

SZENT ISTVÁN UNIVERSITY
FACULTY OF VETERINARY MEDICINE

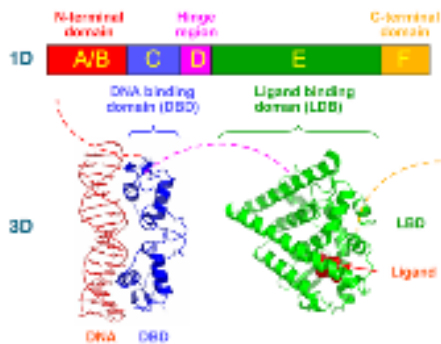
Estrogen and Thyroid Hormone Receptors and their Interaction

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Nuclear Receptors

- What are Nuclear Receptors?
 - Proteins located inside cells
 - Bind Response Elements on DNA
 - Regulate transcription
 - Modulated by binding of ligands
 - Lipophilic endogenous hormones
 - Fat soluble vitamins

Nuclear Receptors



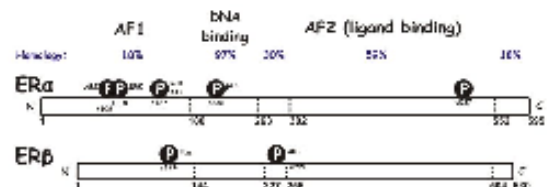
Estrogen Hormone Receptor

- A receptor molecule that could bind 17 β -estradiol.
- Initially discovered in 1958 (*Jensen and Jacobsen*)
- A second receptor was discovered in 1966
 - ER α
 - ER β

ER α and ER β

- High degree of similarity in their **DBD**
- Moderate degree of similarity in their **LBD**
- Poorly homologous in their **N terminus**
 - ER β has a weaker **AF-1** related function
 - Depends more on ligand dependent **AF-2**

ER α and ER β



ERβ Expression in Normal and Tumoral Canine Mammary Glands (De Las Mulas, et al., 2004)

- 35 tumoral lesion were collected from 28 female dogs.
- Compared with non altered mammary tissues taken from healthy glands.
- The type of tumor was histologically evaluated.
- The tumors were qualitatively and quantitatively analyzed for detection of the β isoform.

ERβ Expression in Normal and Tumoral Canine Mammary Glands

- Expression in benign canine mammary tumors:

Type of tumor	Total number	Estrogen Receptor β Positive	% of ERβ+ in ERβ total
Phyllodes tumor	1	1	100
Complex adenoma	1	0	-
Complex adenocarcinoma	1	1	100
Invasive ductal tumor	2	1	50
Total	5	3 (60%)	60

ERβ Expression in Normal and Tumoral Canine Mammary Glands

- Expression in malignant canine mammary tumors:

Type of tumor	Total number	Estrogen Receptor β Positive	% of ERβ+ in ERβ total
Complex adenocarcinoma	6	1	16.7
Simple ductal carcinoma	12	2	16.7
Invasive carcinoma	1	0	-
LCIS	9	1	11.1
Total	18	4 (22.2%)	22.2

ERβ Expression in Normal and Tumoral Canine Mammary Glands

- The results suggest that ERβ positive tumors are more frequently benign.
- Additionally, malignant ER β positive tumors are more frequently complex/mixed than simple.

The Relationship of the Expression of ER in Cartilage cells and Osteoarthritis Induced by Bilateral Ovariectomy in Guinea Pig (Guofeng, et al., 2005)

- 30 two month old female guinea pigs divided into two 15 member groups.
- First group underwent Ovariectomy (OVX group) while the other served as the control group.
- Measurement of serum estrogen, ER expression, along with SEM and TEM.

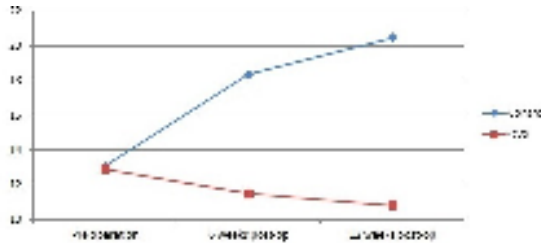
The Relationship of the Expression of ER in Cartilage cells and Osteoarthritis Induced by Bilateral Ovariectomy in Guinea Pig (Guofeng, et al., 2005)

- The serum levels of estrogen, gestone and ER:

	Group	Estrogen (pg/ml)	Progesterone (ng/ml)	ERβ (ng/ml)
Estrogen (pg/ml)	Control	11.5 ± 5.1	11.4 ± 5.0	1.17 ± 0.13
	OVX	5.1 ± 4.8	11.5 ± 5.1	1.18 ± 0.13
Progesterone (ng/ml)	Control	21.6 ± 5.2	4.93 ± 0.28	4.19 ± 0.19
	OVX	22.8 ± 5.8	5.45 ± 0.37	5.33 ± 0.33
ERβ (ng/ml)	Control	11.1 ± 2.1	1.8 ± 0.2	1.14 ± 0.1
	OVX	12.0 ± 2.4	1.8 ± 0.2	1.18 ± 0.1

The Relationship of the Expression of ER in Cartilage cells and Osteoarthritis Induced by Bilateral Ovariectomy in Guinea Pig (Guofeng, et al., 2005)

ER expression in OVX and Control groups:



The Relationship of the Expression of ER in Cartilage cells and Osteoarthritis Induced by Bilateral Ovariectomy in Guinea Pig (Guofeng, et al., 2005)

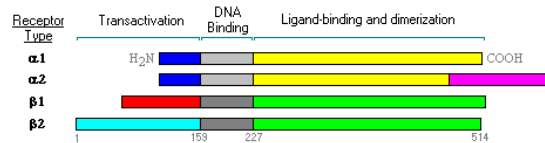
Results

- Statistically significant decrease in estrogen, gestone and ER levels in the OVX group.
- Joint cartilage degeneration at 6 weeks post op in the OVX group.
- Severe degenerative lesions of cartilage at 12 weeks post op in the OVX group.
- No changes at 6 weeks and slight degeneration at 12 weeks post op in the control group.

Thyroid Hormone Receptor

- A receptor which binds T3 was discovered in 1972.
- Main Isoforms: TR α 1, TR β 1 and TR β 1
- Share a homologous amino acid sequence with steroid hormone receptors, despite having a structurally different ligand.
- Isoforms generally show a high DBD and LBD homology but low amino terminal homology.

Thyroid Hormone Receptor Isoforms



Thyroid Hormone Resistance and TR β Mutation (Adams, et al., 1994)

- 20 Patients with generalized- and 9 patients with pituitary resistance to TH were analyzed.
- All were affected by a mutation of the TR β gene.
- No association established between type or site of mutation and clinical signs.
- Significance?

Link between Alteration of TR Expression and Human Breast Cancer (Silva, et al., 2002)

- A series of samples of tumoral and control tissues from 70 patients analyzed by RT-PCR.
- Samples found to contain alterations were subsequently sequenced.

	Number of samples showing alteration	Percentage of total samples
TR α 1	6	8.57%
TR β 1	4	5.71%
TR α 1 + TR β 1	2	2.86%
Truncated TR β 1 RNA	6	8.57%
TR β 2	0	0.00%

Lordosis behavior, TR and ER (Morgan, et al., 2000)

- Testing the effect of thyroid hormones on estrogen induced lordosis in mice.



Lordosis behavior, TR and ER (Morgan, et al., 2000)

First experiment

OVX, n=56	Estradiol benzoate implant	Vehicle
Daily T4 injection (20 µg)	EB + T4(high)	T4(high)
Vehicle	EB	Veh

OVX/TX, n=58	Estradiol benzoate implant	Vehicle
Daily T4 injection (5 µg)	EB + T4(low)	T4(low)
Vehicle	EB	Veh

Lordosis behavior, TR and ER (Morgan, et al., 2000)

Second experiment

- Aimed to assess whether a T4 pretreatment will produce a more pronounced and rapid onset of suppression of lordosis.

OVX, n=23	Estradiol benzoate implant	Placebo pellet
T4 Implant	EB	EB + T4

Lordosis behavior, TR and ER (Morgan, et al., 2000)

Behavioral test

- Females placed with males
- LQ = Receptive responses/number of mounts x 100
- LS = Total value of receptive responses/number of mounts.
- Value of receptive response:
 - 0: Female did not stop moving during mounting
 - 1: Female paused and allowed for mounting, but ended interaction afterwards
 - 2: Female froze in lordosis posture until dismounting of male.

Lordosis behavior, TR and ER (Morgan, et al., 2000)

Results

- First experiment
 - OVX mice: suppression of lordosis in EB+T4(high) group only by test day 4.
 - OVX/TX mice: no significant difference between groups.
- Second experiment:
 - Suppression of lordosis in EB+T4 group by test day 2

Lordosis behavior, TR and ER (Morgan, et al., 2000)

Conclusions

- Increased levels of T4 result in suppression of estrogen mediated sexual behavior in female mice.
- Pre treatment speeds up the initiation of this suppression, when compared to the non pretreated group.

Thyroid- and Estrogen Mediated Response in Neuroblastoma Cells (Zhao, et al., 2005)

- Previous studies:
 - Non genomic EH membrane actions could potentiate transcription from an ERE in neuroblastoma cells. (*Vaseudevan, et al., 2001*)
 - T4 application increased cell proliferation in MCF-7 breast carcinoma cells, mimicking estradiol. (*Tang, et al., 2004*)

Thyroid- and Estrogen Mediated Response in Neuroblastoma Cells (Zhao, et al., 2005)

- Can non genomic TH potentiate transcription by 17 β -estradiol from a consensus ERE in neuroblastoma cells?
- Cell were transfected with TR α 1 or TR α 2 and with ER α to allow for the respective hormone activities.
- A “two pulse paradigm” of T3 and 17 β -estradiol preparations, or two 17 β -estradiol preparations was used to mimic the hypothesized non genomic potentiation.

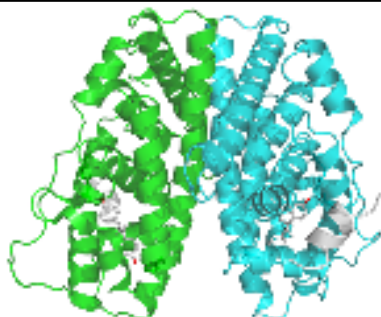
Thyroid- and Estrogen Mediated Response in Neuroblastoma Cells (Zhao, et al., 2005)

Results

- Both T3 and 17 β -estradiol were able to potentiate ER mediated transcription from a consensus ERE, by using the “two pulse paradigm”.
- Neither T3, nor 17 β -estradiol had any effect on transcription when given in a single pulse.

Acknowledgments

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Thank you very much for your attention!