Minireview

Estrogen receptor β
Potential functional significance of a variety of mRNA isoforms

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Abstract Recent cloning of estrogen receptor β (ERβ) was followed by the discovery of a variety of its isoforms. This review describes the complexity of ERβ mRNAs in various species for which most data have been gathered so far. The most surprising finding is the great variation in isoform structure among various mammalian species. This may reflect either the fact that only a very limited number of isoforms have been described so far or between-species specificity, especially as common elements in closely related species could still be noted. Isoform variations, as detected mainly at the mRNA sequence level, should result in profound functional differences at the level of proteins as already shown in selected cases. Thus, it is proposed that the diversity of ERβ isoforms implies a functional role of this phenomenon in cellular physiology and pathology of estrogen response.

Key words: Estrogen receptor; mRNA isoform; Alternative splicing

1. Introduction

Two estrogen receptor types, named ERα and ERβ, have been found to be the major mediators of a variety of biological functions of estrogens [1–4]. However, their exact roles are still poorly elucidated, especially in the case of the recently discovered ERβ [1]. On the other hand, it is becoming increasingly clear that both receptor types are responsible for different biological functions, as indicated by their specific expression patterns and various consequences in gene knockouts [5–8]. Moreover, both ERs work as either homo- or heterodimers, when inducing transcription from gene promoters equipped with estrogen-responsive elements (ERE) [9–12]. An interesting feature of the ERβ and ERα receptors is the outstanding variety of their mRNA isoforms. The isoforms of ERα have already been discussed previously [13–15]. In this review we want to summarize the current knowledge about the ERβ isoforms in selected mammalian species. In order to provide adequate background information for considering functional differences between isoforms, we will first briefly summarize the ERβ gene and protein structure.

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2. ERβ: gene and protein structure

ERβ was first cloned in rat [16] and then in human [17]. The gene is considered to contain eight exons (however, see also below and Fig. 1) and has a different chromosomal localization from that of ERα [18,19]. The human ERβ gene promoter has recently been described, and it is considered to have at least two major transcription start sites [20]. The human ERβ also has two untranslated exons in the 5′ untranslated region of the mRNA transcript [21] and an additional exon at the 3′ region of the gene, which may contribute new amino acids to the protein [22].

ERβ is a member of a nuclear receptor superfamily and shares a similar overall protein domain structure with the other members [23]. Starting from the N-terminal end there is the first transactivational domain (AF-1) and then the DNA binding domain (DBD) with a dual zinc finger motif (Fig. 1). Next there is the hinge (H) domain with a nuclear localization signal (NLS). The following is the ligand binding domain (LBD) together with the subsequent second transactivational domain (AF-2) whose activity, in contrast to AF-1, is ligand-dependent [24]. There is more than one description of the structure of the domains and their amino acid content [19,25]. In this review we will follow the arrangement described by Enmark et al. [19]. Initially, the recognition of ERβ function relied mainly on the homology with ERα. However, further analysis has shown that differences in domain sequence homology, particularly in AF-1 and AF-2, result in differential functions [8]. The AF domains interact with a number of transcriptional cofactors such as steroid receptor coactivators: SRC-1, SRC-2, SRC-3 [26–30] and a more general coactivator, the CREB binding protein (CBP/p300) [31]. The structure of the ERβ AF domains and particularly the C-terminal part of the second AF domain named helix 12 determines the protein's ability to interact with the coactivators [32,33].

3. ERβ mRNA isoforms

A number of ERβ mRNA isoforms have been described, either in a form of research papers or just as GenBank depositions. As there are significant species variations in this regard, we will describe them separately for each species. In each case we will first present the sequence structure of the isoforms, next we will analyze a potential protein domain

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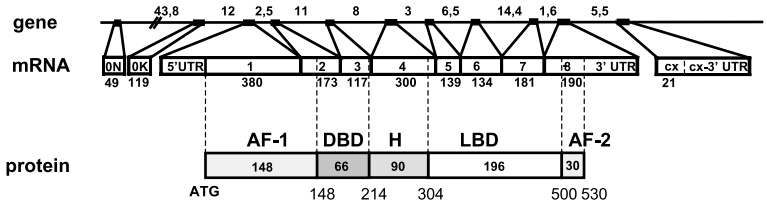

Fig. 1. Structure of the human ERβ gene, mRNA, and protein. **Gene**: exons are shown as thick boxes and introns as thin lines. The numbers above introns indicate their size in kb. **mRNA**: the digits within boxes designate the exon number; the numbers below indicate the length of each exon size in nucleotides; vertical dotted lines between mRNA and protein point to protein domain junctions. **Protein**: the names above the scheme designate the protein domains. The AF-1 domain is considered to be responsible for transcription transactivation. The DNA binding domain (DBD) binds the DNA regulatory sequence named ERE. The hinge domain (H) is responsible for protein flexibility allowing different spatial conformations and it contains a putative nuclear localizing signal (NLS). The ligand binding domain (LBD) is responsible for ligand binding. The second transactivation domain (AF-2) is involved in recruiting the ligand to LBD. The numbers within boxes show the number of amino acids for each domain, numbers below indicate the total size of the protein in amino acids.

composition and its functional consequences, and then present data on the expression pattern of the isoforms.

3.1. Human ERβ mRNA isoforms

The apparent full-length human mRNA encodes 530 amino acids (aa) and is called hERβ1 [34]. Additionally, several full or partial sequences of other isoforms have been described to date: hERβcx, hERβ2spldel5, hERβ3iso, hERβ4spl, hERβ5spl, hERβdel2, hERβ5del2,5,6, hERβdel3, hERβdel4, hERβdel5, hERβ2,5, hERβdel6, hERβdel2,6, hERβdel2,3,6, hERβdel5,6 [33–37]. The first three are described as complete sequences and for this reason are most likely to be translated in vivo. The isoform named hERβ with C-terminal exchanged (hERβcx, GenBank AB006589) is also known as ERβ 2 splice variant (hERβ2spl, GenBank AF051428). It has a novel sequence inserted in place of exon 8 and for the purpose of this paper we will describe it as composed of two parts: the first 17 nt, to be called block 'A', and the following 92 nt, referred to as block 'B' (Fig. 2). Another isoform was also named hERβ2spl (GenBank AF124790), but it has a different structure than that of hERβcx. It resembles the latter by having the sequences referred above to as block 'A' and block 'B' instead of exon 8. However, in addition it has a deletion of exon 5, hence we will call it hERβ2spldel5.

The isoform called hERβ3iso (GenBank AF060555) yet again has a novel sequence instead of exon 8 but it is not similar to the ones described as block 'A' and block 'B'. Here we will refer to it as block 'C'. In addition to the afore-mentioned full-length clones of mRNA isoforms, the transcripts described below are reported as incomplete sequences, without an identified translation start sites, and their structure is shown in Fig. 2, hERβ4spl (GenBank AF061054) and hERβ5spl (AF061055). Additionally, isoforms termed hERβdel2, hERβ5del2,5,6, hERβdel3, hERβdel4, hERβdel5, hERβ2,5, hERβdel6, hERβdel2,6, hERβdel2,3,6, hERβdel5,6, have recently been described [36]. Their schematic representation is shown in Table 1.

It is important to note that in addition to the afore-mentioned isoforms, another level of complexity is provided by the diversity in the 5′ region of the mRNA. There are two

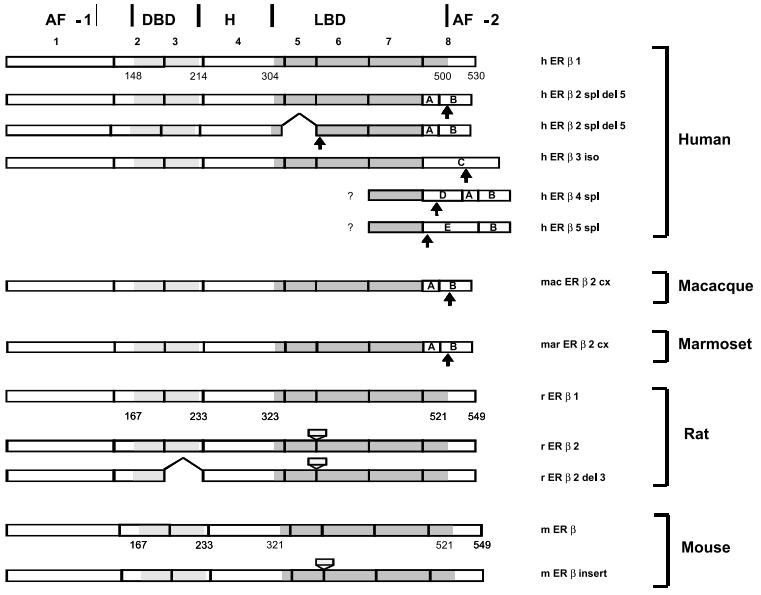

Fig. 2. Schematic representations of mammalian ERβ mRNA isoforms with inserts. mRNAs are presented as boxed lines. Boxes designate exons and shaded areas reflect the encoded protein domains. Respective exon numbers and domain names are indicated at the top. Inserted sequences are shown as boxes and shaded or marked with letters A, B, C, D, E (see the main body of the text for details). The thin line bridges designate exon deletions. The arrows point to location of stop codons. Question marks indicate the nucleotide submission ends within the reading frame. Numbers below show the amino acid count per protein domain for particular species. Isoform names are on the right of the respective sequence.

alternatively spliced exons contributing to this part of mRNA. The first exon is termed '0N' [21] and is present in the ERβ1 transcript [17,20,34]. In contrast the hERβcx transcript lacks this exon '0N' but instead has yet another untranslated exon named '0K' [22]. Since these exons do not contribute directly to the protein open reading frame their significance remains unknown.

The protein encoded by hERβcx has all the domains of hERβ1 except the terminal part of the LBD (33 aa out of 274) along with the entire AF-2 domain (28 aa) [22]. The deletion removes the amino acids encoding helix 12, which is replaced by 25 new amino acids from the inserted nucleotide sequence. The lack of helix 12 suggests that ERβcx product is unable to interact with the coactivators while still displaying the DNA and ligand binding ability.

The functional experiments on this product have given equivocal results. The data obtained by Ogawa et al. [22] suggest that hERβcx has no ligand binding affinity, whereas Moore et al. [34] reported such a property. Additionally this isoform does not show ligand-dependent transactivation ability of the ERE-containing promoter [22]. hERβcx forms a dimer preferentially with hERα rather than hERβ, inhibiting DNA binding by hERα. Therefore, it is considered to act as a selective inhibitor of estrogen activity via hERα transactivation [22]. The deletion of the fifth exon in the hERβ2spldel5 isoform results in a frameshift and a termination of the polypeptide chain with 5 aa after the exon 4/5 border. The hERβ2spldel5 protein lacks 264 out of 274 aa of the LBD together with the AF-2 domain, and has no ligand binding affinity [37]. Moreover, hERβ2spldel5 by itself has no effect on ERE transcriptional activation, but it does act as a dominant negative receptor, inhibiting the estrogen-mediated transcription through both ERα and ERβ [36]. The ERβ3iso transcript again alters the amino acid sequence of the LBD and of the second transactivation domain. The insert encodes a 43 amino acid tail at the C-terminus. hERβ3iso can bind to the ERE promoter in a gel shift assay as a homodimer, and can also bind as a heterodimer with proteins described here as hERβ1 and hERβcx [34].

The expression patterns of human ERβ mRNA isoforms have been determined mostly by RT-PCR [22,34] and by the use of antibodies directed against the N- [38,39] or C-terminus [22]. hERβ1 is mainly expressed in testis, ovary, uterus, and spleen. hERβcx was found predominantly in spleen, thymus, testis, ovary, and colon. Moreover, it is predominantly expressed in breast cancer tissue at higher levels than ERβ1 [35]. hERβ3iso transcript was found in a testis cDNA library only. hERβ2spldel5 was found mainly in mammary gland [40]. There are also several studies describing hERβ isoform expression in human cancer tissues suggesting their influence on tumor progression [39,41–47]. Unfortunately the concentration of alternative ERβ mRNAs, relative to that of the wild-type homologue, was not determined, and the expression of alternative forms of the ERβ protein was not evidenced.

3.2. Marmoset and macaque ERβ transcripts

Only limited information is available on ERβ expression in other primates, that is in macaque [48,49] and in marmoset [50,51]. Two recent submissions to the GenBank provide the first information on ERβ isoform transcripts found in those species. The sequences for stump-tailed macaque *Macaca arctoides* (AF393815) and white-tufted-ear (common) marmoset *Callithrix jacchus* (AF393816) have exactly the same design as the human ERβcx isoform (Fig. 2). More interestingly, the amino acids introduced by alternative splicing in place of exon 8 share significant similarity (12 out of 15 subsequent amino acids) in all three species of primates studied to date.

3.3. Rat ERβ mRNA isoforms

In the rat, the originally identified mRNA has been named rERβ1 [16]. In addition, four mRNA isoforms, named rERβ2, rERβ1δ3, rERβ2δ3, and rERβ1δ4, have been identified to date [52–55]. The predicted mRNA isoforms encoding putative proteins are shown in Fig. 2 and Table 1. The rERβ1

Table 1
The protein structure of ERβ isoforms characterized by exon deletions

Isoform name	Protein domains of human ERβ					Reference
	AF-1 (148)	DBD (66)	H (90)	LBD (196)	AF-2 (30)	
hERβdel2	126*	0	0	0	0	[36]
hERβdel2,5,6	126*	0	0	0	0	[36]
hERβdel2,5	126*	0	0	0	0	[36]
hERβdel2,6	126*	0	0	0	0	[36]
hERβdel2,3,6	126*	0	0	0	0	[36]
hERβdel3	148	30	90	196	30	[36]
hERβdel4	148	66	3	183	30	[36]
hERβdel5	148	66	90	13*	0	[36]
hERβdel5,6	148	66	90	105	30	[36]
hERβdel6	148	66	90	59*	0	[36]
	Protein domains of rat ERβ					
	AF-1 (167)	DBD (66)	H (90)	LBD (198)	AF-2 (28)	
rERβ1del3	167	30	84	198	28	[54]
rERβ1del4	?	66	3	198	?	[55]
	Protein domains of mouse ERβ					
	AF-1 (167)	DBD (66)	H (88)	LBD (200)	AF-2 (28)	
mERβdel5	167	66	88	154*	0	[57]
mERβdel6	?	66	88	155*	0	[57]
mERβdel5,6	167	66	88	109	28	[57]

Next to the names of the domains at the top, the numbers of their amino acid content is shown in parentheses. The numbers in the table show the remaining number of amino acid residues in each domain. 0 stands for a missing domain, * indicates the frameshift and truncation of the polypeptide, ? signifies non-availability of appropriate information.

mRNA sequence represents all eight exons identified so far in the ERβ gene. rERβ2 mRNA contains an additional 54 nt, located within the reading frame, between exons 5 and 6 [52,53]. Thus, this transcript encodes a protein with 18 additional amino acids in the LBD. rERβ1δ3 and rERβ2δ3 share a deletion of exon 3, but in rERβ2δ3 this feature is also combined with the same 54 nt insert as present in rERβ2 [54]. The lack of exon 3 results in deficiency of one zinc finger of the DBD. Another isoform, named rERβ1δ4, was described as an incomplete sequence without the start or stop codons [55].

The afore-mentioned differences among the mRNA isoforms produce characteristic functional consequences for the encoded proteins. Specifically, insertion of 18 aa in the LBD in rERβ2 and rERβ2δ3 causes a dramatic loss of ligand binding affinity, when compared to the receptor encoded by rERβ1 [54], and unlike the full transcript protein the rERβ2 was unable to interact with SRC-1 transcription coactivator [56]. Furthermore, under conditions in which rERβ1 was acting as the transcriptional activator, rERβ2 behaved as a dominant negative regulator of estrogen action. rERβ2 acts as a homodimer and it does not have the ability to induce transcription, and even inhibits transcriptional activity of rERα and rERβ1 [53]. However, in another study, rERβ2 was found to be capable of activating transcription in response to estradiol, but it required an approximately 1000-fold greater estradiol concentration than that needed to activate rERβ1 [56]. Isoforms without part of the DBD (rERβ1δ3 and rERβ2δ3) do not bind to DNA and hence are apparently not capable of activating transcription.

As far as the expression patterns of various isoforms are concerned, RT-PCR-based studies have shown that rERβ1 and rERβ2 mRNAs coexist in most rat organs, such as the brain (hippocampus, cortex, hypothalamus), lung, kidney, ovary, and uterus [54,55]. The ratio of rERβ1 to rERβ2 mRNA is approximately 1:1 in the prostate, ovary, and muscle [54]. In the nervous system, the rERβ1 mRNA was found to be more abundant than rERβ2. The rERβ1δ3 and rERβ2δ3 mRNA isoforms are expressed in the prostate, ovary, and hypothalamus, although at a lower abundance than full-length ERβ mRNA.

3.4. *Mouse ERβ mRNA isoforms*

In mouse, the originally identified mRNA has been named mERβ1 [18]. Additionally, four mRNA isoforms named mERβ2, mERβδexon5, mERβδexon6, and mERβδexon5,6 have been identified to date [57]. The putative proteins encoded by these mRNA variants are shown in Fig. 2 and Table 1. The mERβ1 sequence represents all eight exons of the ERβ gene. mERβ2 mRNA is the variant with an additional 54 nt, located within the reading frame, between exons 5 and 6 [57]. Thus, the protein encoded by this transcript has an 18 aa insertion in the LBD. Moreover, the inserted amino acid sequence shares significant (16 out of 18 aa) homology with the respective insert in the rat ERβ2 isoform. Two other isoforms, mERβδexon5 and mERβδexon6, have a deletion of exon 5 or 6 respectively, but in another isoform mERβδexon5,6 this feature is combined by deletion of both exons 5 and 6 [57]. mERβδexon5 and mERβδexon6 have a frame shift, which introduces stop codons into the reading frame [57]. Because of the deletions, these three isoforms encode proteins lacking various parts of the LBD. The differences among the mRNA isoforms cause characteristic functional consequences for the encoded proteins.

The insertion of 18 amino acids in the LBD in mERβ2 causes a 30-fold decrease in ligand binding affinity, when compared with mERβ1 [58]. Furthermore, mERβ2, acting as a homodimer, did not display transactivating activity under conditions in which mERβ1 was active [58]. Interestingly, proteins designated mERβ1 and mERβ2 were able to bind to classical ERE both in the presence and in the absence of a ligand as well as inhibiting transcriptional activity of mERα and mERβ1 [58]. It seems that mERβ1 may act as a negative regulator or a modulator of estrogen action. The functional significance of proteins encoded by variants mERβδexon5, mERβδexon6 and mERβδexon5,6 has not yet been tested. It appears that proteins with deletion of regions encoded by exons 5 and/or 6 are unlikely to bind a ligand, because of partial deletion of the LBD.

RT-PCR studies revealed that two isoforms, mERβ1 and mERβ2, are expressed in ovary and lung at similar levels [57]. However, in the placenta, uterus, breast, heart, brain, skin, and kidney there are higher levels of mERβ2 mRNA expression, relative to mERβ1 [57]. Furthermore, mERβ2 is expressed predominantly in the liver, pancreas, gut, and bone [57].

4. Concluding remarks

From an overview of ERβ isoforms some general themes readily emerge. First, a number of ERβ mRNA isoforms are observed in a variety of mammalian species. However, the structure of isoforms is not uniform but varies from species to species. This may reflect either a possibility for remaining transcripts to be cloned, or between-species isoform specificity. On the other hand, some of the isoforms share common elements between closely related species. For instance, transcripts similar to human ERβcx are found in both macaque and marmoset. Furthermore, when putatively translated, the inserts replacing exon 8 share considerable amino acid sequence similarity. In both rats and mice, the ERβ2 isoforms have the same feature of a novel insert in LBD between exons 5 and 6. These 18 amino acid elements also show significant sequence resemblance. Notably, the above-mentioned inserts are able to change the ERβ function. Specifically, in primates the ERβcx are apparently characterized by altered interactions with other components of the transcriptional machinery, whereas in rodents the binding of the ligand appears to be mostly affected in the isoforms. In conclusion, the emerging picture of multiple ERβ mRNA isoforms, and thus also a multitude of differentially built proteins, strongly suggests their synthesis to be considered as yet another level of complexity of estrogen signaling.

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