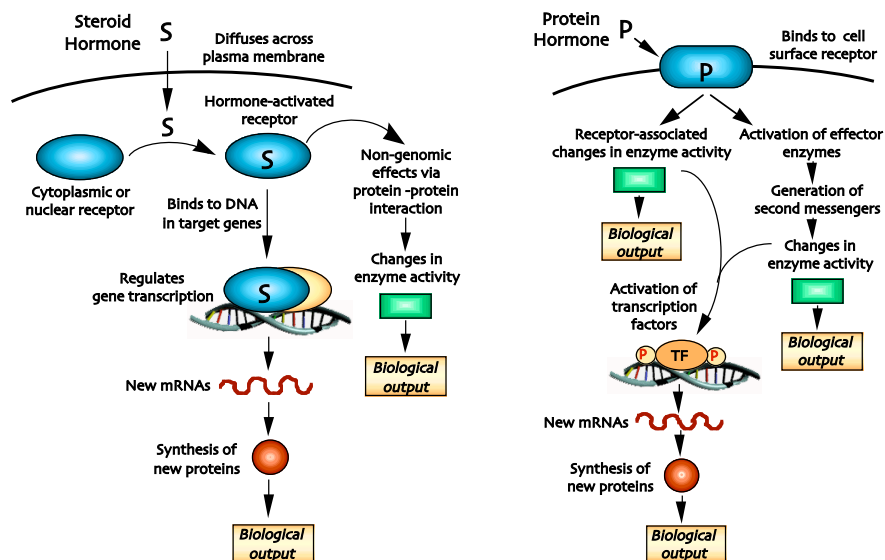


Frontiers in Reproductive Endocrinology
Serono Symposia International

Mechanisms of Hormone Action:
Steroid Hormones

Kelly Mayo
Northwestern University

General Mechanisms of Action
of Steroid and Peptide Hormones



Select Families of Nuclear Hormone Receptors

Steroid Receptors

Estrogen Receptor (ER)
Androgen Receptor (AR)
Progesterone Receptor (PR)
Glucocorticoid Receptor (GR)
Mineralocorticoid Receptor (MR)

Non-Steroid Hormones

Thyroid Hormone Receptor (TR)
Vitamin D Receptor (VDR)
Retinoic Acid Receptor (RAR)
9-Cis Retinoic Acid Receptor (RXR)
Ecdysone Receptor (EcR)

Ex-Orphan Receptors

Benzoate X Receptor (BXR)
Steroid and Xenobiotic Receptor (SXR)
Constitutive Androstane Receptor (CAR)
Also RXR, LXR, FXR, PPARs

Mevalonate Pathway

Liver X Receptor (LXR)
Pregnane X Receptor (PXR)
Farnesoid X Receptor (FXR)

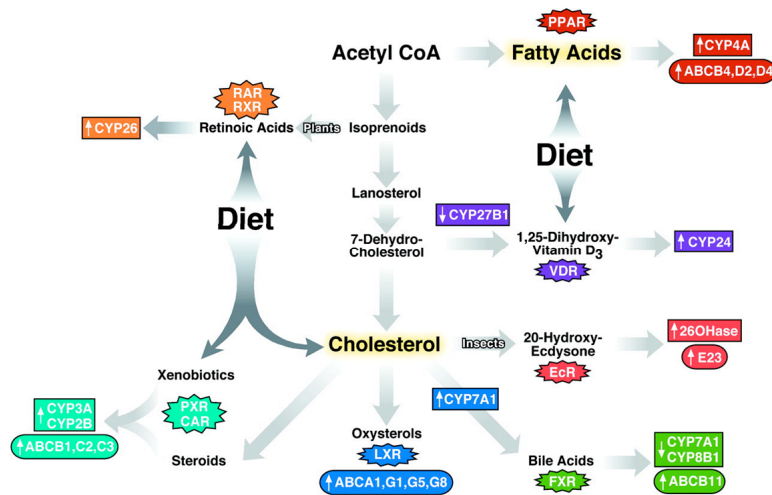
Peroxisome Proliferators

PPAR α (fibrates)
PPAR γ (thiazolidinediones)
PPAR δ

Orphan Receptors

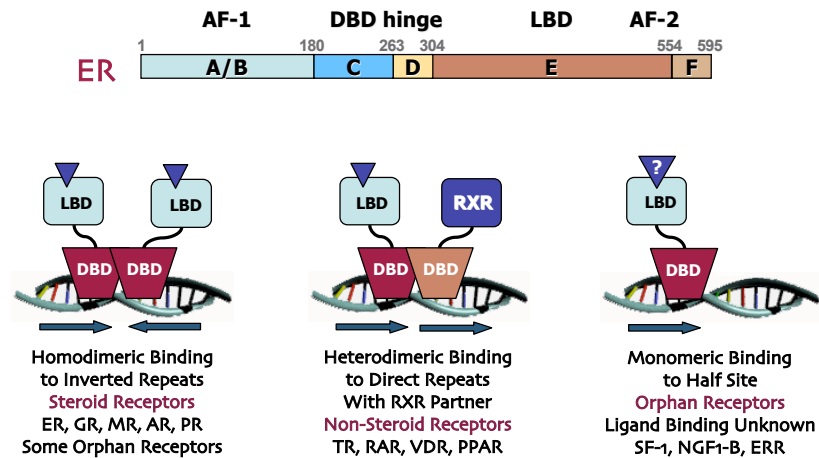
ERR family
NGF1-B family
COUP TF family
NGF1-B family
RVR family
SF-1
LRH-1
Dax-1
HNF-4
GCNF

Metabolic Pathways of Nuclear Receptor Ligands

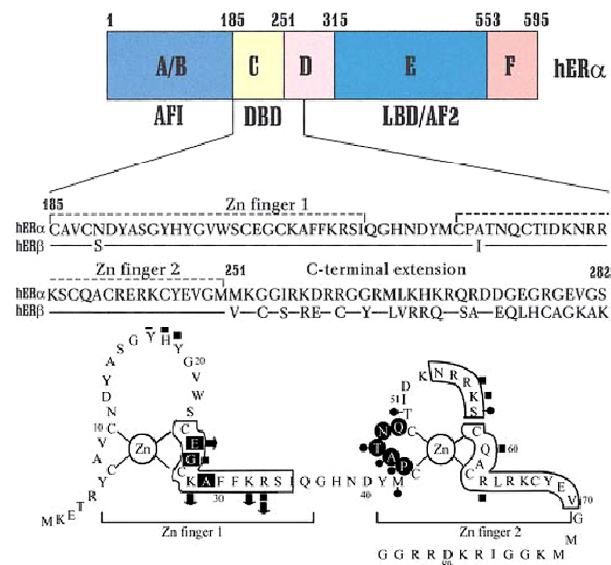


Chawla et al Science 294:1866, 2001

Domain Structure of Nuclear Receptors and Dimerization and DNA Binding Properties



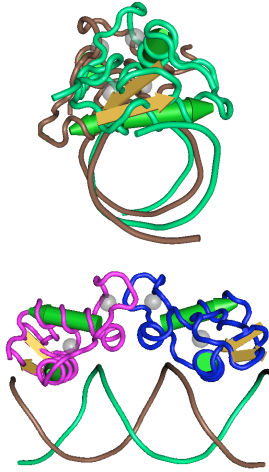
DNA Binding by Nuclear Hormone Receptors



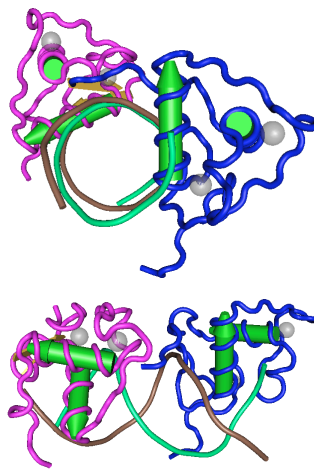
Sanchez et al, *BioEssays* 24:244, 2002

DNA Binding by Nuclear Hormone Receptors

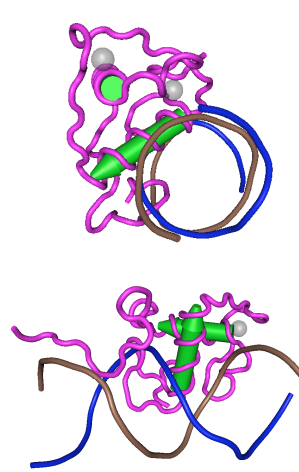
ER LBD Homodimer



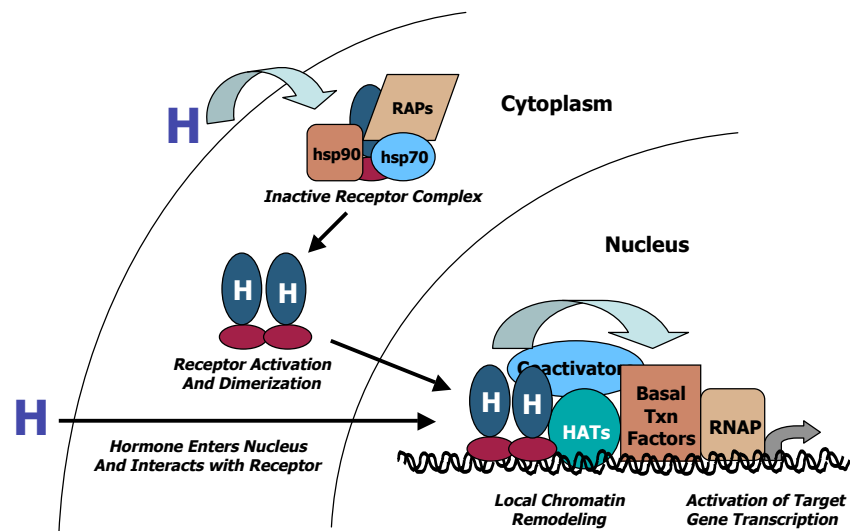
RAR-RXR LBD Heterodimer



NGF1-B LBD Monomer

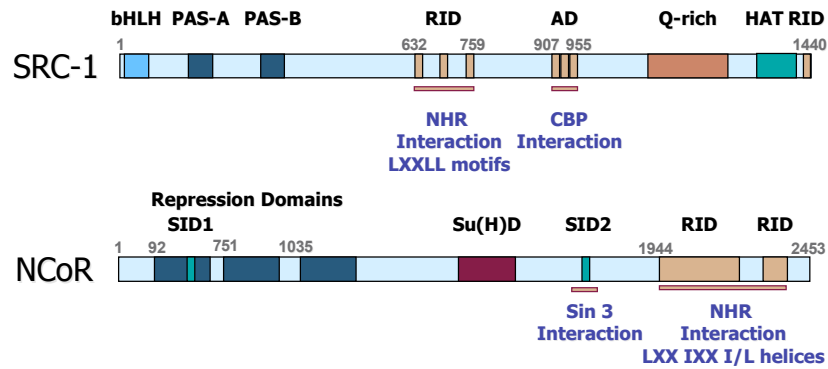


Nuclear Receptor Signaling Pathways

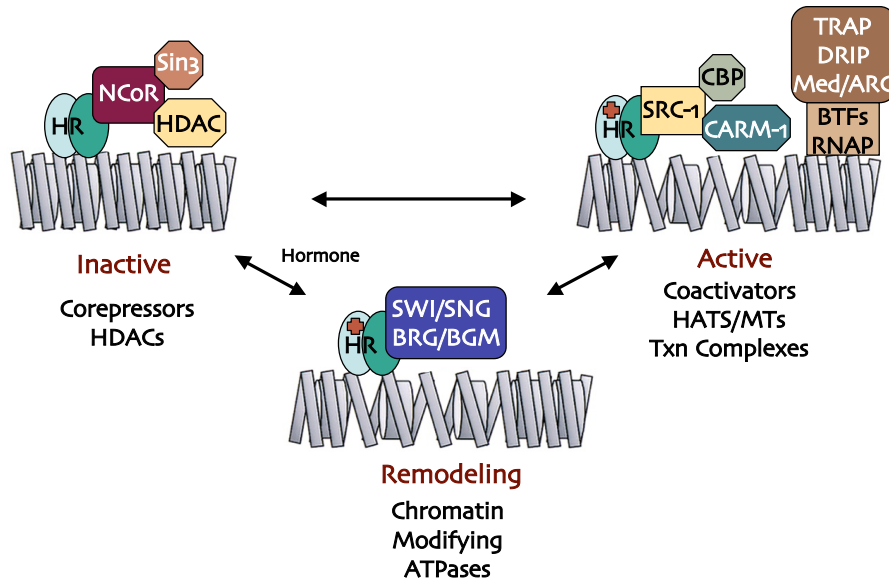


Nuclear Receptor Coactivators and Corepressors

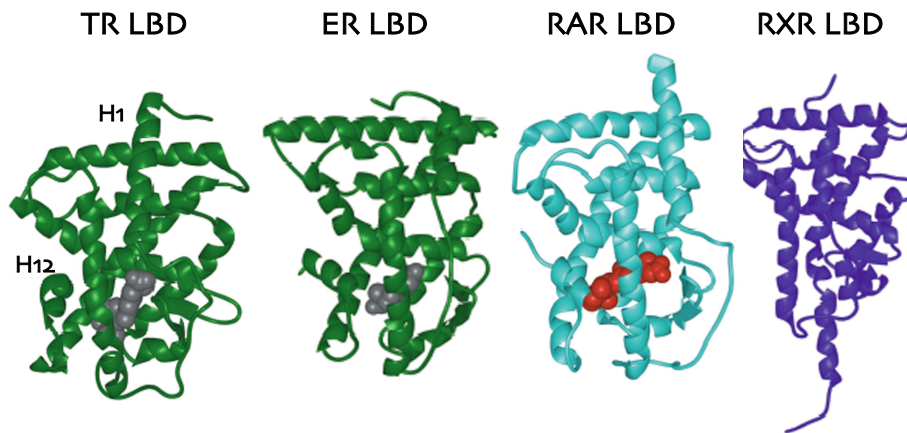
Coactivators	Integrators/Complexes	Corepressors
SRC-1, NCoA-1	CBP, p300	NCoR
GRIP-1, TIF-2, SRC-3	TRAPs, DRIPs	SMRT
pCIP, ACTR, SRC-3	SWI/SNF	REA
Many others	pCAF/CARM	TRUP, SURF-3



Coregulators and Chromatin Remodeling

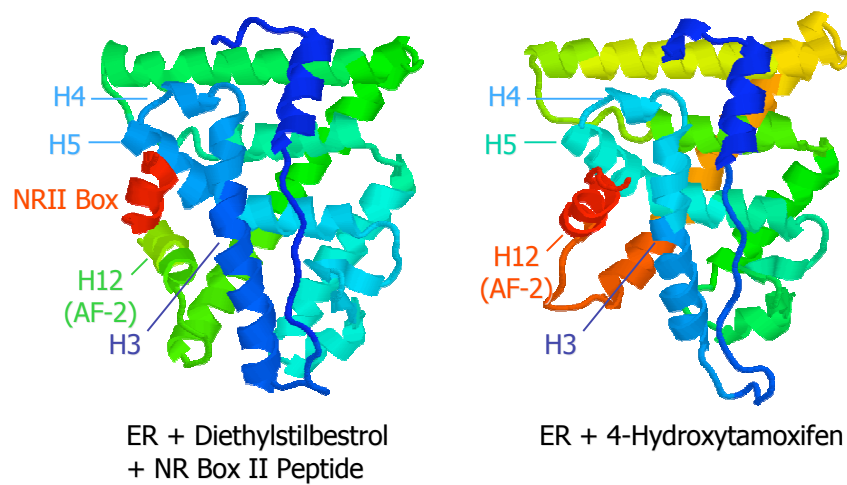


Some Nuclear Receptor Ligand-Binding Domains



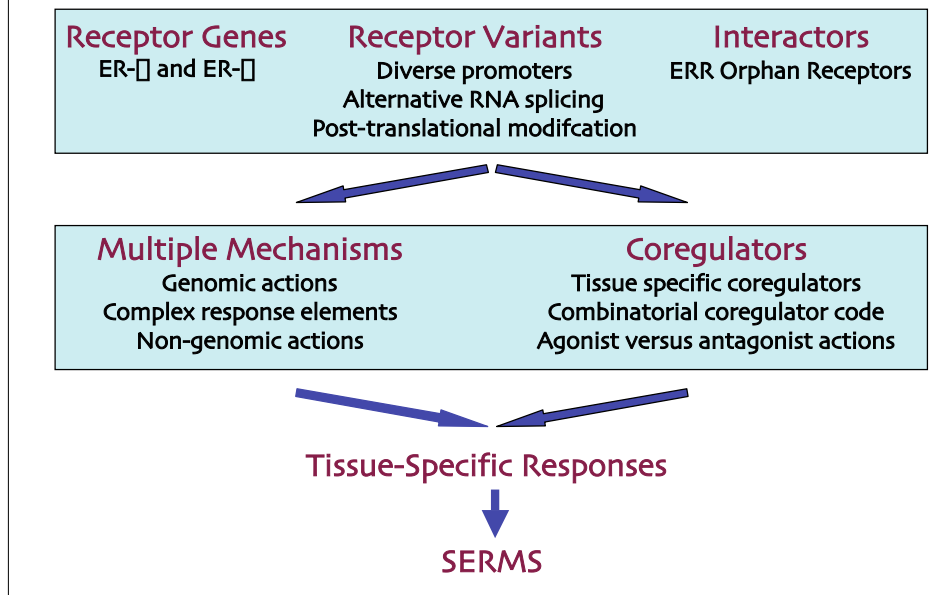
Weatherman et al, Ann Rev Biochem 68: 559, 1999

Structures of Agonist and Antagonist Bound Estrogen Receptor Ligand Binding Domain

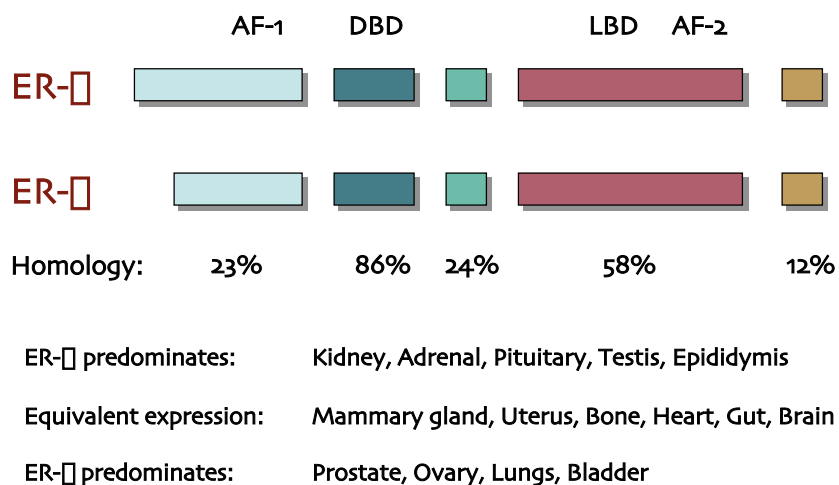


Shiau et al Cell 95:927-937, 1998

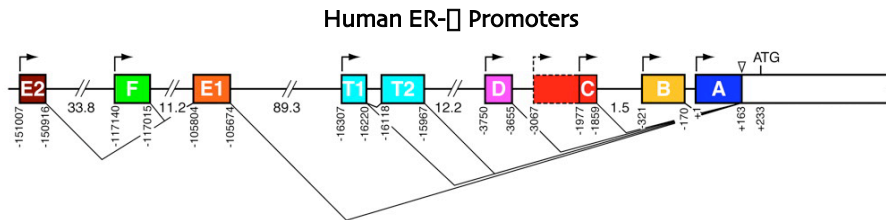
Complexities in Steroid Hormone Action: Estrogen



Generation of Diversity in Nuclear Receptors: Multiple Estrogen Receptor Genes



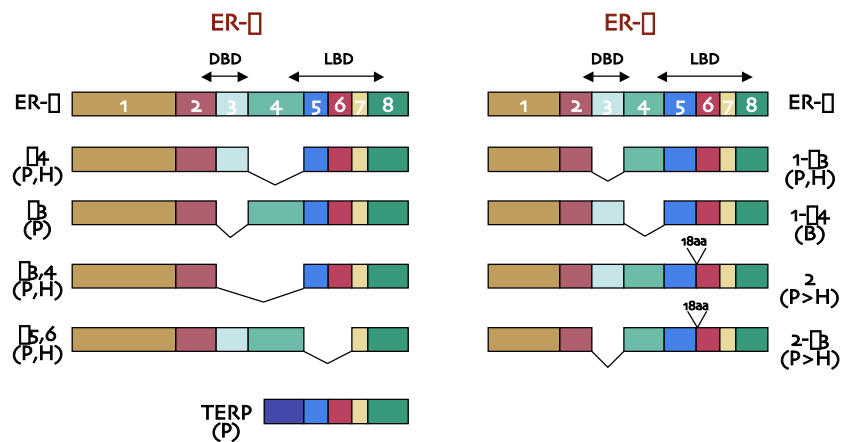
Generation of Diversity in Nuclear Receptors: Multiple Estrogen Receptor Gene Promoters



Potential Implications:
 Tissue- or cell-specific ER expression
 Developmental-specific ER expression
 Alternative splicing of ER transcripts

Kos et al, Mol Endocrinol 15:2057, 2001

Generation of Diversity in Nuclear Receptors: Multiple Estrogen Receptor Splice Variants



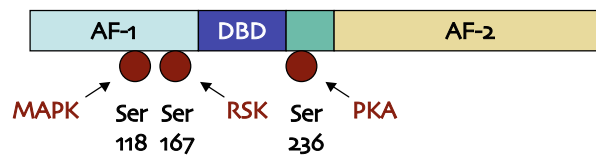
Shupnik, J Neuroendocrinol 14:85, 2002

Generation of Diversity in Nuclear Receptors: Phosphorylation of the Estrogen Receptor

In response to estrogen binding:

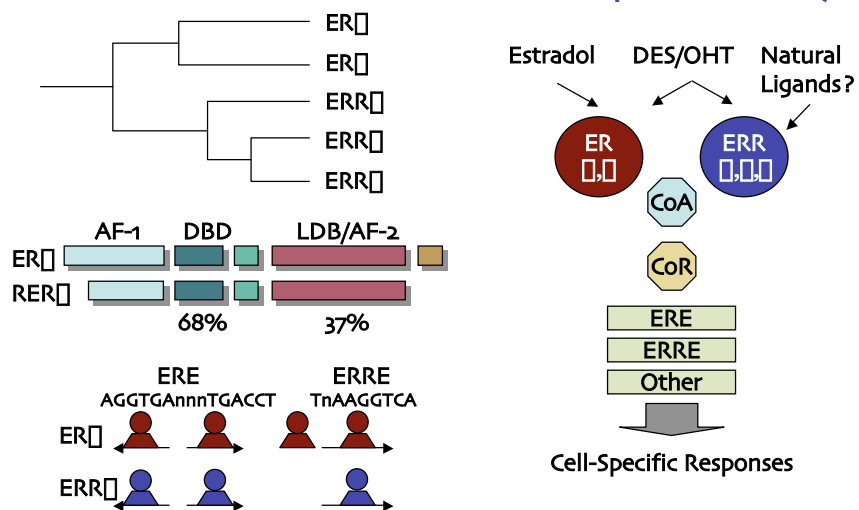


In response to second messenger pathways:



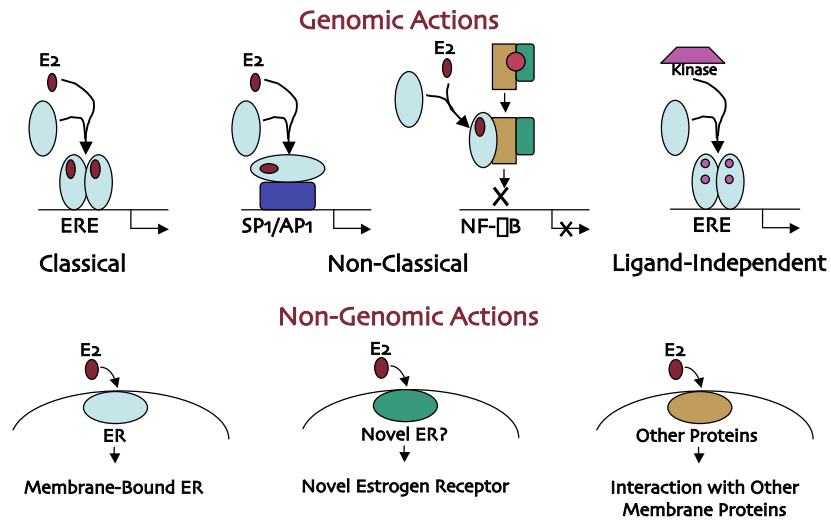
Lannigan, Steroids 68:1, 2003

Generation of Diversity in Nuclear Receptors: Interaction with Other Nuclear Receptor Pathways

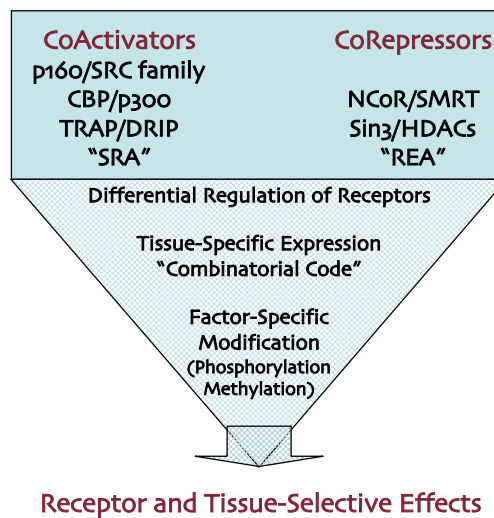


Giguere, Trends Endocrinol Metab 13:220, 2002

Generation of Diversity in Nuclear Receptors: Multiple Mechanisms of Action



Generation of Diversity in Nuclear Receptors: Combinatorial use of Coregulatory Proteins



Selective Estrogen Receptor Modulators (SERMs)

Examples of SERMs:

Tamoxifen (breast cancer)
Antagonist in breast, but agonist in bone/endometrium

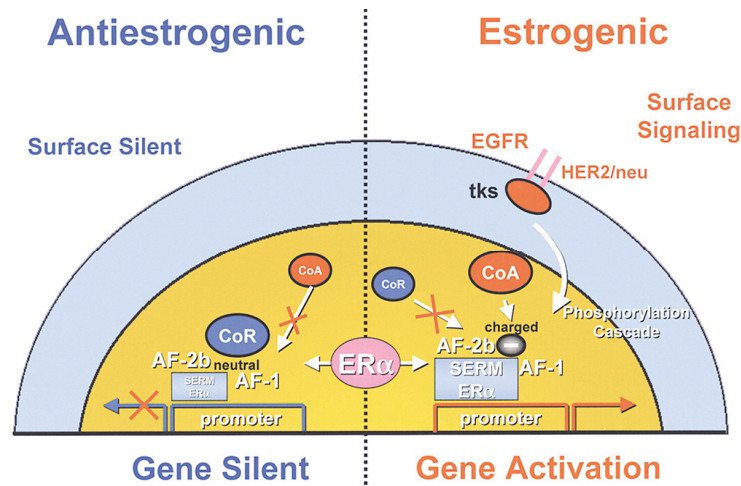
Raloxifene (osteoporosis)
Agonist in bone, antagonist in breast/endometrium

Determinants of SERM Action:

Each ligand (SERM) will induce a unique conformation of the estrogen receptor that impacts its interaction with coregulatory proteins

Each tissue or cell type will contain a unique complement of coregulatory proteins and a distinct pattern of activation state of these proteins

Cell-Selective Actions of SERMs



Jordan Cancer Cell 1:215, 2002

Additional Pathways of Intracellular Hormone Action

Extrinsic Signals

Arylhydrocarbon Receptor
 Intracellular dioxin receptor
 Ligand activated transcription factor
 Binds to xenobiotic response element

Nitric Oxide Receptor
 Cytoplasmic form of guanylyl cyclase
 α/β heterodimer with heme cofactor
 Increases cGMP and PKG activity

Intrinsic Signals

Sterol Sensing
 Proteolysis of membrane-bound SREBP
 bHLH domain regulates transcription
 Proteolysis regulated by sterols

Oxygen Sensing
 Prolyl and Asn hydroxylases regulated by O_2
 Hydroxylation regulates HIF- α
 Heterodimer with ARNT regulates transcription

Mutations of Hormones, Receptors and Signaling Proteins in Reproductive Disease

Hormones

FSH Delayed puberty, primary amenorrhea in females; male hypogonadism
 LH Luteal insufficiency, infertility in female; delayed puberty, azoospermia in male
 MIS Persistence of Mullerian duct derivatives in males

Receptors

GnRH-R Partial to complete hypogonadotropic hypogonadism, males and females
 FSH-R Primary or secondary amenorrhea in females, variable/mild oligospermia in males
 LH-R (Loss) Amenorrhea or oligomenorrhea in females, range of defects to complete feminization in males
 LH-R (Gain) Male-limited precocious puberty, no phenotype in females
 Estrogen R Normal puberty, tall stature and unfused epiphyses in male
 Androgen R Many mutations, broad range of phenotypes to complete feminization in males
 MIS R-II Persistence of Mullerian duct derivatives in males
 RET Multiple endocrine neoplasia type 2

Signaling Proteins

Gs protein β McCune-Albright Syndrome (gain), male precocious puberty (loss/gain)
 Gi protein β Ovarian and adrenal tumors?
 Smads Mutations in many cancers, including Smad4 mutation in seminoma testicular germ cell tumor

Transcription Factors

Dax-1 Hypogonadotropic hypogonadism/adrenal failure in male
 SF-1 XY sex reversal/adrenal failure
 Prop-1 Variable hypogonadotropic hypogonadism in males and females

Emerging and Future Issues in Hormone Action

- Cross-talk between different signaling pathways
 - Integration of multiple signals in target cell
- Generation of diverse responses from common stimuli
 - Combinatorial codes for signaling diversity
- Spatial regulation of signaling complexes
 - Temporal dynamics of cell signaling
- Discovering new signaling pathways
- Discovering ligands for orphan receptors
- Structural solutions to membrane receptors
- Mechanistic structural studies on signaling molecules
- Genetic approaches to hormone action
 - Hormone action and human disease
 - Rationale drug design

Additional Readings on Steroid Hormone Action

- Evans (1988) The steroid and thyroid hormone receptor superfamily. *Science* 240:889.
- Tsai and O'Malley (1994) Molecular mechanisms of action of steroid/thyroid receptor superfamily members. *Ann Rev Biochem* 63:451.
- Rosenfeld and Glass (2001) Coregulator codes of transcriptional regulation by nuclear receptors. *J Biol Chem* 276:36875.
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- Kumar and Thompson (1999) The structure of nuclear hormone receptors. *Steroids* 64:310.
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- Willson and Moore (2002) Genomics versus orphan nuclear receptors: a half-time report. *Mol Endocrinol* 16:1135.
- Yudit and Cidlowski (2002) The glucocorticoid receptor: coding a diversity of proteins and responses through a single gene. *Mol Endocrinol* 16:1719.
- Gellman (2002) Molecular biology of the androgen receptor. *J Clin Oncol* 20:3005.
- Conneely et al (2002) Reproductive functions of progesterone receptors. *Rec Prog Horm Res* 57:339.