gene and that also possesses a DZF domain [16]. The DZF domain presents structural similarities to the nucleotidyltransferase family of RNA-modifying enzymes [16], but lacks catalytic activity. An NES is also located in the N-terminal region of all the NF90 isoforms except for NF90 [2,17]; Fig. 1]. A nuclear localization signal (NLS) is located downstream of the DZF domain, close to the first of two dsRNA binding domains (DRBDs) that are part of these dsRNA binding proteins (dsRBPs). Since the proteins shuttle between the nucleus and the cytoplasm under particular physiological circumstances, we suggested that the putative NES and NLS could be involved in this process [18–21]; alternatively, as a result of viral infection the NES and NLS could participate in affecting virus amplification [20,22–24]. The two DRBDs contained in all the isoforms bind to highly structured RNAs, to cellular and viral dsRNAs [20,23,24], and to the dsRNA-dependent protein kinase (PKR) [25]. The C-terminal region of most isoforms contains an RGG-rich motif, and certain isoforms terminate with a Gly-Gln-Ser-Tyr-rich (GQSY-rich) region, both of which are absent from NF90 (Fig. 1).

The GQSY-rich region interacts with cellular proteins such as YM155 [26] and allows protein–protein interaction with other cellular proteins such as FUS and PRMT1 [8,27]. When NF90 isoforms participate in regulating biological cell functions such as gene expression, transcription, RNA editing, RNA splicing, RNA stability and RNA export, they are located in the nucleus, whereas when they are implicated in translation regulation, dsRNA signaling events and antiviral activity, they are located in the cytoplasm [13,22]. A characteristic that distinguishes the spacer region between the two DRBDs of the different isoforms, is the presence or absence of the tetrapeptide NVKQ [1] whose function is unknown.

Below, we present an overview of the various roles played by the NF90 isoforms in transcription and/or translation of viral genomes, when they interact with the viral genome or with viral and/or other cellular proteins.

1.2. NF90 isoforms are involved in the viral life-cycle by recognition of the viral genome or of viral RNAs

Besides being involved in stabilization and export of cellular mRNAs, NF90 isoforms also bind viral RNAs or DNAs. Depending on the virus, the NF90 isoforms can act as negative or positive regulators of viral genome expression [20]. For example, NF90 inhibits transcription of the major late I promoter of the dsDNA-containing Adenovirus when NF45 its heterodimeric partner to which it normally binds is absent. Conversely, NF90 activates transcription of the immediate-early promoter of the dsDNA-containing Cytomegalovirus that acts as a heterodimer with NF45; thus the NF90/NF45 complex is involved in transcription regulation and activates NF90 [20].

A remarkable feature of the single-stranded (ss) RNA genomes of all viruses of the Flaviviridae family, such as Dengue virus (DENV) is that the 3′ stem loop (SL) is highly conserved and is required for viral genome expression and replication [28]. Different cell proteins