

# Hormone receptor Agonist & Antagonist

### 고려의대 산부인과

신 정호



# **Hormone Receptor**



### **Nuclear receptor superfamily**

 Estrogen, Androgen, Progestogen, Glucocorticoids, Thyroxin, Vitamin A & D





### The Receptor Superfamily





### **The Estrogen Receptors**







- ✤ D Region, The Hinge
  - movement of the receptor to the nucleus following synthesis in the cytoplasm
  - site of rotation in achieving conformational change





- E Region, The Hormone-Binding Domain
  - TAF-2
  - 12 helices with a folding pattern that forms a pocket
  - site for binding by heat shock proteins & cofactors
  - dimerization





- C Region, The DNA-Binding Domain
  - Hormone binding induce conformational change which allow C region to bind DNA.
  - Very similar among superfamily but Zinc finger terminal.
  - Specificity = Zinc finger







- ✤ A/B Region, The Regulatory Domain
  - Most variable in superfamily, 20 aa ~ 600aa
  - Transcription activation function called TAF-1,
  - absent activity in ERβ
  - TAF-1 can stimulate transcription without Hormone binding.



• Timing issue.... Ligang binding



✤ F Region

- influences antiestrogen efficacy in suppressing estrogenstimulated transcription
- Conformational influence differ in cell type & protein context.



### Ligand-Dependent Nuclear Activity





### Ligand-Dependent Nuclear Activity







### Ligand-Independent Nuclear Activity





### ER homodimer / heterodimer

- Cell express one receptor subtype, response one homodimer
- Cell express both could respond to a homodimer or heterodimer.





## **Different Roles for ER-** $\alpha$ and ER- $\beta$

Characteristics	of ERKO and	<b>BERKO MICE</b>
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ERKO Mice	BERKO Mice		
Normal lifespan	Normal lifespan		
Anovulatory	Oligovulatory		
Absent breast response at puberty	Normal breast glands and function		
Normal G-U development but no adult response	Normal G-U development and normal adult response		
Increase in visceral adiposity and insulin resistance	Normal body fat distribution and insulin secretion		
Infertile males and females	Fertile males, subfertile females with reduced follicular growth		



### **ER-** $\alpha$ **VS ER-** $\beta$

### • ER- $\beta$ lacks TAF-1.

- ER-β dominant: some area of brain, cardiovascular system
- ♦ ER- $\beta$  only: granulosa cell, colon
- Decreased ER- $\beta$  expression in EM, colon, prostate cancer



# The ratio of estrogen receptor $\alpha$ to estrogen receptor $\beta$ in adipose tissue is associated with leptin production and obesity

Jung-Ho Shin<sup>a</sup>, Jun-Young Hur<sup>a,\*</sup>, Hong Seog Seo<sup>b</sup>, Yu-A Jeong<sup>a</sup>, Jae Kwan Lee<sup>a</sup>, Min-Jeong Oh<sup>a</sup>, Tak Kim<sup>a</sup>, Ho Suk Saw<sup>a</sup>, Sun Haeng Kim<sup>a</sup>

<sup>a</sup> Department of Obstetrics and Gynecology, College of Medicine, Korea University, Seoul, Republic of Korea

<sup>b</sup> Department of Cardiology, College of Medicine, Korea University, Seoul, Republic of Korea



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![](_page_16_Picture_6.jpeg)

0.2

0.0

0.4

Sc-Om ratio of the ER subtypes

0.6

1.0

0.8

![](_page_17_Figure_1.jpeg)

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# $ERR\alpha$ , $ERR\beta$ , $ERR\gamma$

- Orphan receptors
- Expressed in most tissues, action as typical estrogenic activity
- Nevertheless, they don't combine with Estrogen..., no endogenous ligand found yet.

![](_page_18_Picture_4.jpeg)

### Ligand–Cell Membrane Extranuclear Receptor Activity

- Rapid responses mediated by estrogen receptors in cell membranes
- Ligand-Dependent, ERE-Independent Activity
  - Negative feedback inhibition of LH secretion not through the classical pathway

![](_page_19_Picture_5.jpeg)

### **The Progesterone Receptor**

![](_page_20_Figure_1.jpeg)

#### The Progesterone Receptor-A

#### The Progesterone Receptor-B

![](_page_20_Figure_4.jpeg)

![](_page_20_Picture_5.jpeg)

### **The Androgen Receptor**

- By intracellular conversion of testosterone to Dihydrotestosterone(DHT), intracrine activity
- 2. By **Testosterone** itself, endocrine activity
- 3. By intracellular conversion of testosterone to **Estradiol**(aromatization), intracrine activity

![](_page_21_Picture_4.jpeg)

### **The Androgen Receptor**

#### The Androgen Receptor

![](_page_22_Figure_2.jpeg)

A & B subtypes

Resembles PR,(>) MR, GR.

![](_page_22_Picture_5.jpeg)

### The tree of progestogens

![](_page_23_Figure_1.jpeg)

### **Comparison of Progestins**

	Progestogenic activity	Androgenic activity	Antiandrogenic activity	Antialdosterone activity	Glucocorti- coid activity
Progesterone	+	-	(+)	+	-
Drospirenone	+	-	+	+	-
CPA	+	_	+	-	(+)
Desogestrel	+	(+)	_	-	_
Dienogest	+	_	+	-	-
Gestodene	+	(+)	_	(+)	_
Levonorgestrel	+	(+)	-	-	-
MPA	+	(+)	_	-	(+)
Norethisterone	+	(+)	-	-	-
Norgestimate	+	(+)	_	-	-
Tibolone	+	+	_	-	-
		untu no potivitu	I I		

+ relevant activity; (+) activity not clinically relevant; – no activity CPA: cyproterone acetate; MPA: medroxy progesterone acetate

KOREA UNIVERSITECHINDER AE et al. *Maturitas.* 2003;46(suppl 1):S7-S16; Rübig A. *Climacteric.* 2003;6(suppl 3):49-54.

# **Agonists and Antagonists**

![](_page_25_Picture_1.jpeg)

### **Short-Acting Antagonists**

![](_page_26_Picture_1.jpeg)

• mixed combination of agonism and antagonism

![](_page_26_Figure_3.jpeg)

![](_page_26_Picture_4.jpeg)

### **Long-Acting Antagonists**

### Clomiphene and tamoxifen

- Mixed estrogen agonists and antagonists
- GnRH : a decapeptide
  - antagonists : substitutions at multiple positions
  - agonists : substitutions at the 6 or 10 positions

![](_page_27_Picture_6.jpeg)

### **Long-Acting Antagonists**

![](_page_28_Figure_1.jpeg)

![](_page_28_Picture_2.jpeg)

### **Long-Acting Antagonists**

![](_page_29_Figure_1.jpeg)

![](_page_29_Picture_2.jpeg)

### Antiestrogens

### **Pure antiestrogens**

# Mixed agonistic-antagonistic compound

![](_page_30_Picture_3.jpeg)

### Mixed agonist-antagonist compounds

![](_page_31_Figure_1.jpeg)

### **Pure antiestrogens**

![](_page_32_Figure_1.jpeg)

![](_page_32_Picture_2.jpeg)

### The Antiestrogen Tamoxifen

Sensitizes breast cells to the apoptotic effects of women's own estrogen level.

### Tamoxifen

Bind to estrogen receptor

competitively inhibit estrogen binding

estrogen receptor binding affinity → 100–1,000 times greater than tamoxifen

concentration 100–1,000 times greater than estrogen → inhibit breast cancer cells

![](_page_33_Picture_7.jpeg)

### The Estrogenic action of Tamoxifen

### Tamoxifen

Antithrombin III cholesterol LDL-cholesterol SHBG

![](_page_34_Picture_3.jpeg)

1. Stimulate progesterone receptor synthesis

- 2. maintenance of bone
- 3. estrogenic effects on the vaginal mucosa and the endometrium

Daily 20 mg → potent as 2 mg estradiol → lowering FSH levels in postmenopausal women

### **Tamoxifen Mechanism of Action**

#### Cytoplasm

![](_page_35_Figure_2.jpeg)

![](_page_35_Picture_3.jpeg)

### **Tamoxifen Treatment of Breast Cancer**

![](_page_36_Figure_1.jpeg)

![](_page_36_Picture_2.jpeg)

## SUMMARY

### **Steps in the Steroid Hormone Receptor Mechanism**

- Binding of the hormone to the hormone-binding domain that has been kept in an inactive state by various heat shock proteins.
- 2. Activation of the hormone-receptor complex, by **conformational change**, follows the dissociation of the heat shock proteins.
- 3. **Dimerization** of the complex.
- Binding of the dimer to the hormone-responsive element on DNA at the zinc finger area of the DNA-binding domain.
- Stimulation of transcription, mediated by TAFs, and influenced by the protein context of the cell, and by phosphorylation.

![](_page_37_Picture_7.jpeg)

# SUMMARY

### Factors that Determine Biologic Activity

- 1. Affinity of the hormone for the hormone-binding domain of the receptor
- 2. Target tissue differential expression of the receptor subtypes (e.g., ER- $\alpha$  and ER- $\beta$ )
- 3. The concept of **conformational shape** 
  - the structure of the ligand-receptor complex
  - dimerization and the recruitment of regulating proteins
- 4. The concept of cellular context
  - the differential expression of target tissue regulating proteins, coactivators and corepressors, and phosphorylation, yielding various biological responses

![](_page_38_Picture_9.jpeg)

# **Thank You for Your Attention !**

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