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Inter-species functional interactome of nuclear steroid receptors (R1)

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1. ABSTRACT

Steroids exert their actions by binding to the glucocorticoid, mineralocorticoid, androgen, estrogen and progesterone classes of receptors. Despite an exponential increase in our knowledge of steroid receptors, their interactions with other molecules, subcellular location and functions still need further elucidation. To unravel the mechanism(s) of action of the steroid hormones, as well as the function of their cognate nuclear receptors, an interaction network was created (henceforth referred to as "R1 Interactome")- illustrating that robust interactions have been preserved in rodents, frog, zebra fish and drosophila. The generated interactome of the retrieved orthologs across species revealed: a. interactions among surface-cytosol-nuclear receptors, and/or orphan receptors and genes, and b. nuclear corepressor 1 (NCOR1) as a major "hub", through which most steroid receptors interact. These mechanisms (i) integrate social behavior and environmental stimuli with intrinsic cellular functions, (ii) provide an explanatory mechanism of the major Public Health problem of "non-ionizing" radiation impact, surpassing the existing conflict over the "thermal"/ "non- thermal" consequences of radiation, linking all the so far proposed mechanisms, and addressing all reported effects in humans, rodents and insects, and (iii) reveal biologically or clinically important pathways and/or regulatory networks.

2. INTRODUCTION

The new approach of "translational systems medicine" corresponds to the rising new field of P4 medicine (predictive, preventive, personalized, and participatory)(1). This new research approach requires clinical scientists' contribution to resolve complex target goals. Comparison of biomolecular networks or biophysical conditions among species represents a new approach to discovering and interpreting the major mechanisms involved in the physiology of living organisms. Such comparative analyses may reveal biologically or clinically important pathways and/or regulatory networks.

Steroid hormone receptors (either cytoplasmic, nuclear or membrane related) mediate signal transduction of steroid hormones, which eventually lead to changes in gene expression patterns, lasting from a few minutes, to hours to days. They may be either nuclear (subfamily 3) or

cell surface receptors (G-coupled receptors or ion channels) and are implicated in endocrine disorders, when malstructured or malfunctioning. Steroid hormone receptors may also bind to diverse gene regulators (orphan receptors), the ligands of which are currently unknown. Gene regulation involves multi-level crosstalk between inner cell and membrane receptors through a) phosphorylation cascades, b) nuclear receptors, and c) transcriptional proteins and/or enzymes. Nuclear receptors, together with other proteins, regulate the expression of downstream genes so as to control body's homeostasis, development, metabolism, immune function, behavior and reproduction. Their ability to directly interact with and regulate genomic DNA highlights their prominent role in the intra-uterine embryonic development and postnatal body's homeostasis (2, 3).

A great number of multi-disciplinary experiments and a large amount of expenses are often required for addressing any research question. The development of systems biology methods, such as phylogenomic studies and biological networks, enables biomedical researchers to unravel currently unknown molecular pathways and complex associations among biomolecules in a relatively fast, inexpensive and effective manner. This would help to further develop research rationales and to enable medical practitioners to make more precise decisions in their daily practice.

3. METHODS

The protein sequence database UniProt (4) and the biomedical literature were mined, through the PubMed (5) search engine, for genes/gene products related to the human steroid receptors in *Homo sapiens* using the key term 'steroid hormones.' The interactions among these molecules were examined through STRING v10 (6), a database of both known and predicted associations among genes/proteins; a high confidence interaction score above the threshold value of 0.7. was chosen. The nodes connecting the input nodes were also predicted, with a maximum number of 20 interactors. Only the gene/gene products that could form a network were considered in the subsequent steps of this analysis. The sequences of those *Homo sapiens* proteins that were part of the network were used as queries to search for orthologous *Drosophila melanogaster* (fruitfly*)* protein sequences by employing reciprocal BLASTp (7). A network was also created for drosophila using the same method and parameters. In the case a novel interactor was identified in the *Drosophila* network, its corresponding protein sequence served as a probe to search for orthologs in the human with the usage of BLASTp (7). This process was iterated until no more components could be added in the two networks. Subsequently, orthologs of the components of the human network were detected in the well-annotated genomes of *Mus musculus* (mouse), *Xenopus tropicalis* (frog) and *Danio rerio* (zebrafish), by performing BLASTp (7) searches.

4. RESULTS

The retrieved protein sequences along with their UniProt accession number are listed in Table 1. The subcellular localization of each protein is presented in Table 2 and Figure 1. The components of each species network are shown in Table 3.

The networks for each species under investigation are presented in Figure 2. The networks of human and *Drosophila melanogaster* were projected in a way that the associations among the orthologs are highlighted. The orthologs are shown at corresponding mirror positions (Figure 3).

The orthologous components are associated, either directly or indirectly, in the human and the fruitfly (Figure 2) by forming part of the 'R1' network.

The nuclear ecdysone receptor (EcR) mediates the actions of the hormone ecdysone (8). In *Drosophila*, the *ecdysone less (ecd*[1]*)* temperature-sensitive mutant impairs production of ecdysone, and causes defects in Drosophila development and oogenesis (9). EcR and ecd in *D. melanogaster*, as well as NR1H3 and ECD, respectively, in the human, are predicted to be associated. In *D. melanogaster*, EcR is linked through the ecdysone receptor co-activator taiman (tai) to the ecdysone-induced protein 78C (Eip78C). In the fruitfly, EcR and ecd are predicted to be linked to the ecdysone-induced protein 74EF (Eip74EF) (Figure 2).

Based on curated databases, NR1H3 and EcR are suggested to interact with the glucocorticoid receptor NR3C1 and the estrogen-related receptor (ERR) in the human and fruitfly, respectively. However, the human receptor NR1H3 is also associated with other NR3 (nuclear receptor subfamily 3) receptors, such as AR (androgen receptor), ESRRA (estrogen-related receptor alpha), ESR1/2 (estrogen receptor 1/2), PGR (progesterone receptor), through NCOR1 (nuclear receptor corepressor 1) (Figure 2).

The human counterpart of Eip78C, NR1D2 (nuclear receptor subfamily 1, group D, member 2), is linked to NR1H3 through NCOR1. NR1D2 appears to be connected directly to different members of the "NR3" subfamily.

Likewise, the human orthologs ECD, NR1H3 and ELF2 (E74-like factor 2) are also predicted to share many similarities (Figure 2). In humans, both ECD and NR1H3 are suggested, based on

Table 1. Proteins under study

Drosophila melanogaster (Fruitfly)		
ecd	ecdysoneless	Q9W032
EcR	ecdysone receptor	P34021
Eip74EF	ecdysone-induced protein 74EF	P20105
Eip78C	ecdysone-induced protein 78C	P45447
hsp23	heat shock protein 23	P02516
hsp27	heat shock protein 27	P02518
Eip71CD	ecdysone-induced protein 28/29kD	P08761
Eig71Ea	ecdysone-induced gene 71Ea	Q9VUS3
Eig71Ef	ecdysone-induced gene 71Ef	Q24074
Eig71Eg	ecdysone-induced gene 71Eg	Q24058
Eip55E	Eip55E	Q7JXZ2
Ubi-p63E	ubiquitin-63E	P0CG69
ERR	estrogen-related receptor	Q9VSE9
tai	Taiman (ecdysone receptor co-activator)	Q9GS19
Homo sapiens **(Human)**		
ECD	ecdysoneless homolog (Drosophila)	O95905
NR1H3	nuclear receptor subfamily 1, group H, member 3	Q13133
ELF2	E74-like factor 2 (ets domain transcription factor)	Q15723
NR1D2	nuclear receptor subfamily 1, group D, member 2	Q14995
HSPB1	heat shock 27kDa protein 1	P04792
MSRA	methionine sulfoxide reductase A	Q9UJ68
CTH	cystathionase (cystathionine gamma-lyase)	P32929
UBC	ubiquitin C	P0CG48
AR	androgen receptor	P10275
ESR1	estrogen receptor 1	P03372
ESR2	estrogen receptor 2 (ER beta)	
ESRRA	estrogen-related receptor alpha	P11474
ESRRB	estrogen-related receptor beta	O95718
ESRRG	estrogen-related receptor gamma	P62508
NR3C1	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	P04150
NR3C2	nuclear receptor subfamily 3, group C, member 2	P08235
PGR	progesterone receptor	P06401
NCOR1	nuclear receptor corepressor 1	O75376
HSP90AA1	heat shock protein 90kDa alpha (cytosolic), class A member 1	P07900
Mus musculus **(Mouse)**		
Ecd	ecdysoneless homolog (Drosophila)	Q9CS74
Nr1h3	nuclear receptor subfamily 1, group H, member 3	Q9Z0Y9
Elf2	E74-like factor 2	Q9JHC9
Nr1d2	nuclear receptor subfamily 1, group D, member 2	Q60674
Hspb1	heat shock protein 1	P14602
Msra	methionine sulfoxide reductase A	Q9D6Y7
Cth	cystathionase (cystathionine gamma-lyase)	Q8VCN5
Ubc	ubiquitin C	P0CG50
Ar	androgen receptor	P19091
Esr1	estrogen receptor 1 (alpha)	P19785
Esr2	estrogen receptor 2 (beta)	O08537
Esrra	estrogen related receptor, alpha	O08580
Esrrb	estrogen related receptor, beta	Q61539

Esrrg	estrogen related receptor gamma	P62509
Nr3c1	nuclear receptor subfamily 3, group C, member 1	P06537
Nr3c2	nuclear receptor subfamily 3, group C, member 2	Q8VII8
Pgr	progesterone receptor	Q00175
Ncor1	nuclear receptor co-repressor 1	Q60974
Hsp90aa1	heat shock protein 90, alpha (cytosolic), class A member 1	P07901
Xenopus tropicalis **(Frog)**		
ecd	ecdysoneless homolog	F7A2A5
nr1h2	nuclear receptor subfamily 1, group H, member 2	Q0IHW4
elf2	E74-like factor 2 (ets domain transcription factor)	F7BYM4
nr1d2	nuclear receptor subfamily 1, group D, member 2	K9J7Q4
hspb1	heat shock 27kDa protein 1	F6TYT7
msra.1	methionine sulfoxide reductase A, gene 1	F7E3T1
msra.2	methionine sulfoxide reductase A, gene 2	B0BM35
cth	cystathionase (cystathionine gamma-lyase)	Q6P849
ubc	ubiquitin C	F7DNS3
ar	androgen receptor	F6W9U4
esr1	estrogen receptor 1	Q25C14
esr2	estrogen receptor 2 (ER beta)	Q25C13
esrra	estrogen-related receptor alpha	A0JM86
esrrb	estrogen-related receptor beta	F7ETJ5
esrrg	estrogen-related receptor gamma	A4IIT9
nr3c1	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	F6XE59
nr3c2	nuclear receptor subfamily 3, group C, member 2	F6SI83
pgr	progesterone receptor	F6V3Y1
ncor1	nuclear receptor corepressor 1	Q4KKX4
hsp90aa1.1.	heat shock protein 90kDa alpha (cytosolic), class A member 1, gene 1	F6SX68
Danio rerio **(Zebrafish)**		
ecd	ecdysoneless homolog (Drosophila)	F1QAN3
NR1H3	nuclear receptor subfamily 1, group H, member 3	Q56A56
elf2b	E74-like factor 2b (ets domain transcription factor)	Q9YH24
nr1d2a	nuclear receptor subfamily 1, group D, member 2a	B3DHW0
nr1d2b	nuclear receptor subfamily 1, group D, member 2b	Q6GMI3
hspb1	heat shock protein, alpha-crystallin-related, 1	Q5PR64
MSRA	methionine sulfoxide reductase A	Q5TZ05
cth	cystathionase (cystathionine gamma-lyase)	Q6NWE3
ubb	ubiquitin C	Q6IS68
ar	androgen receptor	A4GT83
esr1	estrogen receptor 1	P57717
esr2a	estrogen receptor 2a	Q7ZU32
esr2b	estrogen receptor 2b	Q5PR29
esrra	estrogen-related receptor alpha	Q6Q6F6
esrrb	estrogen-related receptor beta	Q6Q6F5
esrrga	estrogen-related receptor gamma a	Q6Q6F4
nr3c1	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	Q501U9
nr3c2	nuclear receptor subfamily 3, group C, member 2	A6YIH7
pgr	progesterone receptor	C9V3N7
ncor1	nuclear receptor co-repressor 1	A8B6H7
hsp90aa1.1.	heat shock protein 90, alpha (cytosolic), class A member 1, tandem duplicate 1	Q90474

Symbols, names and UniProt accession codes

Table 2. Distribution of the investigated proteins in human cell compartments by confidence level

Protein symbol	Cell compartments /confidence										
	nucleus	cytosol	ER	Golgi A	Cytosceleton	Membrane	Peroxysome	Extra Cellular	Mitochondrion	Endosome	Lysosome
ECD	81-100%	81-100%			21-40%	<20%					
NR1H3	81-100%	41-60%					21-40%	21-40%			
ELF2	81-100%	81-100%									
NR1D2	81-100%	81-100%									
HSPB1	81-100%	81-100%	21-40%		81-100%	61-80%	<20%	81-100%	41-60%		
MSRA	81-100%	81-100%			81-100%			81-100%	81-100%		
CTH	60%	81-100%	<20%					81-100%	21-40%		
UBC	81-100%	81-100%	21-40%		<20%	61-80%		81-100%	81-100%		
AR	81-100%	81-100%	<20%		21-40%	41-60%	<20%	21-40%	21-40%		
ESR1	81-100%	41-60%	21-40%	81-100%	21-40%	81-100%	21-40%	21-40%	21-40%	<20%	21-40%
ESR2	81-100%	21-40%	21-40%		21-40%	21-40%	<20%	61-80%	81-100%		
ESRRA	81-100%				81-100%		21-40%	61-80%	21-40%		
ESRRB	81-100%										
ESRRG	81-100%						<20%		21-40%		
NR3C1	81-100%	81-100%	<20%		61-80%	21-40%	21-40%	21-40%	81-100%		
NR3C2	81-100%	<20%	100%		<20%	21-40%		21-40%	<20%		
PGR	81-100%	41-60%	21-40%		21-40%	21-40%			80%	61-80%	
NCOR1	81-100%	81-100%			81-100%		21-40%				
HSP90AA1	81-100%	81-100%	21-40%	21-40%	21-40%	81-100%	<20%	81-100%	41-60%	21-40%	81-100%

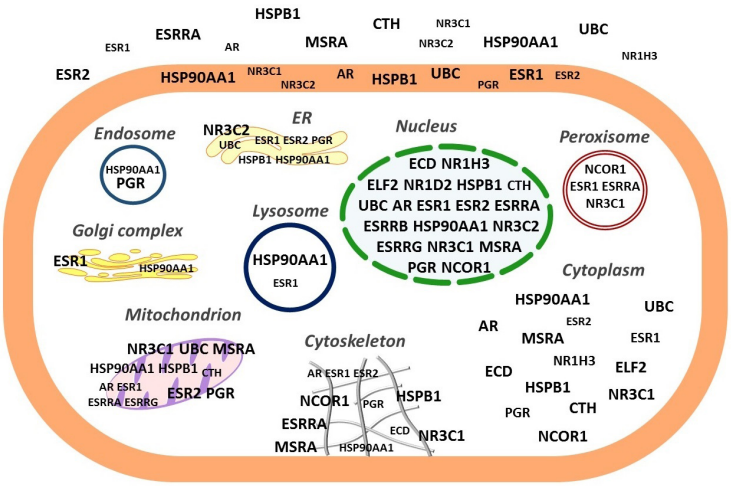

Figure 1. Localization of proteins in Table 2 in the human cell compartments. The size of the protein letters depicts the confidence level at each position (http://www.genecards.org/).

Table 3. Network components

Human	Mouse	Frog	Zebrafish	Fruitfly
ECD	Ecd	ecd	ecd	ecd
NR1H3	Nr1h3	nr1h2	NR1H3	EcR
ELF2	Elf2	elf2	elf2b	Eip74EF
NR1D2	Nr1d2	nr1d2	nr1d2a	Eip78C
			nr1d2b	
HSPB1	Hspb1	hspb1	hspb1	hsp23
				hsp27
MSRA	Msra	msra.1	MSRA	Eip71CD
		msra.2		Eig71Ea
n.d.	n.d.	n.d.	n.d.	Eig71Ef
n.d.	n.d.	n.d.	n.d.	Eig71Eg
CTH	Cth	cth	cth	Eip55E
UBC	Ubc	ubc	ubb	Ubi-p63E
AR	Ar	ar	ar	ERR
ESR1	Esr1	esr1	esr1	
ESR2	Esr2	esr2	esr2a	
			esr2b	
ESRRA	Esrra	esrra	esrra	
ESRRB	Esrrb	esrrb	esrrb	
ESRRG	Esrrg	esrrg	esrrga	
NR3C1	Nr3c1	nr3c1	nr3c1	
NR3C2	Nr3c2	nr3c2	nr3c2	
PGR	Pgr	pgr	pgr	
n.d.	n.d.	n.d.	n.d.	tai
NCOR1	Ncor1	ncor1	ncor1	n.d.
HSP90AA1	Hsp90aa1	hsp90aa1.1.	hsp90aa1.1.	n.d.

The orthologous proteins are presented in the same row; n.d.: not detected.x

experimental evidence, to be linked to the Eip71CD's ortholog MSRA (methionine sulfoxide reductase A) through UBC (ubiquitin C). In *D. melanogaster*, Ecd is predicted to be associated with Eip71CD (ecdysone-induced protein 28/29kD).

Similarly,, in humans, NR1H3 is predicted to be associated with the ortholog of Hsp23 and Hsp27, HSPB1 (heat shock protein 1), through HSP90AA1 (heat shock protein 90kDa alpha, class A member 1). The components of the human 'R1" network, are also conserved in fellow vertebrates such as the mouse, frog and zebrafish, and the patterns of their associations are quite similar (Figure 2).

Conversely, human UBC's counterpart in fruitfly, Ubi-p63E (Ubiquitin-63E), is connected to Eip71CD via Eip55E, the latter being an ortholog of human CTH (cystathionase); CTH is associated with UBC and MSRA (Figure 2).

5. DISCUSSION

The created interactome in humans comprises molecules of the Hypothalamic –Pituitary – Adrenal and -Gonadal axes. Glucocorticoids modulate the stress response at a molecular level by altering gene expression, transcription, and translation, among other pathways. Glucocorticoids also modulate the growth, reproductive and thyroid axes and influence immunity and behavior.

Taken together, our findings lead to the suggestion that the mechanism by which steroids exert their effects are evolutionarily conserved. Given that evolutionary sequence (nucleotide or protein) conservation can be indicative of functional conservation (10), we suggest that the orthologous proteins that comprise these networks in several other species investigated here have similar functions. We assume that evolutionary pressure has been exerted

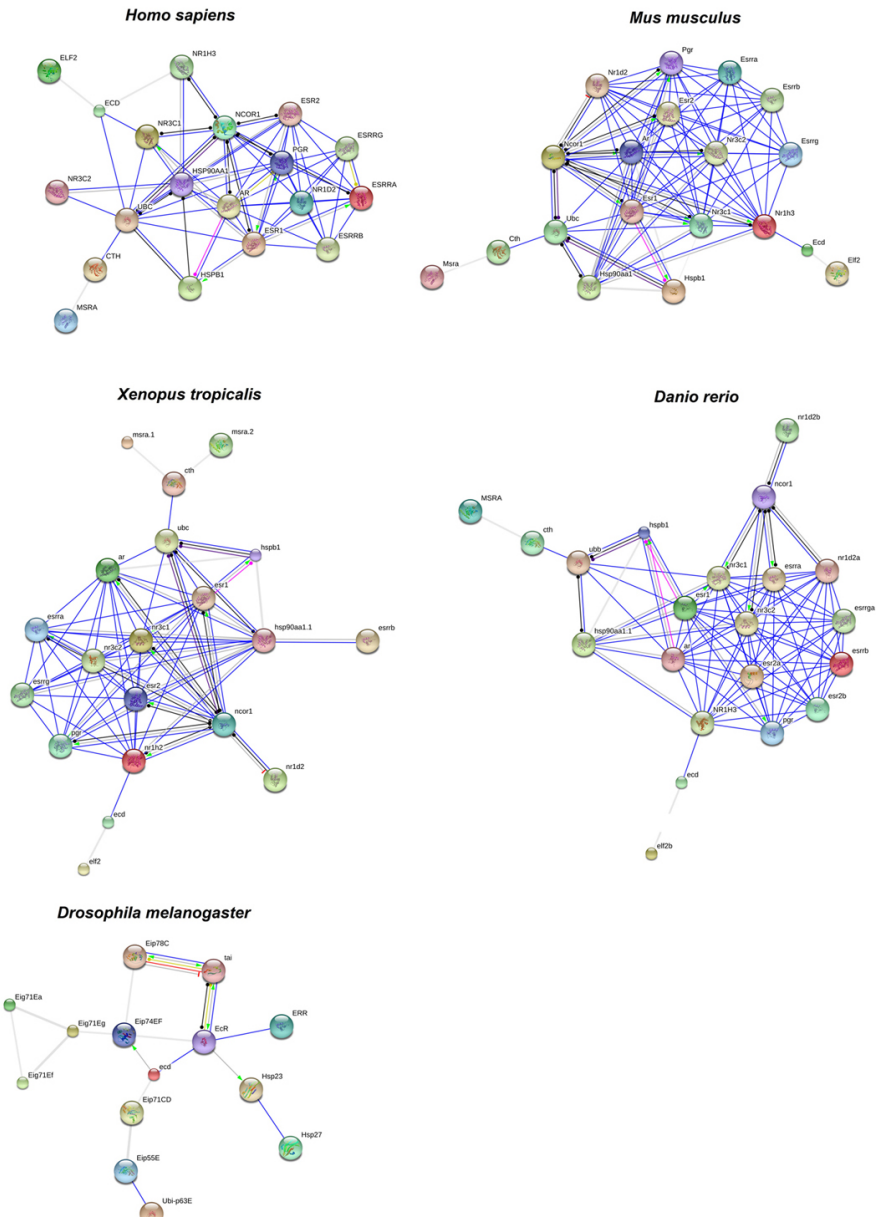

Figure 2. Network illustrating the interactions among the ecdysone-related gene/gene products of *Homo sapiens* (human), *Mus musculus* (mouse) and *Xenopus tropicalis* (frog) and *Danio rerio* (zebrafish) and *Drosophila melanogaster* (fruitfly). The nodes represent the molecules and the edges denote the predicted mode of action.

on the genes encoding these protein sequences to maintain a functionally conserved network through which the ancestral hormone ecdysone exerts its effects. Given that NCOR1 was identified as a major hub in this network, it could be suggested that most receptors and axes interact with each other via this node (NCOR1).

5.1. Intra- and inter-species functional interactome

The orthologs across species are presented in Table 3. Human NR1H3 (implicated in homeostasis and cholesterol uptake regulation through MYLIP) (11-13) is orthologous to Nr1h3 in *Mus musculus* (which is implicated in cholesterol homeostasis and circadian physiology (14)), to NR1H3 in *Xenopus tropicalis* (whose functionality is documented based on cDNA project results (15, 16)), to *Danio rerio's* nr1h2 (plays a role in cholesterol /glucose metabolism and homeostasis (11, 17)) and to EcR in *Drosophila melanogaster* (regulates development and reproduction) (18).

Similarly, human NR3C1 (nuclear receptor subfamily 3, group C, member 1) or glucocorticoid

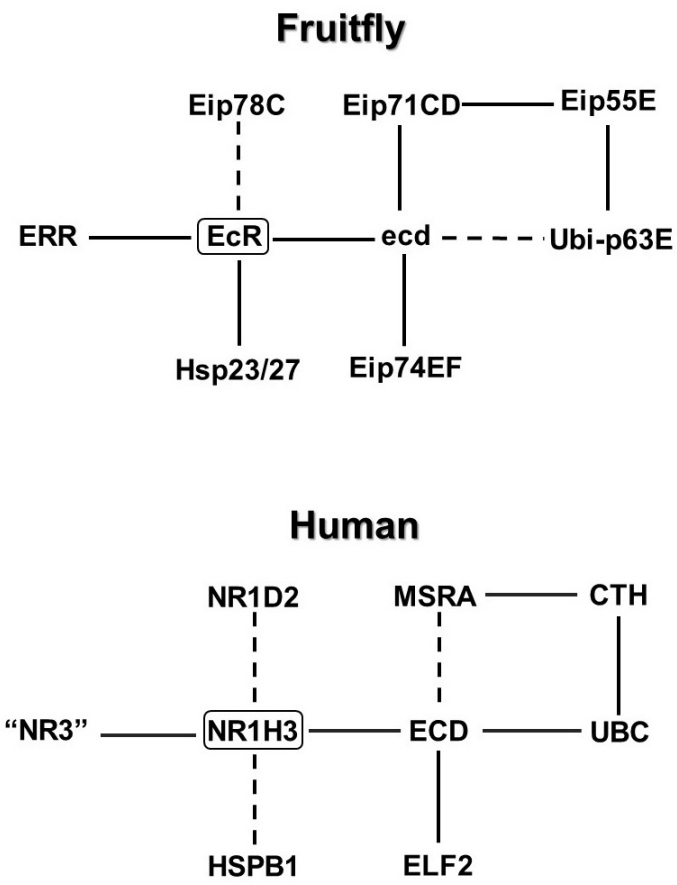

Figure 3. Reduced network depicting the orthologous components of the ecdysone networks. The ecdysone receptors, EcR and NR1H3, are boxed. The solid lines indicate direct link; the dashed lines indicate indirect link.

receptor is expressed in almost every cell of the human body, regulating development, immune function, metabolism, etc. (19-25). It is orthologous to Nr3c1, the corresponding gene encoding glucocorticoid receptors (26, 27) and their circadian expression patterns (28), *Danio rerio's* nr3c1 glucorticoid receptor (29, 30), nr3c1 in *X. tropicalis* (15, 16), and ERR in the fruitfly, which triggers a metabolic switch that supports growth (31). Human NR3C2 or aldosterone or mineralocorticoid receptor is a protein with equal affinity for mineralocorticoids and glucocorticoids.

Human ECD is orthologous to Ecd in *Mus musculus,* which has been recently identified as a novel key regulator of the cell cycle, since upon binding to hypophosphorylated Rb, facilitates Rb-E2F dissociation and cell cycle progression (32), ecd in *Xenopus tropicalis* (15, 16), Ecd in *Drosophila melanogaster* regulates the stability and function of p53, while, it activates the expression of glycolytic genes and influences the cell-cycle (32).

Human ELF2 participates in cancer growth and metastasis (33). Its murine Elf2 or E74-like factor 2 ortholog is a transcription factor whose transcripts are equally expressed in all tissues except thymus, where it is over-expressed. It is implicated in leukemia (34), mesenchymal to epithelial signaling in pancreatic development (35) and embryonic cardiac development (36). The frog ortholog of ELF2 is ELF2B (15, 16), whilst, fruitfly's ortholog is Eip74EF, a transcription factor involved in circadian physiology (37).

Human NR1D2 encodes a hormone receptor, which belongs to the NR1 subfamily of receptors. The encoded protein functions as a transcriptional repressor and may play a role in circadian rhythms and carbohydrate and lipid metabolism. Alternatively, spliced transcript variants of NR1D2 have been described (38-41). Its ortholog in *Mus musculus* is Nr1d2, in *Xenopus tropicalis* nr1d2a/b, in *Danio rerio* Nr1d2, which follows a circadian pattern with peak expression at ZT0-02 (42, 43)), and in *D. melanogaster* Eip78C (with an identical function).

HSPB1, or heat shock protein 1, is related to estrogen stimulation and is also involved in actin regulation and stress resistance (44, 45). It is

orthologous to Hsb1 in *Mus musculus,* hspb1 in *Danio rerio,* and Hsp23/27 in *Drosophila melanogaster.*

Human MSRA encodes a ubiquitous and highly conserved protein that repairs oxidatively damaged proteins to restore biological activity (46-50). The similarity in functionality of the pro-msra ortholog in *Xenopus tropicalis* is verified based on cDNA project results (15, 16). MSRA is orthologous to Msra in *M. musculus*, msra1/2 in *Danio rerio* and Eip71CD in *D. melanogaster*, the latter of which is suggested to confer protection against oxidative stress (51), while it regulates sleep in the same species.

Human CTH is implicated in amino acid metabolism, female reproductive capacity (52), cardiovascular pathology (hyperhomocystinemia) (53), diseases associated with disorders of sulfur metabolism (hypertension, diabetes mellitus, septic and hemorrhagic shock, and pancreatitis) (54). It is orthologous to Cth in mouse, cth in *the* frog and zebrafish, and Eip55E in *the* fruitfly.

Human UBC Ubi-p63E is a polyubiquitin precursor. Ubiquitination has been associated with protein degradation, DNA repair, cell cycle regulation, kinase modification, endocytosis, and regulation of other cell signaling pathways; furthermore, its expression is increased by glucocorticoids (55). It is orthologous to Ubc in M*us musculus,* ubc in *Xenopus tropicalis*, ubb in *Danio rerio* and Ubi-p63E in *D. melanogaster*.

Human AR (androgen receptor or NR3C4) is activated by specific binding of androgenic hormones and plays a role in male phenotype development and reproductive capacity maintenance (56-58). Like the GR, the AR is a known DNA binding transcription factor which regulates gene expression (56) and induces the rapid activation of kinase-signaling cascades which, in turn, modulate intracellular calcium levels (57). Its ortholog in mouse is Ar, in frog and zebrafish is ar, and the ancestral ERR in fruitfly.

Estrogen receptors ESR1 and ESR2 are activated by estrogens in humans (59-61). ESR2 function is associated to cardiovascular targets, including the ATP-binding cassette transporter A1 and apolipoprotein A1. It may also have anti-proliferative effects, thereby opposing the activity of ESR1 in reproductive tissues (62), and play an important role in the adaptive function of the fetal lung (63). Their orthologs in *Mus musculus, Xenopus tropicalis, Danio rerio* and *Drosophila melanogaster* are Esr1/2, esr1/2, esr1/2a/2b and ERR, respectively.

Human progesterone receptor PGR is another nuclear receptor activated by progesterone through self-dimerization and DNA binding. Genes are transcribed to mRNA, which is translated by ribosomes into certain proteins. PGR's role in breast and endometrial cancer is currently under investigation. Its ortholog in *Mus musculus* is Pgr, in *X. tropicalis* and *D. rerio* is pgr, while in *Drosophila melanogaster* is ERR.

Human NCOR1 is known to modulate multiple autonomous repression domains, which are suggested to be mediators of hormone action (including the thyroid hormones) (64). Its ortholog in *Mus musculus* is Ncor1, in *Xenopus tropicalis* and *Danio rerio* is ncor1, while no ortholog was detected in *D. melanogaster.*

HSP90AA1 is a protein expressed as soon as a cell experiences proteoxic stress. Due to its chaperoning ability, it may be implicated in stress adaptation, while it is also suppressed in the aging brain, and in Alzheimer and/or Huntington diseases (65). Its clinical role includes prognosis of leukemia, breast and pancreatic cancers, and chronic obstructive pulmonary disease (66-69). HSP90AA1's expression is increased by the cytokines IL-2, IL-4 and IL-13 in human T-cells (70). Its ortholog in M*us musculus* is Hsp90aa1, in *Xenopus tropicalis* and *Danio rerio* is hsp90aa1, while there is no known ortholog in *Drosophila melanogaster.*

Of particular interest, the complicated and elaborate network observed in humans and, to a lesser degree in other mammals, may be attributed to the fact that these organisms are more complex than the other species studied.

5.2. Orphan receptors

The above described interactions are supplemented by nuclear receptors considered as orphan receptors, given that their ligands are currently unknown.

Human ESRRA or NR3B1 is currently considered an orphan nuclear receptor (71, 72), closely related to estrogen receptor, and is required for the activation of mitochondrial genes and/or mitochondrial biogenesis (73), oxidative phosphorylation (74) and fatty acid metabolism (75), as well as regulating other proteins such as lactoferrin, osteopontin, and thyroid hormones. It is implicated in corticosteroidogenesis (76, 77), i.e. in cortisol and aldosterone production in the adrenal gland (78). It has been suggested to play a pivotal role in the mammalian circadian clock and metabolic homeostasis (79). On the contrary, ESRRB or NR3B2 is also a nuclear receptor, but, of unknown function in humans, while in mice it has been implicated in placental development. Human ESRRG or NR3B3 is another orphan steroid hormone receptor that acts as a constitutive activator of transcription of still unknown physiological function. Yet, it is deactivated

by 4-hydroxytamoxifen and diethylstilbestrol or bisphenol A (80). The human ESRRA/B/G orthologs in the other species under study are as follows: Esrr a/b/g in M*us musculus* and *Danio rerio*, esrr a/b/g in *Xenopus tropicalis* and the ancestral ERR in *Drosophila melanogaster*.

5.3. Species-restricted proteins

The Tai, Eig71Ea, Eig71Ef and Eig71Eg are species-specific, limited to *Drosophila melanogaster,* and are part of its ancestral interactome (Table 2, Figure 1). Species-specific gene loss or gain might be attributed to the distinct biochemical and physiological needs of an organism. In particular, during the course of evolution, an organism acquires genes necessary for its survival and adaptation to different environmental conditions (81, 82).

5.4. Multiple orthologs in more complicated organisms

The fruitfly ERR has several orthologs (AR, PGR, five estrogen receptors, NR3C1 and NR3C2) in the other organisms under study (Table 3). This is probably due to fruitfly's "ancestral nature", that is, a primordial *ERR* gene might have existed in *D. melanogaster,* which has undergone several rounds of duplications to give rise to several orthologs during evolution in the more complicated organisms.

5.5. Predictions

Interactions in humans were also predicted: (i) ECD, NR1H3 and ELF2, (ii) NR1H3 and HSPB1 through the membrane HSP90AA1, and (iii) CTH and MSRA. These predictions could provide further insight into the membrane-cytosol-nuclear receptors interactions.

Likewise, in the fruitfly, (a) EcR and ecd are predicted to be associated, (b) EcR is suggested to be linked to Eip74EF, (c) ecd is predicted to activate Eip74EF, (d) EcR is predicted to activate Hsp23 and, (e) tai is suggested to be a co-activator of EcR (Figure 2).

5.6. Surface–cytosol-nucleus interactions and ion channels

The localization of all proteins investigated in this study is presented in Figure 1. We identified interactions of the aldosterone receptor or NR3C2 (which can be found in the endoplasmic reticulum or nucleus as well) with solely nuclear receptors. It has been established that NR3C2 increases the activity of the basolateral Na/K ATPase, ENaC sodium channels and ROMK potassium channels of the principal cell in the kidney distal convoluted tubule and cortical collecting duct of nephrons, bowel, and sweat glands. Cell surface receptors also found in nucleus are ESR1/2, ESRRA/B, NR3C1/C2 and HSP90AA1. The surface membrane receptors are suggested to be activated faster than nuclear receptors. Their translocation might take place through coupling to cytoplasmic proteins and/or adjunct lipid bilayer membranes, so as to interact with extracellular molecules (83).

5.7. R1: an explanatory mechanism of electromagnetic fields' influence

Natural and/or man-made radiation (i.e. radiofrequency fields) is omnipresent in our lives affecting environmental chemicals, electrical devices and living organisms. In the past decade, conflicts in the biomedical community have occurred over the issue of "non-ionizing electromagnetic fields (including cellular phones and base stations antennas) exposure effect on health". World Health Organization (WHO) has classified the exposure to cellular phone use as possibly carcinogenic (B2 level) (84-86). Thus, an increasing research interest originating from social concerns gave rise to a thoughtful and constructive approach, distinctive from loud and impressive evidence that fail to give answers to pivotal queries: is the exposure really detrimental to humans? Which mechanism/s is/are involved? How could one prevent any possible negative effects?

The currently reported effects of electromagnetic fields include influences on human and rat circadian rhythms and, hence, the "biological clock" (84, 87-96), on human fertility (97-102), rat reproduction (103, 104), *Drosophila* fecundity (105-107), and human carcinogenesis and genotoxicity (108-116), (109, 117-119). Also, they may influence other hormones in humans (120,131-134) and rodents (121,129-130), and neurological (135-138) or cardiac function and wellbeing in humans (139-143).

The current explanatory mechanisms of the above stated effects include magnetic alterations in cell membrane energy, cell apoptosis (144, 145), heat stress (146-148), oxidative stress (111, 139, 144, 145, 149-154), resonance (155, 156), alterations of the hydrophilic and hydrophobic properties of the cell membrane (157), electrophysiological dysregulation, alterations of ion channel functions (158, 159) and ecdysone action in the *Drosophila* (106).

The above described effects (in all retrieved organisms from insects to humans), as well as the suggested mechanisms are implicated in the described interactome R1. Of interest, this evolutionarily preserved network seems to be activated upon radiofrequency (RF) exposure, triggering downstream pathways of cell apoptosis, oxidative stress, membrane lipids and/or ion channel function, thereby leading to

acute or chronic adaptation. Additionally, the major hub identified NCOR1 highlights the importance of a common negative feedback in thyroid and steroid hormone, action a revealed previously by Geronikolou *et al* (126). The predictions we revealed suggest that the "thermal vs. non-thermal" concept is too limited.

Finally, the Interactome we created integrates hypothalamic-pituitary-adrenal (HPA), -thyroid (HPT) and -gonadal (HPG) axes and the autonomic nervous system (ANS). The HPA/ANS interactions have attracted increasing research interest in neuroendocrinology.

The functional cross-talk between the hypothalamic-pituitary-adrenal and -gonadal axes integrates social and reproductive behavior (160-162). Thus, the proposed evolutionarily conserved interactome integrates social behavior, environmental exposures and homeostatic and reproductive mechanisms.

6. CONCLUSIONS

We studied the evolutionary relationships of steroid receptors and their implications in clinical and environmental studies. The "R1 inter-interactome" constructed herein connects the HPA, HPT and HPG axes and the autonomic nervous system through NCOR1. Apart from steroid receptors, it comprises heat shock proteins, enzymes, co-repressors, and transcription factors. Furthermore, it integrates social behavior, environment and cell mechanisms, regulating extrinsic /intrinsic influences (160-162). More importantly, we proposed a new explanatory mechanism of the effects of exposure to electromagnetic fields on insects, fish, amphibians, rodents and humans. Its constituent nodes, which correspond to gene/gene products, are implicated in physiologic functions (development, reproduction, homeostasis, circadian thythms, immunity, metabolism, behavior), and pathophysiologic functions (carcinogenesis, cardiovascular pathology, neurodegenerative diseases, inflammation, etc). Future research efforts could be directed towards the study of other types of steroid hormones (as i.e. G-coupled receptors, sex hormone-binding globulin receptor, etc).

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