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Estrogen Receptor α- and β-Interacting Proteins Contain Consensus Secondary Structures: An Insilico Study

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Keywords

Estrogen receptor α · Estrogen receptor β · Estrogen receptor coregulators · Secondary structure · Homology · Insilico study

Abstract

Background: Estrogen receptor (ER)α and ERβ are ligand-activated transcription factors that regulate gene expression by binding to estrogen-responsive elements and interacting with several coregulators through protein-protein interactions. Usually, these coregulators bind to the various conserved and functional domains of the receptor through a consensus LXXLL sequence, although variations can be found. The interaction of receptor domains and the consensus motif can be a possible target for nuclear receptor (NR) pharmacology, since modifications in these are responsible for possible pathogenesis of various diseases. ***Purpose:*** The present study focuses on the secondary structure and conserved domains of the ERα and ERβ interacting proteins, using bioinformatics tools and their relation to the function of the coregulators. ***Methods:*** Bioinformatics-based prediction tools like STRING, PSIPRED, PROTPARAM and Conserved Domain Database (CDD) were used. The prediction tools utilized in this study basically determines the characteristics of a possible coregulator by using an already existing protein as a template and determines the presence of any conserved consensus sequence. Coregulators have been enlisted with the help of NCBI, STRING and iHOP. The secondary structures were analyzed using PSIPRED and conserved domains were determined using CDD. ***Results:*** The analysis of the structure has shown the presence of conserved domains and homology between the various coregulators. Each interacting protein contains conserved domains like the nuclear coactivators' domain, the helix-loop-helix domain and the SRC domain. ***Conclusion:*** Such studies give the characteristic features of ERα and ERβ interacting proteins and maybe useful to determine their family and uses in NR pharmacology in health and diseases.

Introduction

Estrogens are steroid molecules and primarily secreted by the female gonads. Apart from playing an important role in the regulation of the female reproductive systems, they have important functions in bone development, in lipid metabolism and in maintaining the cardiovascular system and the neuronal systems [1, 2]. Estrogens are known to exert their functions through ER, which are ligand-activated transcription factors belonging to the nuclear receptor (NR) superfamily. Like the other members of the NR superfamily, ER contains 6 functional domains

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[3, 4]. The DNA-binding domain shares the highest homology with the other NR superfamily members and is the most conserved domain. The ligand binding domain (LBD) is relatively less conserved in nature and contains the ligand-dependent transcription activation function activation function (AF)-2. The most variable portion of the ER is the A/B domain that also contains a ligand independent, constitutively active transcription activation factor AF-1.

Biochemical analysis has shown the presence of 2 isoforms of the ER, namely, ERα and ERβ. Although ERα an ERβ share the DBD, they differ to some extent in their LBD and thus their ligand-binding affinity and expression patterns. ERβ modulated the function of ERα when they are co-expressed and supplements the activity of ERα. Most effects of estrogen are cell-specific, which can be attributed to the differential expression of the ER in different tissues. Studies have shown the presence of ERα in the uterus, liver, kidney and heart, whereas ERβ is shown to be present in the gastrointestinal tract, ovary, prostate, lung, bladder and the central nervous system. The co-expression of the 2 isoforms is seen in the mammary gland, epididymis, adrenal gland and regions of brain like the hypothalamus and the amygdala [5].

Usually, the ERs are bound to the heat shock proteins 90 present in the cytoplasm [6]. On interaction with the ligand, phosphorylation takes place at the serine and the threonine residues, which causes a conformational change in the receptor. This releases the receptor from the heat shock proteins complex and interaction with the respective response elements (ERE) is facilitated. This acts as a scaffold for the recruitment for a number of other factors termed as coregulators. The coregulators facilitate estrogen-mediated chromatin reorganization. By altering the chromatin structure, the coregulators provide interaction with receptor and the transcription machinery, thereby controlling the transcription.

Coregulators exist as multi-protein complexes and can be broadly classified into 2 categories. The first class contains the interacting proteins that have histone-acetylating or -deacetylating activities. The most widely studied coregulators family under this category is the p160 family of coregulators. As the name suggests, the family contains molecules that are 160kD in size and basically comprise SRC1, GRIP1/TIF2 and AIB1/ACTR/pCIP [7–9]. They function by binding histone acetyl transferases such as p300/CBP and pCAF, which in turn regulated the chromatin remodeling. The second class contains the interacting proteins that facilitate chromatin remodeling through ATP hydrolysis. This class includes the SWI/SNF family of coregulators. They have homology similar to the helicases [10, 11]. The coregulators can be coactivators like SRC1, ERAP140 [12], GRIP1, TRAP220 and so on or can be corepressors like NCoR and SMRT (Table 1). The variation in the expression and interaction of ER coregulators and their dysregulation is shown to have severe consequences for cellular homeostatsis and often contributes to pathogenesis.

In addition, these coregulators have been shown to interact with the receptor through a consensus LXXLL sequence, also called NR boxes [13], although variation is reported. These structural motifs are found as helices. The leucines create a hydrophobic surface that interacts with the hydrophobic groove of the receptor [14]. The interaction between the receptor motifs and the NR boxes is used as a possible target for NR pharmacology studies [15]. The structure and properties of the interacting proteins per se coregulators play an important role in determining their interaction with ERα and ERβ and function. There exists a great deal of homology among various coregulators due to the presence of conserved domains and responsible for specific functions. The present study is focused to determine the secondary structure of ERα and ERβ interacting proteins and their conserved domains using various bioinformatics tools. Such a study may be useful to determine the family of the coregulators, newly identified, and helpful to understand the etiology of different diseases and treatment by NR pharmacology.

Methods

Enlisting ERα and ERβ Interacting Proteins

ERα and ERβ interacting proteins were enlisted using the NCBI, STRING and iHOP databases. STRING is a database that maintains a list of known or predicted protein interactions that are derived from 4 basic sources: genomic analysis, high throughput experiments, conserved coexpression and previously known literature. iHOP provides information about the proteins and their interacting members in a concise manner with access to related literature. NCBI is a database maintained by the National Institutes of Health, USA. Amino acid sequences of the protein can be obtained in the FASTA format from the NCBI database.

Prediction of Secondary Structure of ERα and ERβ Interacting Proteins

The secondary structure was predicted using prediction tools such as PSIPRED. PSIPRED is a tool that predicts the secondary structure by using the information gained from PSI-BLAST. The amino acid sequence of the interacting domain was input in the FASTA format, derived from NCBI database and the secondary structure is determined in the form of helices denoted by cylindrical figures and strands denoted by arrow marks.

Table 1. ERα interacting proteins

S. No.	Name of the protein	Tissue specificity	Disease correlation
1	SRC-1	Brain (hypothalamus, hippocampus, cerebellum, PVN)	Breast cancer, endometrial cancer
2	TIF2	Pancreas, skeletal muscle, liver, lung, placenta, brain, heart	Colorectal cancer, acute mylemonocytic leukemia
3	GRIP1	Muscle, neural tissue, mammary gland	Breast cancer
4	AIB1	Heart, skeletal muscle, pancreas and placenta	Polycystic ovarian syndrome, ovarian cancer, breast cancer
5	ARA70	Adipose tissue, testis	Polycystic ovarian syndrome, prostate cancer
6	NCoA3	Heart, skeletal muscle, pancreas, and placenta	Breast cancer
7	CBP	Brain, skeletal muscles	Rubinstein-Taybi syndrome, Huntington's disease
8	pCAF	Intestines	Colorectal cancer
9	TRAP220 (MED1)	Ubiquitously present	Lung adenocarcinoma, crohn's disease
10	SRA	Mammary gland, ovaries, placenta, adipose tissue	Breast cancer, prostate cancer, ovarian cancer
11	p68	Mammary gland, adipose tissue	Breast cancer
12	ASC-2	Mammary gland, spleen, liver	Breast cancer
13	PNRC	Liver, lung, adipose tissue, NK/T cells	Hepatitis B, breast Cancer
14	SPBP (TCF20)	Brain, heart, testis, kidney, liver, lungs	Arrhythmia, cardiac problems
15	DHX9	Neuronal cells, pituitary, ovary	Werner syndrome
16	STAU1	Brain, pancreas, heart, skeletal muscles, liver, lung, kidney	Cardiac diseases, lung carcinomas
17	EIF4G	Heart, skeletal muscles	Encephalomyocarditis virus infection
18	PELP1	Breast cancer cells	Endometrial cancer, breast cancer
19	PGC1	Heart, brain, skeletal muscles	Obesity, type II diabetes
20	NRIP1	Placenta, ovary, brain, lung, stomach, kidney	Post-menopausal osteoporosis, infertility
21	N-COR	Lung, spleen, brain, mammary gland	Breast cancer, myeloid leukemia
22	SMRT (NCOR2)	Ubiquitous, high levels in embryo	B-cell lymphoma, myeloid leukemia
23	RIP140	Placenta, ovary, liver	Post-menopausal osteoporosis, infertility
24	CARM1	High expression in prostate, epithelial cells	Prostate cancer, vascular diseases
25	SHP	Liver, heart, pancreas, placenta	Obesity, endometrial cancer, insulin resistance.
26	DAX	Adrenal gland, pituitary	Hypogonadism, congenital adrenal hyperplasia
27	HET-SAFB	Mammary gland, stomach, liver	Breast cancer, duodenal ulcer

Prediction of the Physical Parameters of the ERα and ERβ Interacting Proteins

The physical parameters were determined using ExPasy tool and PROTPARAM. The protein sequence was input in the FASTA format from the NCBI database. PROTPARAM gives information about molecular weight, stability index, extinction coefficients, half-life and the amino acid composition of the protein.

Prediction of Conserved Sequences among ERα and ERβ Interacting Proteins

Homology modeling was done using the bioinformatics tool CD Search, which is a part of the Conserved Domain Database (CDD). The amino acid sequence of the target protein is input in the FASTA format or as the PDB ID. The software performs alignment with the help of BLAST and CLUSTAL and provides the ho-

Table 2. ERβ interacting proteins

S. No.	Name of the protein	Tissue specificity	Disease correlation
1	NCoA3	Heart, skeletal muscle, pancreas, and placenta	Breast cancer
2	PELP1	Breast cancer cells	Endometrial cancer, breast cancer
3	TRIM24	Thyroid, mammary gland	Breast cancer, myeloid leukemia
4	ERAP140	Brain, mammary gland, ovary, uterus, stomach, bladder	Breast cancer, ovarian cancer
5	AIB-1	Heart, skeletal muscle, pancreas, and placenta	Polycystic ovarian syndrome, ovarian cancer, breast cancer
6	TRKA	Neuronal cells	Congenital insensitivity to pain with anhidrosis
7	CREB	Brain	Spina bifida, neuroblastoma
8	GRIP1	Muscle, neural tissue, mammary gland	Breast cancer
9	MED1	Ubiquitously present	Lung adenocarcinoma, crohn's disease

mology model based on the entries. It displays a schematic structure of the conserved domains and gives the gi number of the proteins that share homology with these domains.

Results

List of ERα and ERβ Interacting Proteins Using NCBI, STRING and iHOP

A list of the interacting proteins was generated (Tables 1, 2; Fig. 1, 2), based on the literature of the predicted as well as experimentally derived proteins. NCBI, STRING and iHOP maintain a pool of information on the proteins found in the primary protein databases such as the PDB and SWISS PROT and so on.

Secondary Structure of the Interacting Proteins Contain Alpha Helices

The secondary structures predicted using PSIPRED showed the presence of alpha helices in the AF1- and AF2-binding regions of the protein. These alpha helices were found to be rich in leucine residues. The leucine residues are known to form a hydrophobic region that fits into the hydrophobic groove of the receptor (Fig. 3, 4). Biochemical and structural studies clearly showed that the LBDs of the NRs recognize a short alpha helix present in the co-activators. Apart from alpha helices, random coils were also predicted. In addition, the secondary structures of AREG and TRKA showed the presence of beta turns in their interacting regions (Fig. 3). TRKA is widely reported in neuronal cell cultures and have been shown to be downregulated in case of anhidrosis and congenital insensitivity to pain [16]. AREG, on the other hand, has been found to be an essential regulator of ERα in the mammary gland and its dysregulation has been known to cause breast cancer [17].

Homology Prediction Using CDD

The conserved domains were determined using CD SEARCH. The conserved domain of the NCoR-1 and PELP1 molecule was shown in Figure 5. The NCoR-1 conserved domain structure acts as a template for a wide variety of coregulators. PELP1 was chosen as the other template, since it contains the RIX1 superfamily conserved domain, which is absent in the SRC-1 domain structure but is a part of many co-regulators like SCAF. The characteristic feature of any co-activator viz SRC domain (basically contains the NR box), NR coactivators domain (forms an alpha helical structure) and the helix-loop-helix domain that are specifically found in transcription factors were present. Further, proteins were found, which share a similar homology pattern with the NCOR1. Some of the proteins that were determined were NCoA3 (gi 82112094), SCAF14542 (gi 82267094), novel protein similar to vertebrate NCoA1 (gi 82196443) and the others (Fig. 6, 7). Proteins that were found to be homologous with PELP1 were modulators of non-genomic activity of ER (gi 82072956), At1g30240 (gi 122236349), Acetyltransferase catalyses diacyl glycerol esterification (gi 254569024; Fig. 7). There exists a great amount of homology between the interacting proteins. Some of the proteins having homology are enlisted in Table 3.

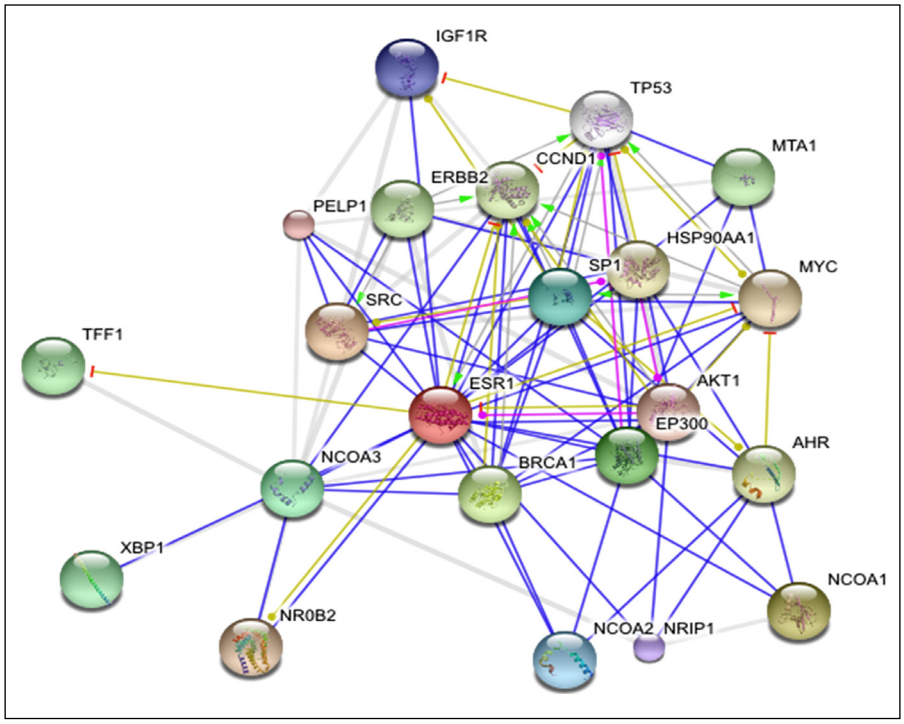

Fig. 1. Interacting proteins of ERα by STRING tool.

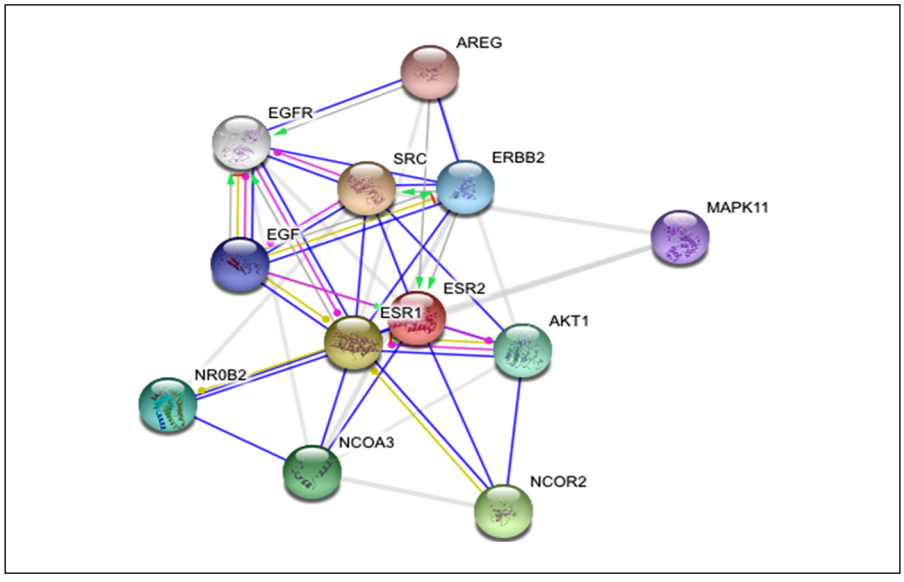

Fig. 2. Interacting proteins of ERβ by STRING tool.

Discussion

Usually, bioinformatics prediction tools, such as the CDD, PSIPRED and STRING, help in utilizing information from different proteins as templates and derive the structure and function of the newly discovered protein. In the present study, the classical example of the coregulators, that is, the members of the p160 family of coregulators were used as template to compare with predicted coregulators enlisted using NCBI, STRING and iHOP. The secondary structure of the enlisted proteins share structural homology with the p160 family of proteins. The AF1 and AF2 interacting domains of the coregulators show the presence of alpha helices, which are con-

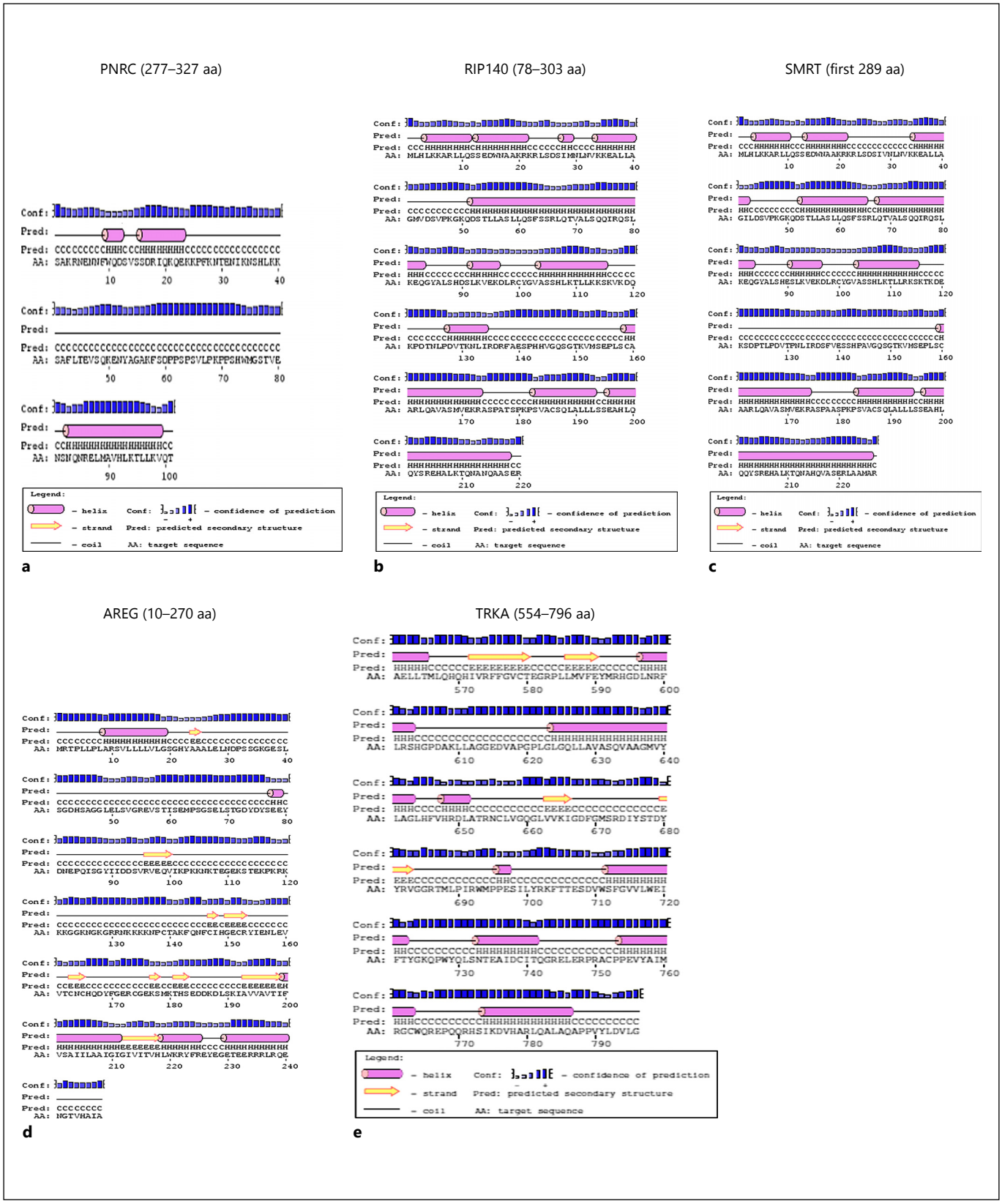

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Fig. 3. Secondary structures of ERα interacting proteins; PNRC (**a**), RIP140 (**b**), SMRT (**c**), AREG (**d**) and TRKA (**e**).

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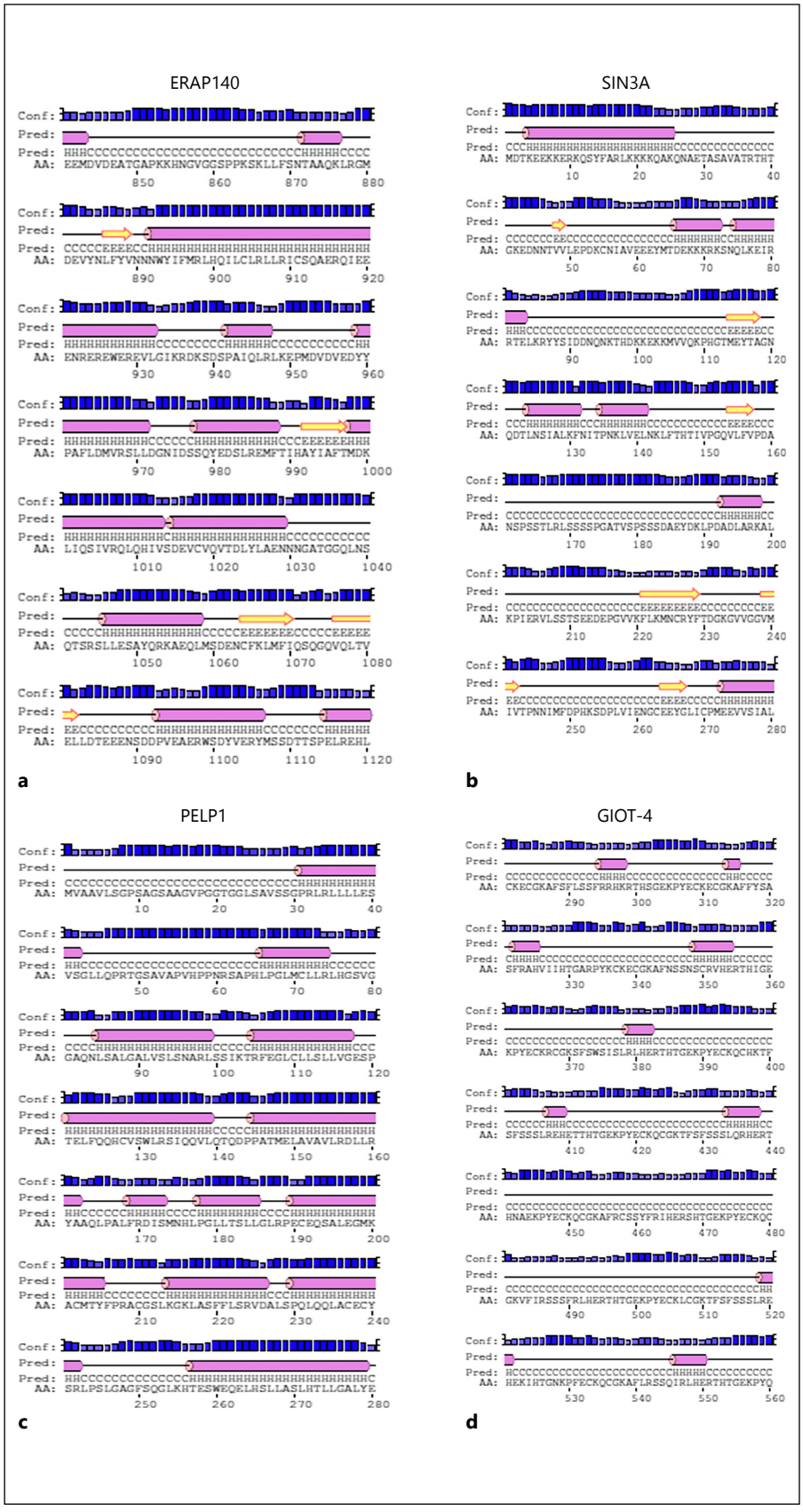
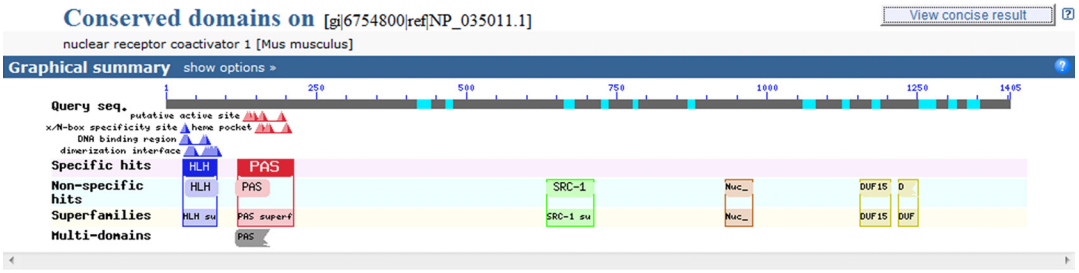
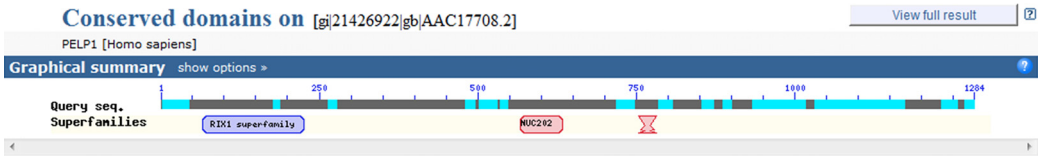


Fig. 4. Secondary structures of ERβ interacting proteins; ERAP140 (**a**), SIN3A (**b**), PELP1 (**c**) and GIOT-4 (**d**).



NCoR-1



PELP1

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Fig. 5. Conserved domains of NCoR-1 and PELP1.

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2PRG_C          8 SH     KLVQLLTTTAEQQ.[10].KDVL.[12].SSGGS     CPSSHS      SLTERHKILHRLLQEG     S 76
query         634 SH     KLVQLLTTTAEQQ.[10].KDVL.[ 6].SSASS.[6].CPSSHS      SLTERHKILHRLLQEG     S 702
gi 82266828   670 HT     KLLQLLTRKPEPL.[12].KDQP.[ 5].AGHNG     GNAHAT      SLKEKHKILHQLLQNN.[1].S 734
gi 82112094   627 HT     KLLQLLTTKTEPI.[15].KDGG.[ 6].GSQGG     NGSHAT      SLKEKHKILHRLLQNS.[1].S 695
gi 82267094   586 HT     KLLQLLTTKADPS.[15].KDQL.[ 5].VDGAG     HNNNPT      SLKEKHKILHRLLQTS.[1].S 653
gi 13626594   638 QT     KLLQLLTTKSDQM.[13].KDST.[ 1].SLPGS     GSTHGT      SLKEKHKILHRLLQDS.[1].S 699
gi 13124365   624 QQ     KLLKLLTTKSDQM.[14].KDSL.[ 4].SNSMS     ASAHGT      SLKEKHKILHRLLQDS.[1].S 689
gi 82196443   540 NQ.[4].KLSQLLDGASAPE      QDSQ.[ 3].SPTSQ     CPASHS      SLTERHKILHRLLQDN     S 593
gi 158518533  627 SQ.[3].KLVQLLTTTAEQQ.[10].KDVL.[12].SSGGS     CPSSHS      SLTERHKILHRLLQEG     S 698
gi 82194874   629 SQ.[4].KLVQLLASTAEQQ.[10].KDSL.[13].PPSST     CPSSHS      SLTERHKILHRLLQEG     S 702
gi 23396770   616 HK     KLLQLLTCFTEER.[12].KDSS.[ 9].SSTSI     GVSSTS.[ 5].MLQEKHRILHKLLQNG.[1].S 689
gi 82268011   151 HK     KLLQLLTSPTDEL.[17].KDGP.[13].SSTGG     NHSTVS.[11].SLQEKHKILHKLLQNG.[1].T 239

2PRG_C         77 PSDITT.[3].E 86
query         703 PSDITT.[3].E 712
gi 82266828   735 PVDLAK.[3].E 744
gi 82112094   696 PVDLAK.[3].E 705
gi 82267094   654 PVELAK.[3].E 663
gi 13626594   700 PVDLAK.[3].E 709
gi 13124365   690 PVDLAK.[3].E 699
gi 82196443   594 PADAGK      E 600
gi 158518533  699 PSDITT.[3].E 708
gi 82194874   703 PSDITT.[3].E 712
gi 23396770   690 PAEVAK.[3].E 699
gi 82268011   240 PDEVAR.[3].E 249
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NCoR-1 homologues proteins of the SRC-1 conserved domain

```
2C52_B          5 EGRNDEKALLEQLVSFLSGKD.[2].ELAELDRALGIDKLV     Q.[8]. 51
query         930 EGRNDEKALLEQLVSFLSGKD.[2].ELAELDRALGIDKLV     Q.[8]. 976
gi 82266828  1093 ANGVDEGALMSQLYTALKDFN     GMEELDRALGIPALV.[1].Q.[8]. 1138
gi 82112094  1061 EGPADEGALLSQLYSALKDFD     GLEEIDRALGIPALV.[1].Q.[8]. 1106
gi 13626594  1071 ESPSDEGALLDQLYLALRNFD     GLEEIDRALGIPELV.[1].Q.[8]. 1116
gi 82267094  1009 ESQPDEGALLNQLCSVLKDYE     GLEEIDKMLGIPTLA.[1].Q.[8]. 1054
gi 82078550    18 EGRNDEKALLEQLVTFLSHTD.[2].ELAELDRALGIDKIV     Q.[5]. 61
gi 82251966   735 EARNDEKALIEQLVTFLSGTD.[2].ELAELDKALGIDKLV     Q.[8]. 781
gi 54036169   930 EGRNDEKALLEQLVSFLSGKD.[2].ELAELDRALGIDKLV     Q.[8]. 976
gi 82268011   610 EGQSDERALLDQLDSLLNTAD.[2].ALQEIDRALGIPEIV.[1].Q.[8]. 657
gi 82260825  1216 EGQSDERALLDQLDSLLNNTD.[2].ALEEIDRALGIPDLV.[1].Q.[8]. 1263
gi 23396768  1052 EGQSDERALLDQLHTFLSNTD.[2].GLEEIDRALGIPELV.[1].Q.[8]. 1099
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NCoR-1 homologous proteins of the nuclear receptor conserved domain.

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Fig. 6. Homologous proteins of NCoR-1.

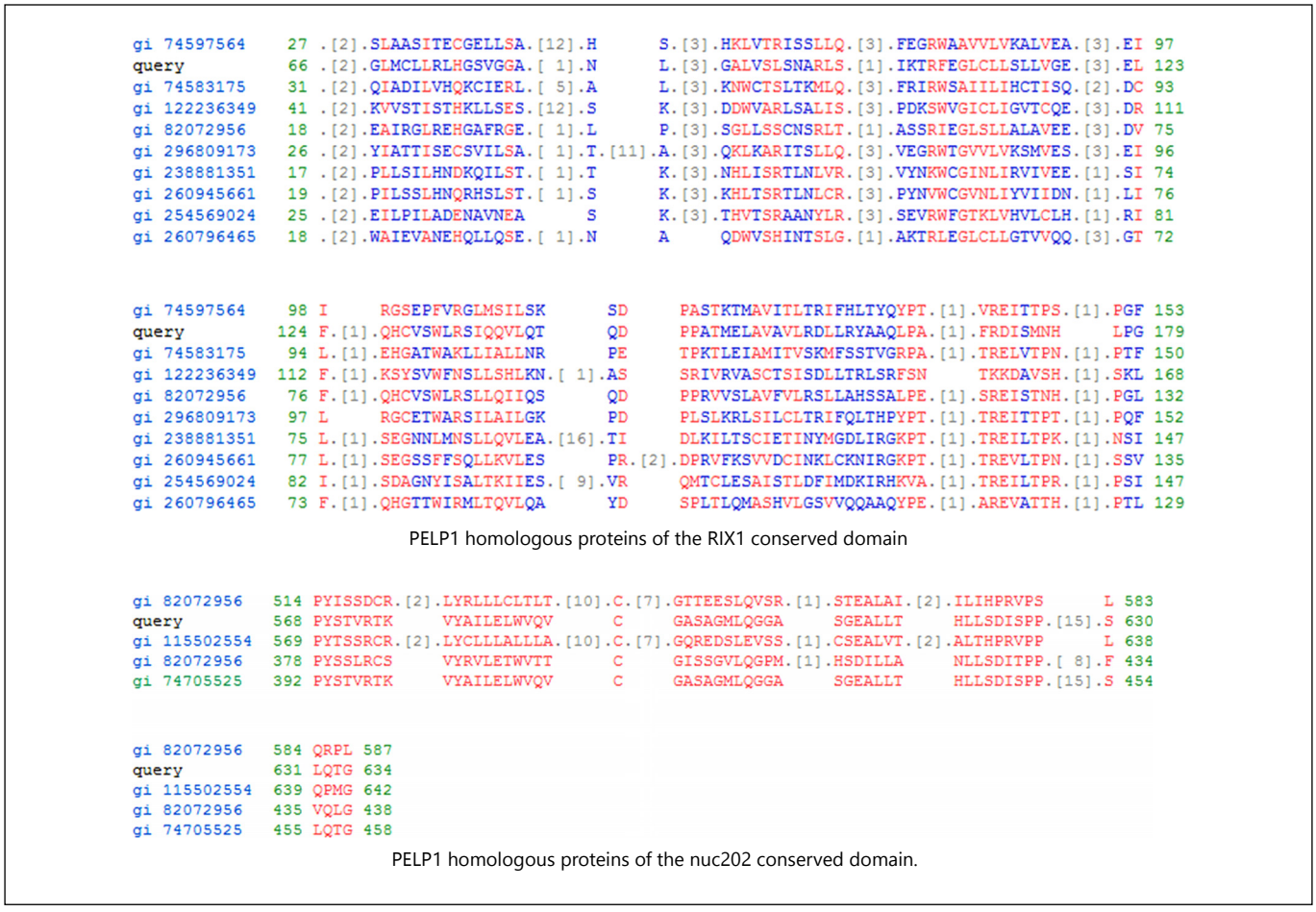

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Fig. 7. Homologous proteins of PELP1.

Table 3. ERα and ERβ interacting proteins by STRING (low confidence level)

ERα						
SRC	NRIP 1	ERBB2	SMAD4	HDAC4	CREBBT	UBC
NCoA1	PELP1	MTA1	ARNT	TP53	CDH1	TRIM24
BRCA1	AKT 1	TFF1	STAT54	JUN	FOX03	
EP300	NROB2	XBP1	CEBPB	MED1	FOXA1	
NCOA3	MYC	IGF1	HDAC9	ESR2	NCOA6	
SP1	HSP90AA1	BCAR1	SAFB	CTSD	SMARCA4	
NCOA2	AHR	EGFR	NR2F1	NCOR2	PRDM2	
IGF1R	CCND1	PIK3R1	GRIP1	CAV1	KAT2B	
ERβ						
SRC	MAPK11	THRB	RARA	TCF19	RORC	
ESR1	AREG	NR1D1	NR4A2	HNF4G	NR2F1	
NCOR2	AHR	VDR	PPARA	RDRB	PPARD	
NCOA3	IGF1	PELP1	NR2 C2	GNA14	NRID2	
AKT1	NCOA1	ESRRB	RARG	NR2E1	GNA15	
NROB2	THRA	PPARG	RARB	GNG2		
ERBB2	OXT	ESRRA	RXRG	GNAL		
EGF	NR5A1	ESRRG	NR2C1	NR2C2AP		

served domains. Some of the interacting proteins, such as TRKA and AREG, possessing beta turn in their interacting domains suggesting that, apart from alpha helices, other secondary structures play an important role in gene regulation.

ERs recruit a host of coregulators for regulating estrogen-dependent gene expression [2]. The level of estradiol decreases during aging in both genders and a sharp decline is reported in females after their menopause [18]. Thus, the optimum level of estrogen, receptors in the normal form and binding of ERs with coregulators are vital factors to decrease risk factors of neurodegenerative diseases.

Here, our study shows that majority of the interacting proteins contain α helices. Their presence may induce the aggregation properties of proteins as shown in earlier studies. The study shows that the intrinsic stabilization of α helix proteins can trigger the formation of α helical aggregates [19]. Further, higher concentration helix-promoting trifluoroethanol induces stabilization of tau protein aggregates [20], a known factor in case of Alzheimer disease. In addition, the microtubule-binding domain of tau, which constitutes the core of paired helical filaments, has significant α helix propensity [21]. Taking together, the present work may provide an insight into the structural abnormalities leading to functional dysregulation and can be an excellent target for NR pharmacology studies.

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Disclosure Statement

The source of funding is Department of Biotechnology, Government of India to MKT. There are no conflicts of interest among authors.

Authors Contribution

V.P. designed, performed the work and analyzed the data. M.K.T. designed the work and analyzed the data. H.K. performed the work.

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