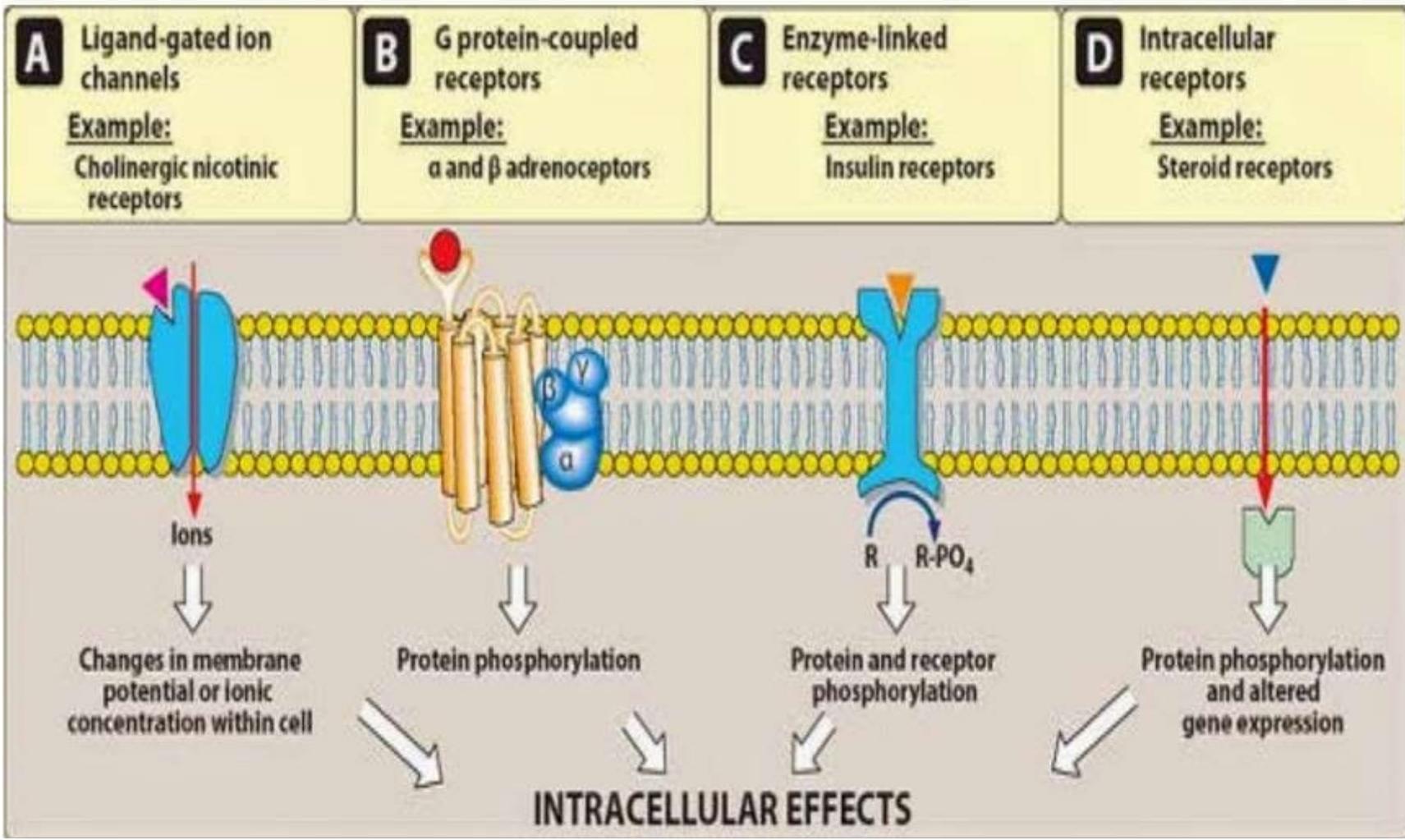


A DISCUSSION ON LIGAND RECEPTOR INTERACTION WITH CERTAIN EXAMPLE.



INTRODUCTION

- ✓ Interaction between a molecule (usually of an extracellular origin) and a protein on or within a target cell.
- ✓ One type of ligand-receptor interaction can be between steroid hormones and their cytoplasmic or nuclear receptors.
- ✓ Another can be between secreted polypeptide ligands and transmembrane receptors.



EXTRACELLULAR SIGNALLING

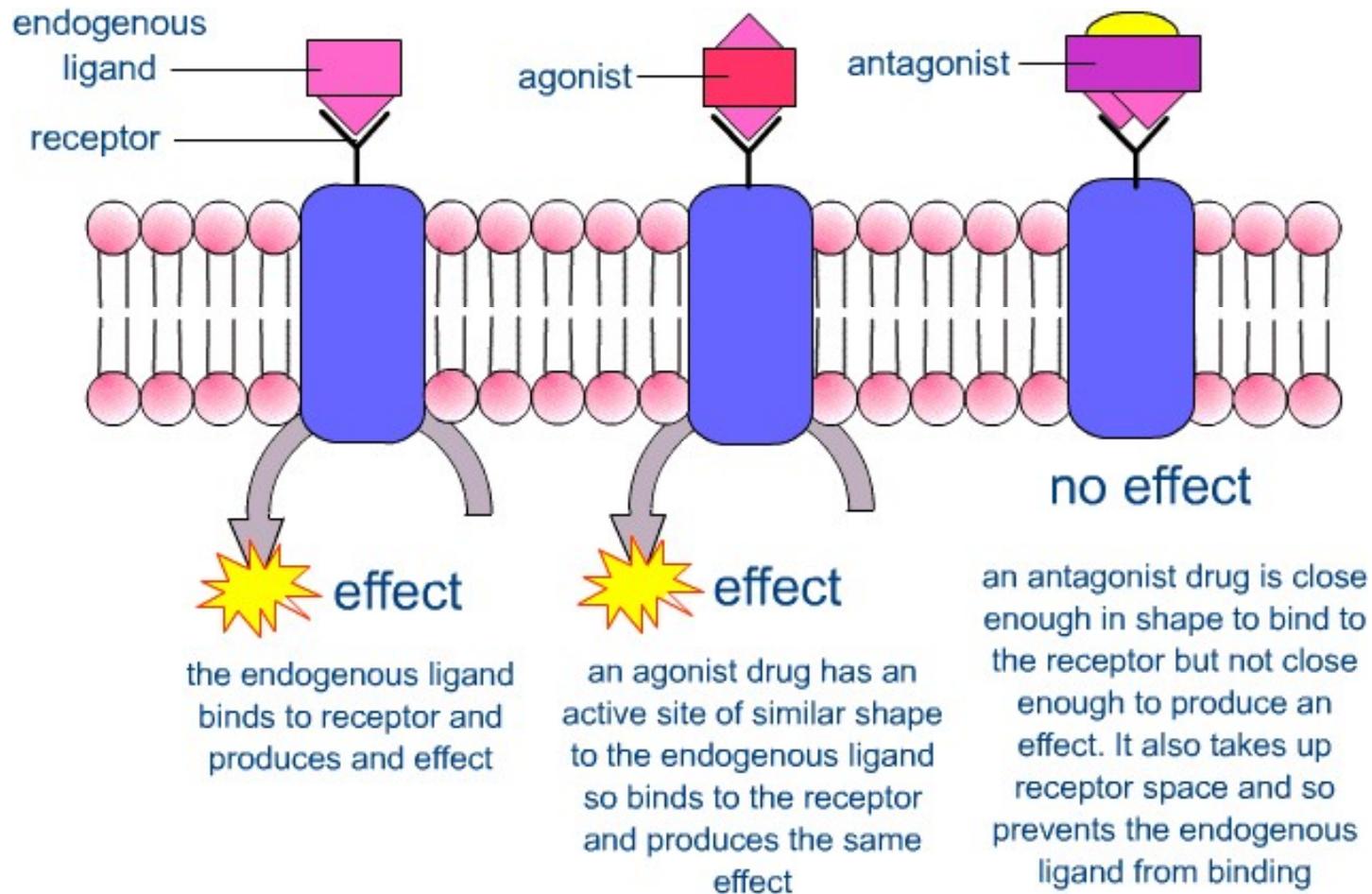
- ✓ Signaling molecules are released by **signaling cells**
- ✓ The signal is called the **ligand** , any molecule that is bound by a protein , from the Latin 'ligare' meaning 'to bind'.
- ✓ The ligand binds to its specific **receptor** on a **target cell**
- ✓ This ligand-receptor interaction induces a conformational or shape-change in the receptor
- ✓ Produces a specific response - called the cellular response
- ✓ Can include a vast array of compounds
 - ✓ e.g. small amino acid derivatives, small peptides, proteins

HISTORY

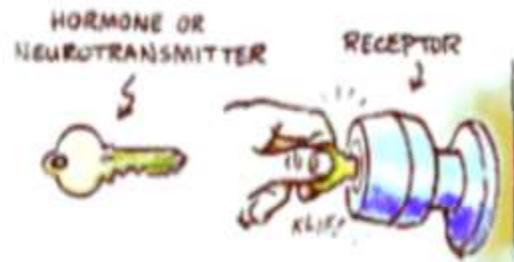
- ✓ Some of the signalling components inside the cell were described in molecular detail before the receptors were.
- ✓ These include the second messenger cyclic AMP (cAMP) and the enzyme adenylate cyclase . (Nobel Prize in Physiology or Medicine 1971 to Earl W. Sutherland)

- 
- The ability of a protein to bind to or interact with a ligand depends on the formation of weak, non-covalent bonds between them.
 - This process relies on the sequence of amino acids in each protein and the way in which their side chains (or **R groups**) interact with each other.
 - Different side chains can form different bonds. Because of this, protein interactions can be very specific.

Basics of agonist and antagonist



The Lock and Key Model of Ligand-Receptor Interaction



- a ligand such as a hormone or neurotransmitter (the "key") bind to specific receptors (the "lock")
- this binding "unlocks" the cell's response.



- many drugs work by mimicking a naturally occurring hormone or neurotransmitter
- if the drug causes the receptor to respond in the same way as the naturally occurring substance, then the drug is referred to as an **agonist**
- these are drugs that can "pick the lock".



- other drugs work in the opposite way - as **antagonists**.
- these drugs bind to the receptor, but do not produce a response.
- because the drug prevents the receptor from binding to the normal hormone or neurotransmitter, it has an inhibitory effect on the naturally occurring substance.

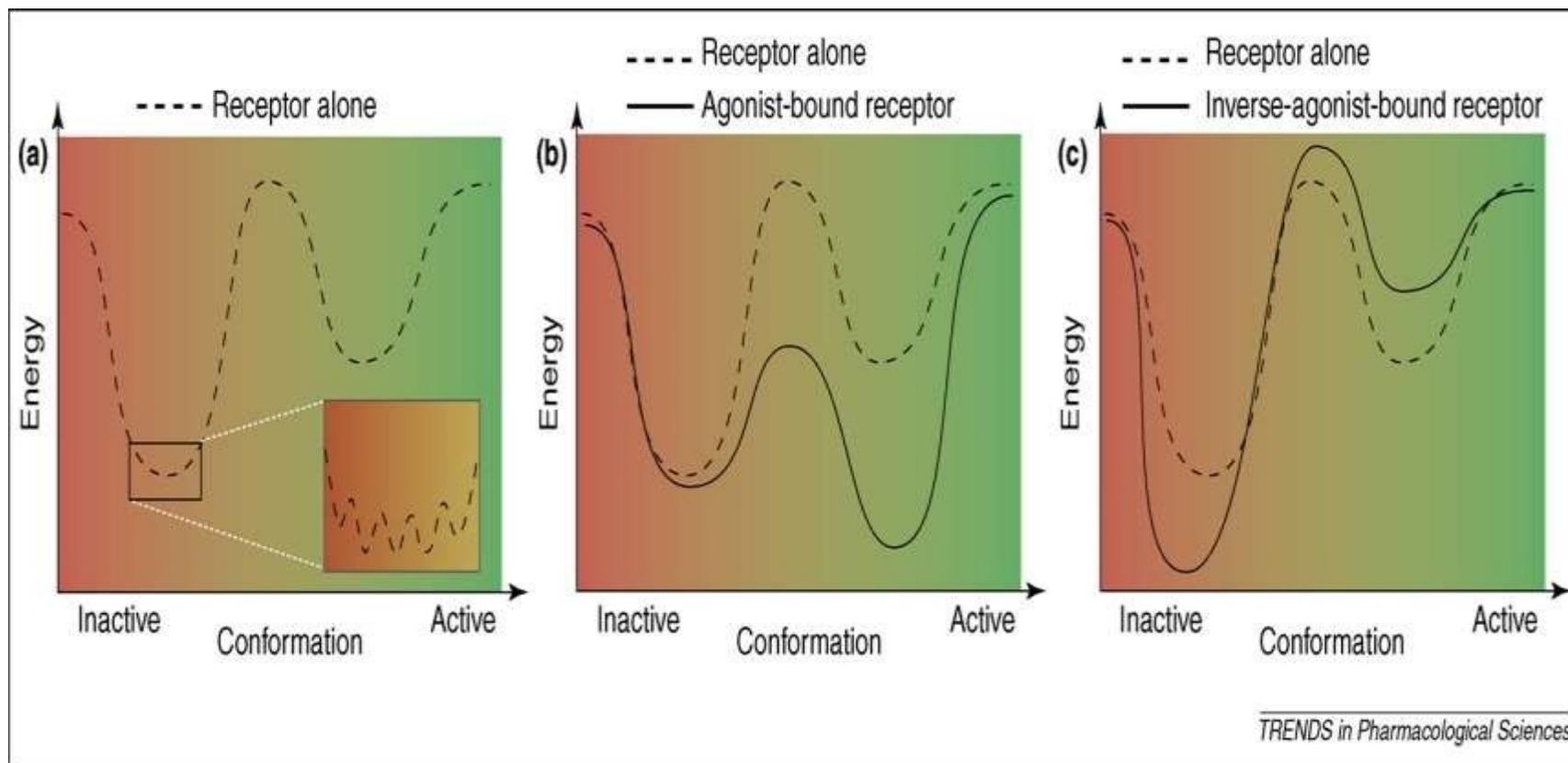
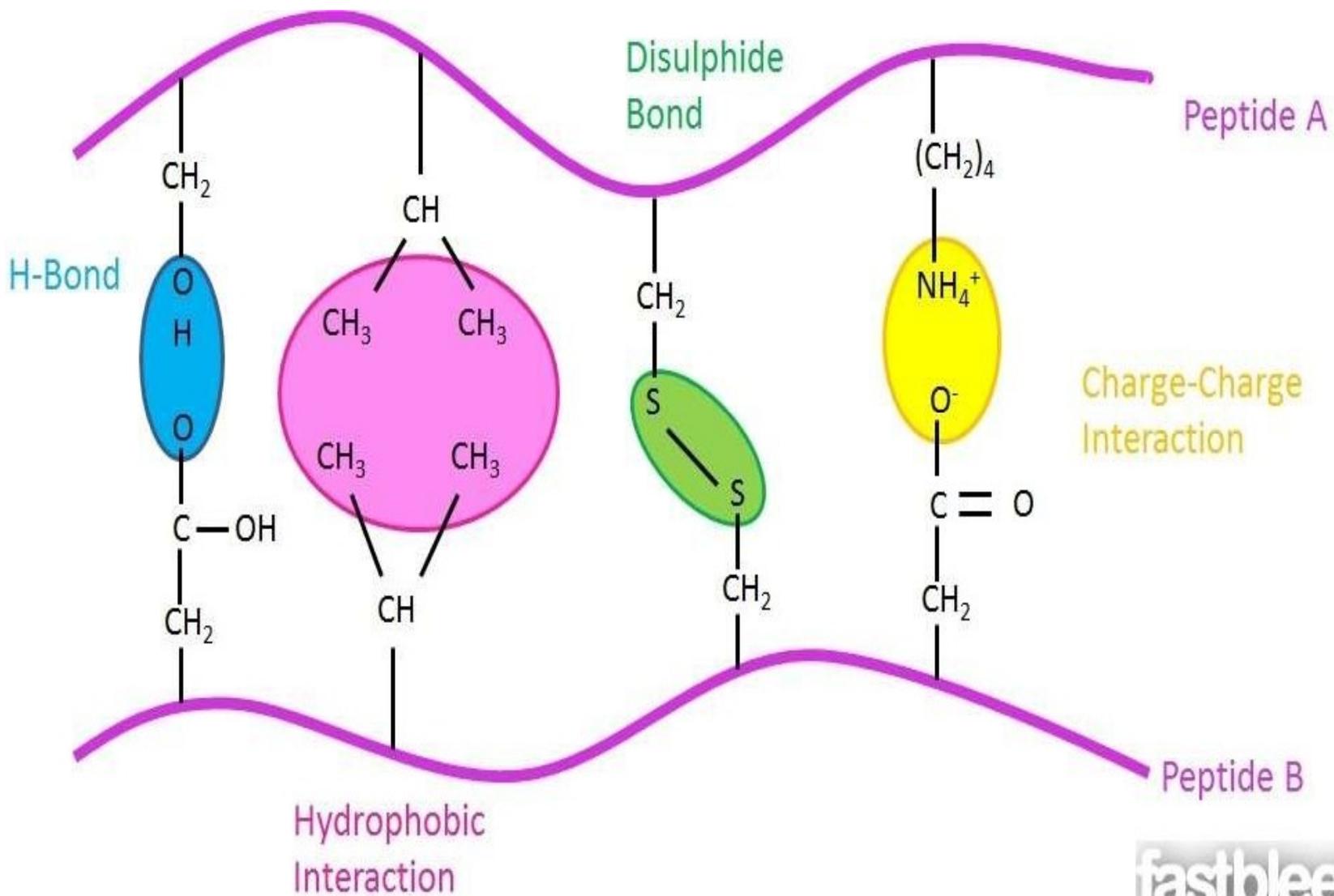


Figure 1. Theoretical energy landscape of a GPCR. (a) Conformational states of an unbound GPCR. (b) Binding of an agonist or partial agonist lowers the energy barrier and/or reduces the energy of the more active conformation relative to the inactive conformation. (c) Binding of an inverse agonist increases the energy barrier and/or reduces the energy of the inactive state conformation relative to the active conformation

Types of chemical interaction between ligand and receptor

1. Covalent interaction-Form when two different atoms share electrons in the outer atomic orbitals Irreversible interaction
2. Non-covalent interaction-
 - Ionic (Electrostatic) bonds
 - Hydrogen bonds
 - Vander Waals interaction



Oestrogen Receptor Interaction

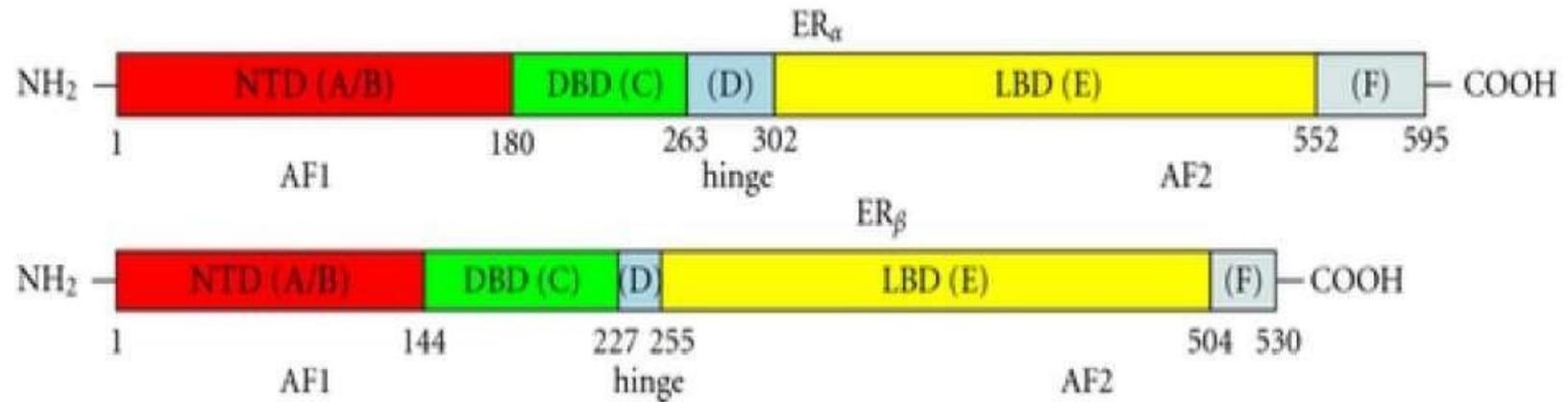
- Oestrogens are involved in the growth, development and homeostasis of a number of tissues
- The physiological effects of these steroids are mediated by a ligand-inducible nuclear transcription factor, the oestrogen receptor (ER)²
- Hormone binding to the ligand-binding domain (LBD) of the ER initiates a series of molecular events culminating in the activation or repression of target genes.
- 17 β -estradiol (E₂) -Natural oestrogen.

MOLECULAR STRUCTURE OF SHR

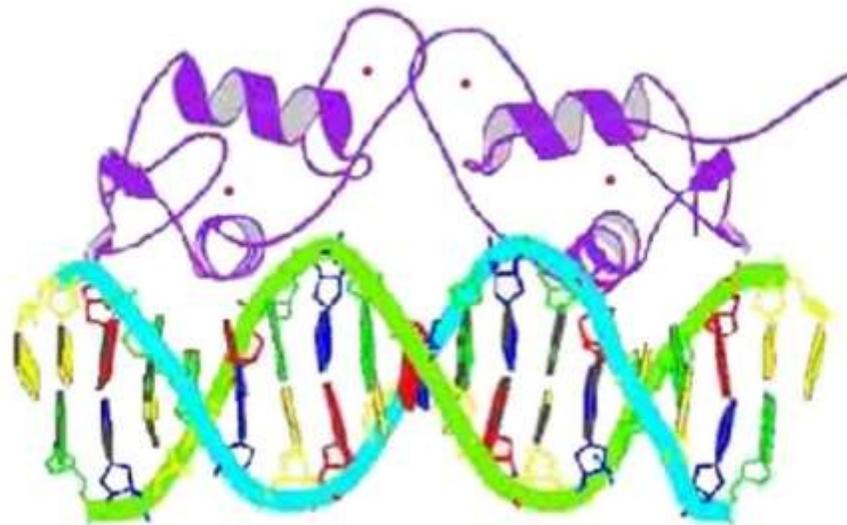
- The molecular structure of SHR shows presence of five distinct regions :
- Two end terminals – N terminal & C terminal.
- A hinge region
- Two domains – DNA binding domain & Ligand binding domain.



DIAGRAMMATIC REPRESENTATION OF STRUCTURE OF SHR



DBD + ERE



Estrogen receptors are a group of proteins found inside cells. They are receptors that are activated by the hormone estrogen (17 β -estradiol).

- ER α and ER β have six domains named A–F from N- to C-terminus, encoded by 8–9 exons .

- **The functional domains of the ER are:**

N-terminus (domains A and B)

modulates transcription in a gene- and cell-specific manner through Activation Function-1 (AF-1)

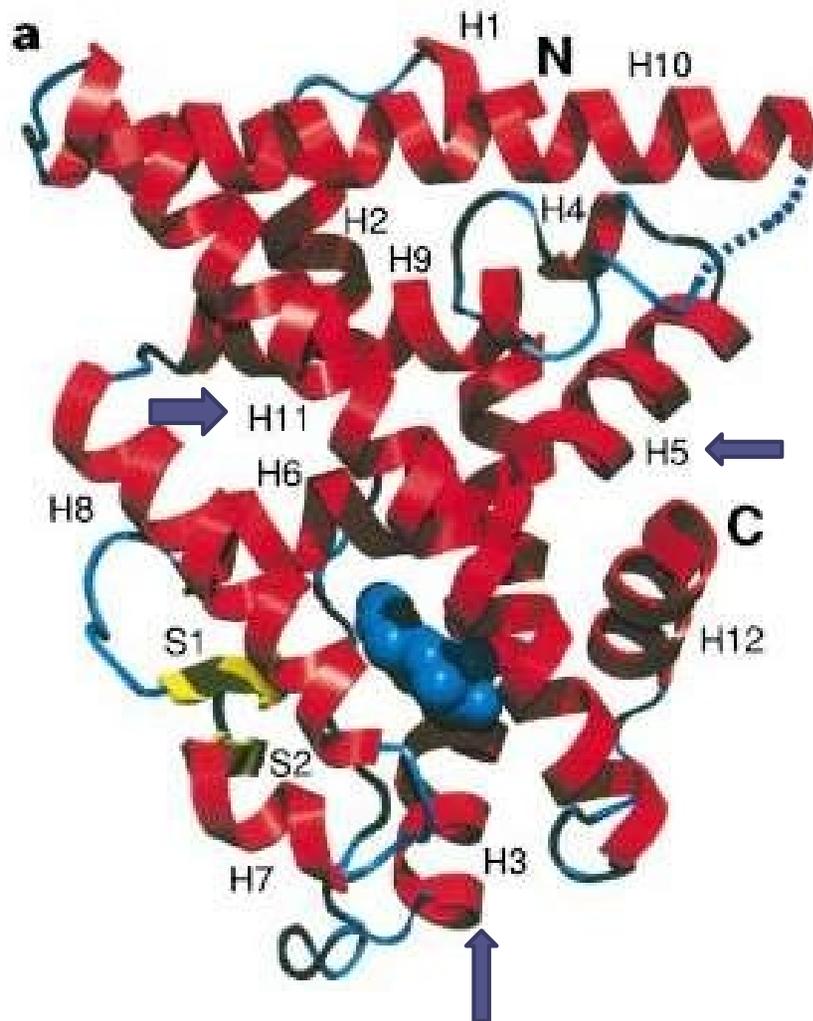
Hinge region (“D” domain)

contains nuclear localization signal which gets unmasked upon ligand, binding serves as a flexible region connecting DBD and LBD, Hinge regions of ER and ER share only 36% homology .

.

C-terminus (F Domain)

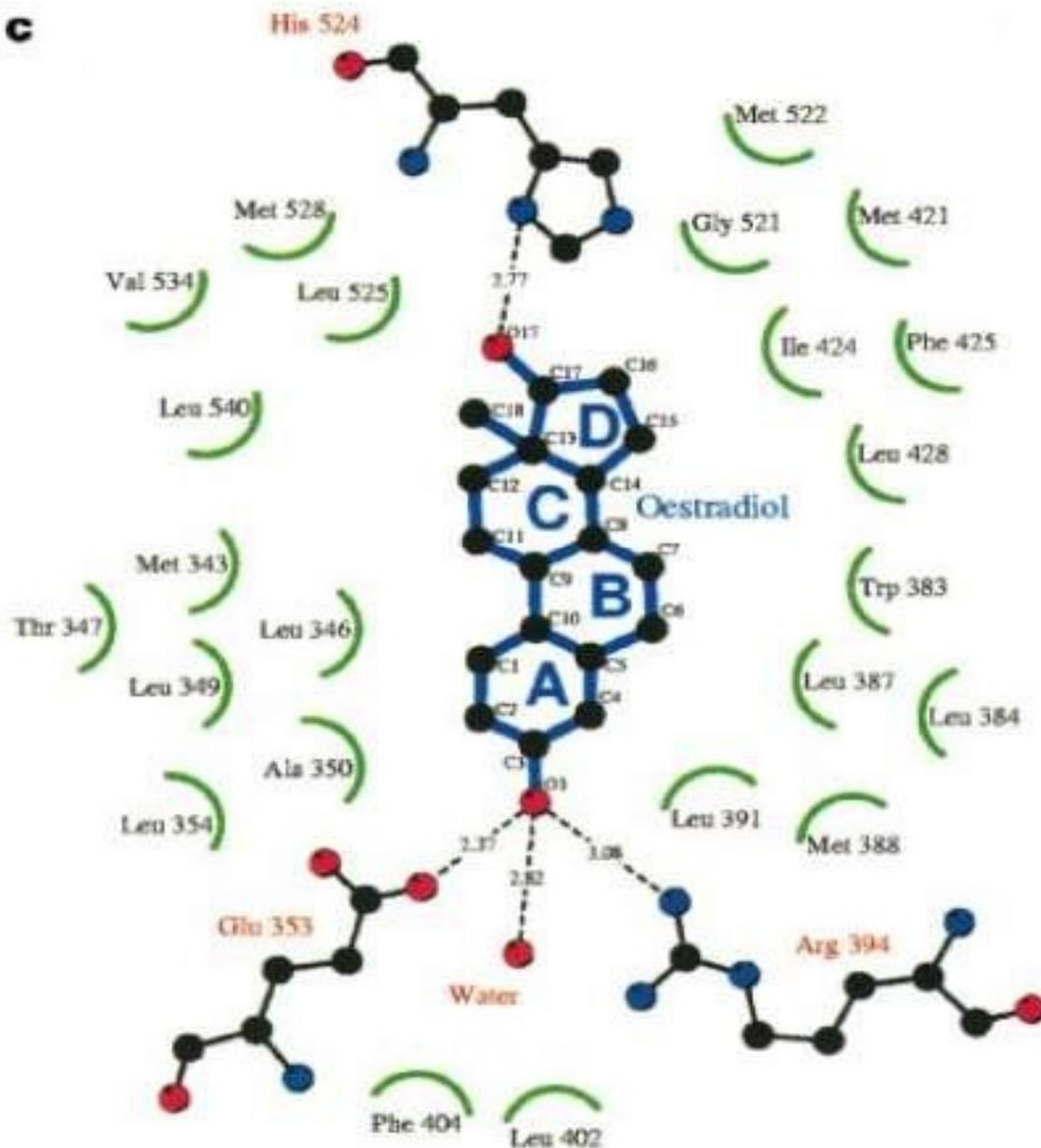
- ✓ In ER α , the F domain plays a role in distinguishing estrogen agonists versus antagonists
- ✓ Contains 42 amino acids
- ✓ The “F” domain was found to modulate gene transcription in a ligand specific manner.
- ✓ It is also known to impact receptor dimerization



✓The **ER LBD (E domain)** structure contains 11 helices (H1–H12)

✓The first crystal structure of an ER LBD bound to its natural ligand 17β -estradiol (E2) showed that in a compact ellipsoid cavity, E2 is buried in a highly **hydrophobic environment** .

✓The hydroxyl groups of the A and D rings are **hydrogen bonded** to Glu353 from H3, Arg394 from H5, and a water molecule and His524 from H11

C

Hydrophobic core is formed by parts of H3 (Met 342 to Leu 354), H6 (Trp 383 to Arg 394), H8 and the preceding loop (Val 418 to Leu 428), H11 (Met 517 to Met 528), H12 (Leu 539 to His 547) and the S1/S2 hairpin (Leu 402 to Leu 410).



- **ER DBD (C Domain)**

- ✓ A highly conserved ,

- ✓ Comprised of two functionally distinct zinc fingers through which ER interacts directly with the DNA helix; and

- ✓ ER DNA binding domain usually binds to the estrogen response element (ERE) composed of a palindromic hexanucleotide
5'AGGTCAnnnTGACCT3

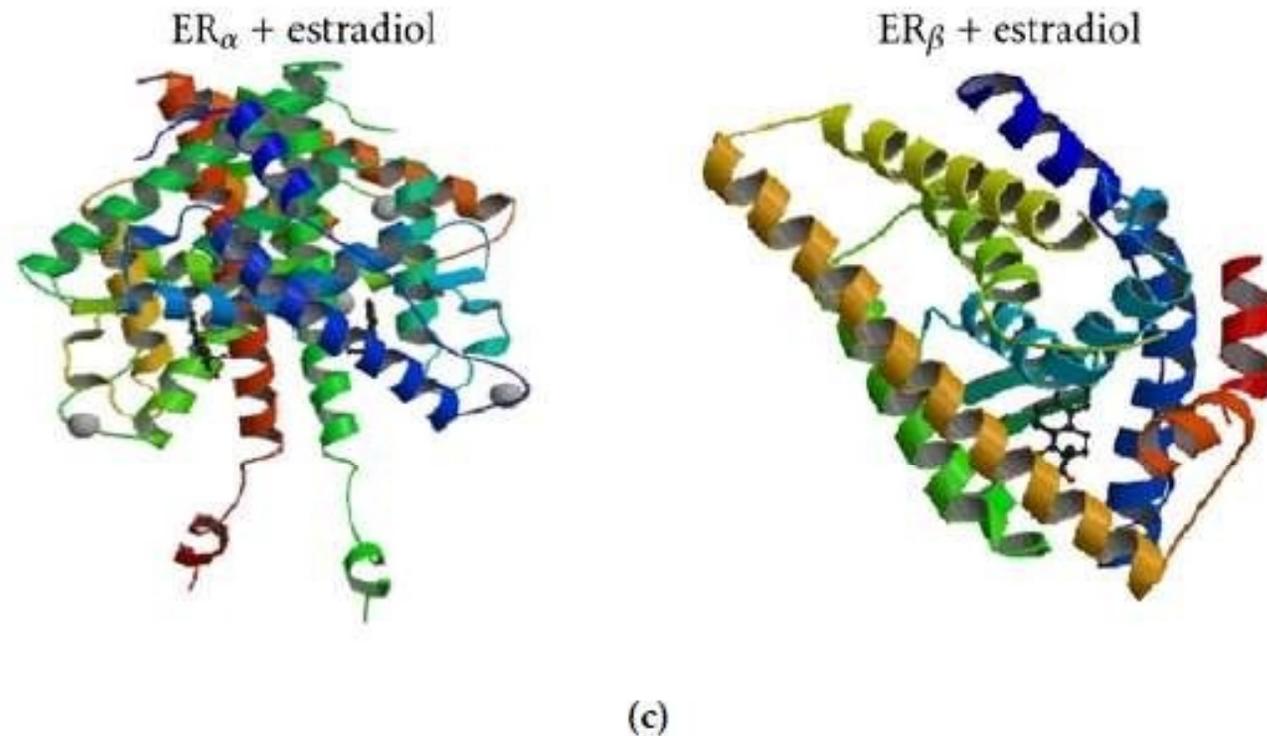
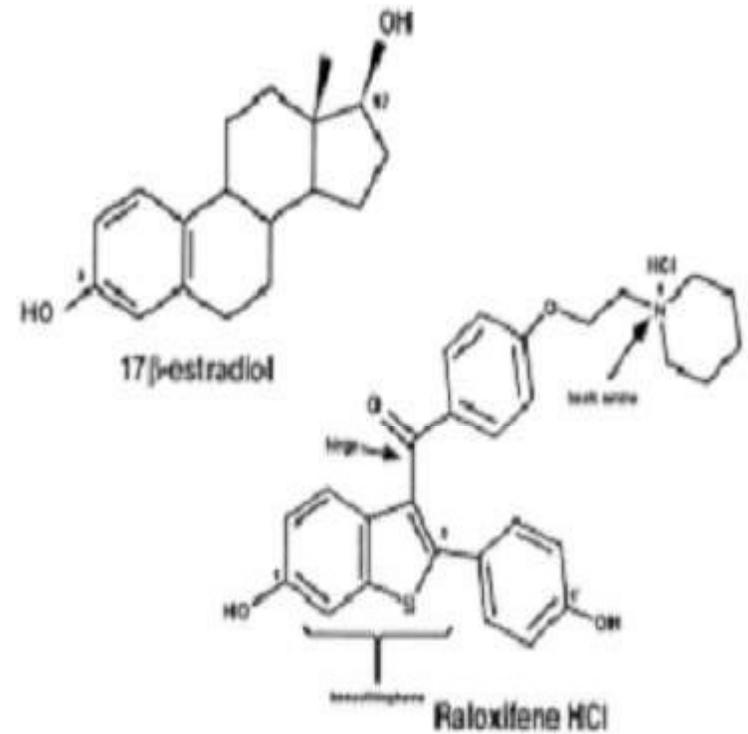
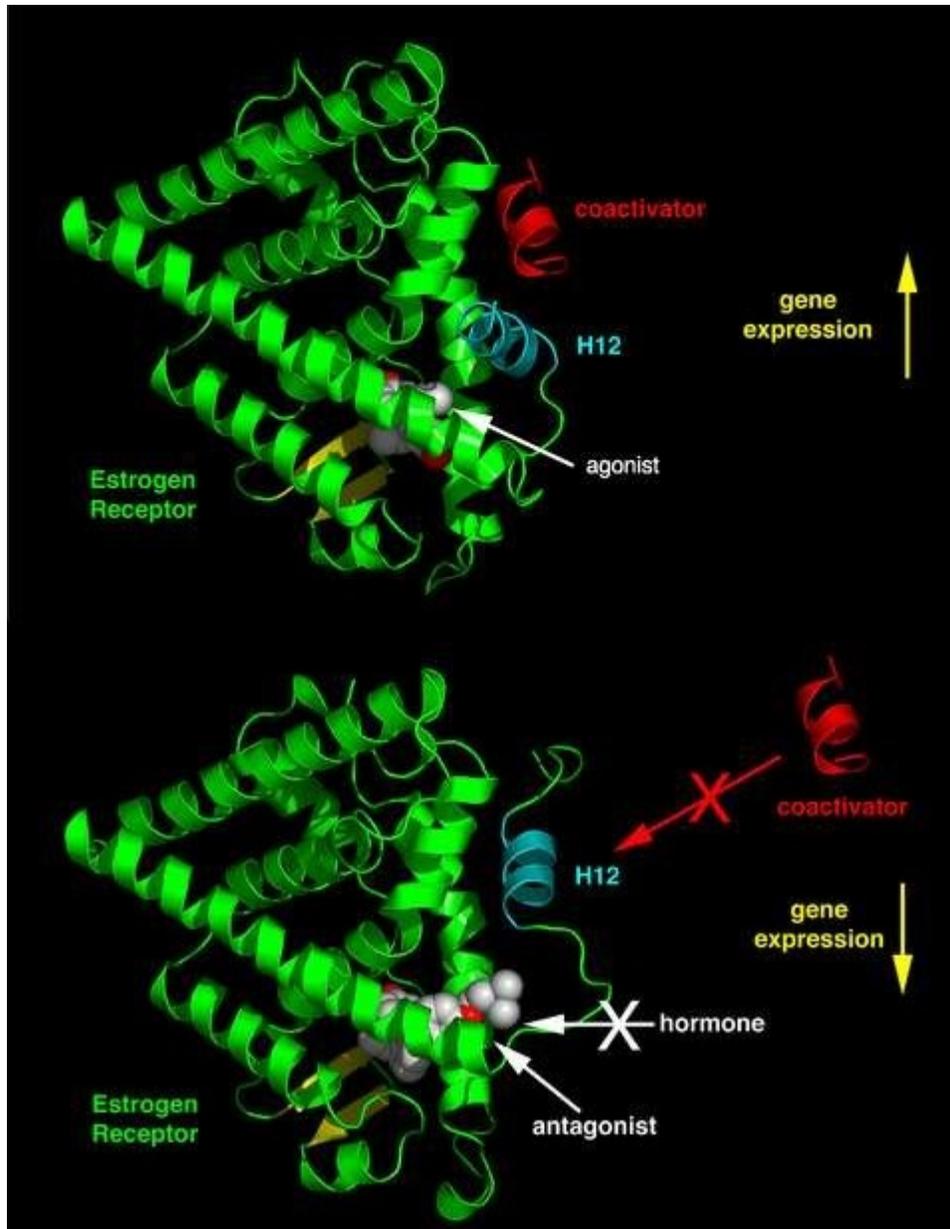
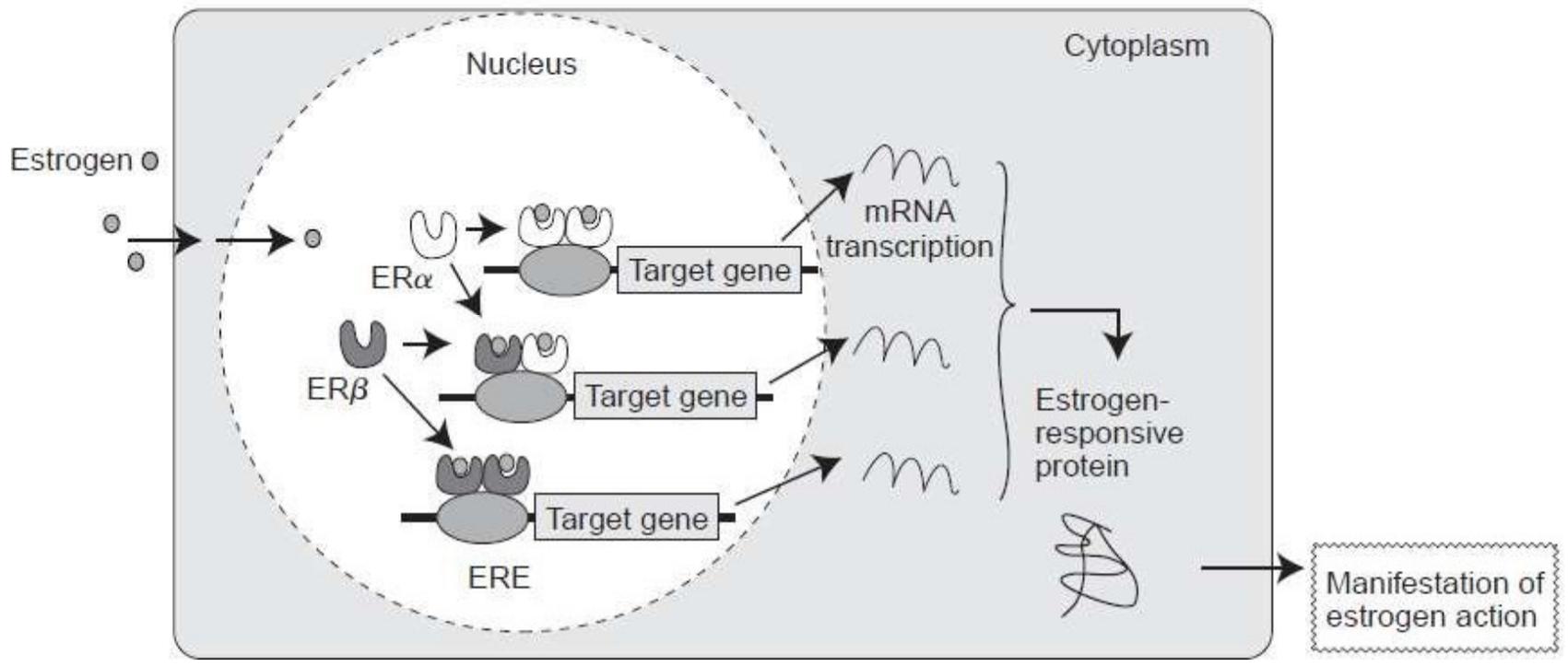


Figure 1: (a) shows the sequence organization of the two isoforms of estrogen receptors, ER_{α} and ER_{β} . Different domains are highlighted in different colors: NTD—amino terminal domain—in red; DBD—DNA binding domain—in green; hinge region—in blue; LBD—ligand-binding domain—in yellow; F region located towards the C-terminal end—in grey. Amino acid sequence position is given for each domain. (b) shows estrogen receptor DBD in complex with DNA-ERE (estrogen response element). Structure 1HCQ from PDB (protein databank) [13]. (c) shows 3-dimensional structures of ER_{α} (left) and ER_{β} (right) bound to estradiol (PDB structures 1A52





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THANK YOU !!