

Glucocorticoid Receptor, Anti-Inflammation

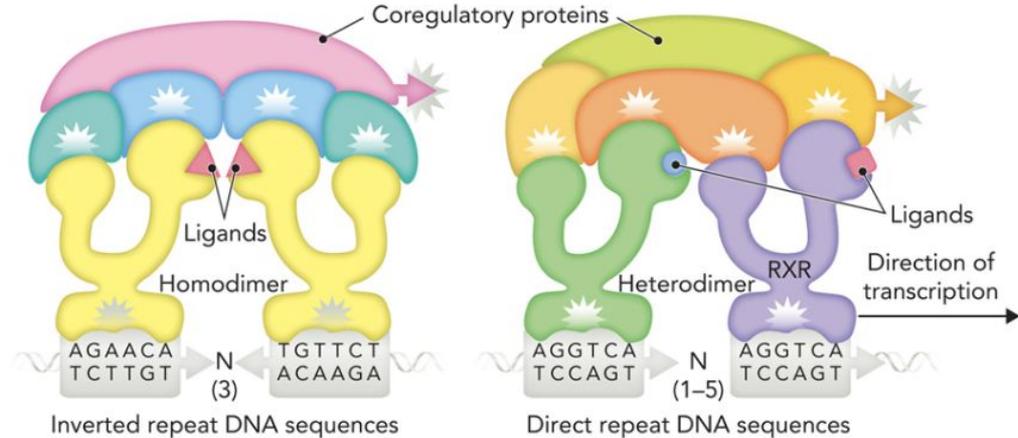
By: Cristina Flores and Johanne Amaya

Nuclear Receptors (A.K.A Intracellular Receptors)

- Receptor signaling protein
 - Receptors are not membrane bound.
- Function as transcription factors that regulate gene expression in response to ligand binding

Nuclear Receptors (continued...)

- The glucocorticoid receptor is a steroid receptor.
- Steroid receptors are head-to-head homodimers, enabling them to bind to inverted repeat DNA sequences
 - **Homodimer:** A protein composed of two polypeptide chains that are identical in the order, number, and kind of their amino acid residues
- The ligands for steroid receptors are physiologic hormones derived from cholesterol



Steroid Receptors
Glucocorticoid receptor
Estrogen receptor
Androgen receptor
Progesterone receptor
Aldosterone receptor

Metabolite Receptors
Retinoid X receptor (RXR)
Vitamin D receptor
Retinoic acid receptor
Thyroid hormone receptor
Peroxisome proliferator-activated receptor

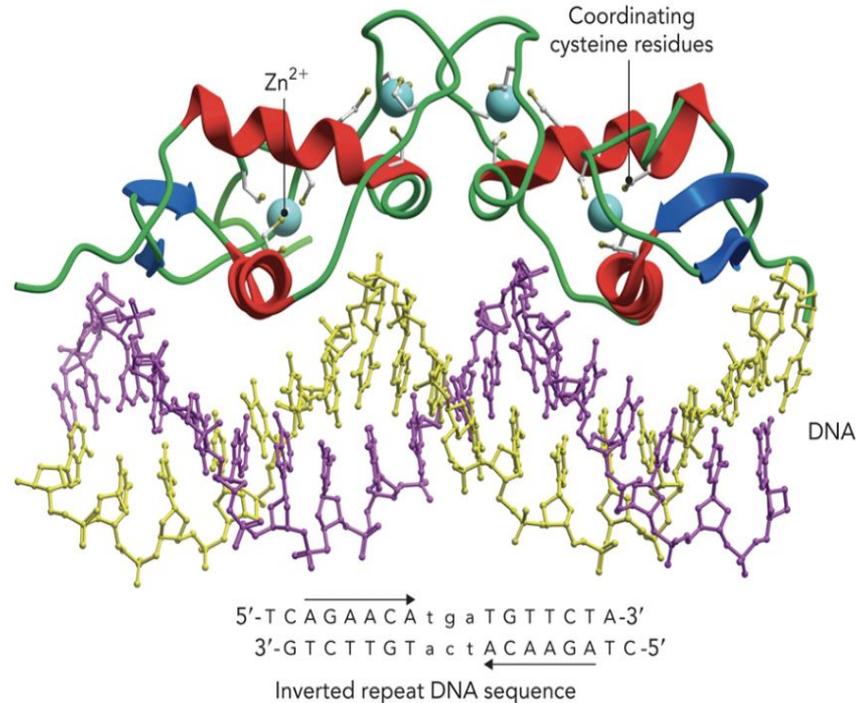
Glucocorticoid Receptor Induces an Anti-Inflammatory Response

Background information:

1. It is required for
 - a. Lung development
 - b. Carbohydrate metabolism in the liver
 - c. Modulation of the inflammatory response
 - d. Neuronal signaling in the brain
2. Glucocorticoids are steroid hormones that are synthesized in the adrenal glands and bind to the glucocorticoid receptor.

Molecular Structure of GR DNA-binding domain

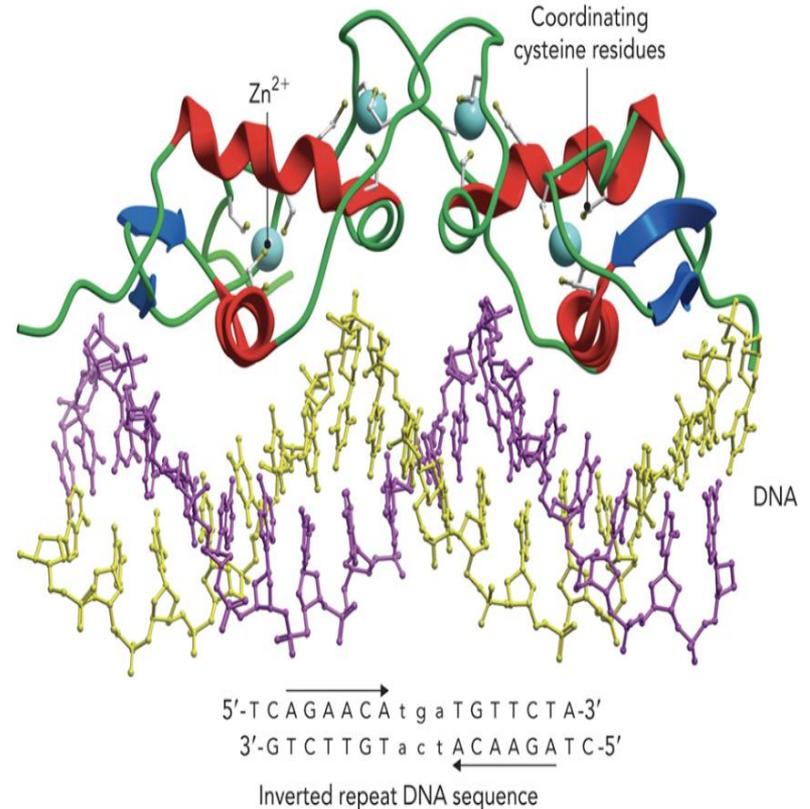
- α -helical amino acids interacting with major groove nucleotides
- Pair of zinc atoms on top of the dimer that stabilizes the protein dimer interface
- Pair of zinc atoms in the middle that stabilize the α -helical region by optimizing amino acid contact with the DNA



- Notice this:

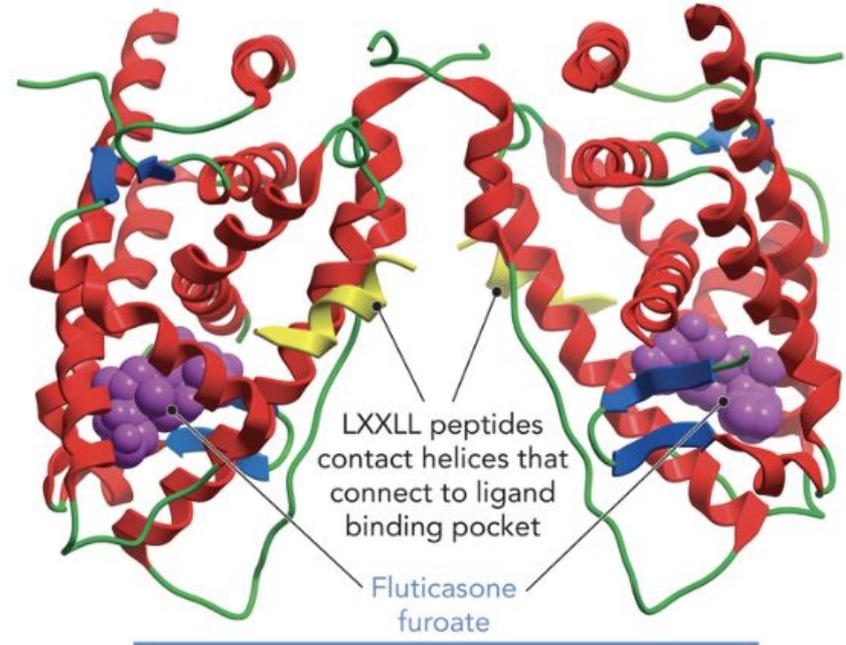
The orientation of the zinc finger α -helices relative to the repeat DNA sequences

- The inverted repeat sequence must be at least partially palindromic to be recognized by a homodimer that binds in a head-to-head configuration
 - **Palindrome:** Same sequence of characters when read in either direction
 - Ex. madam, racecar
- GR DNA-binding domain interacts with a DNA region that contains the sequence
5'-AGAACA t g a T G T T C T A-3'
 - **Palindromic portion in uppercase letters**



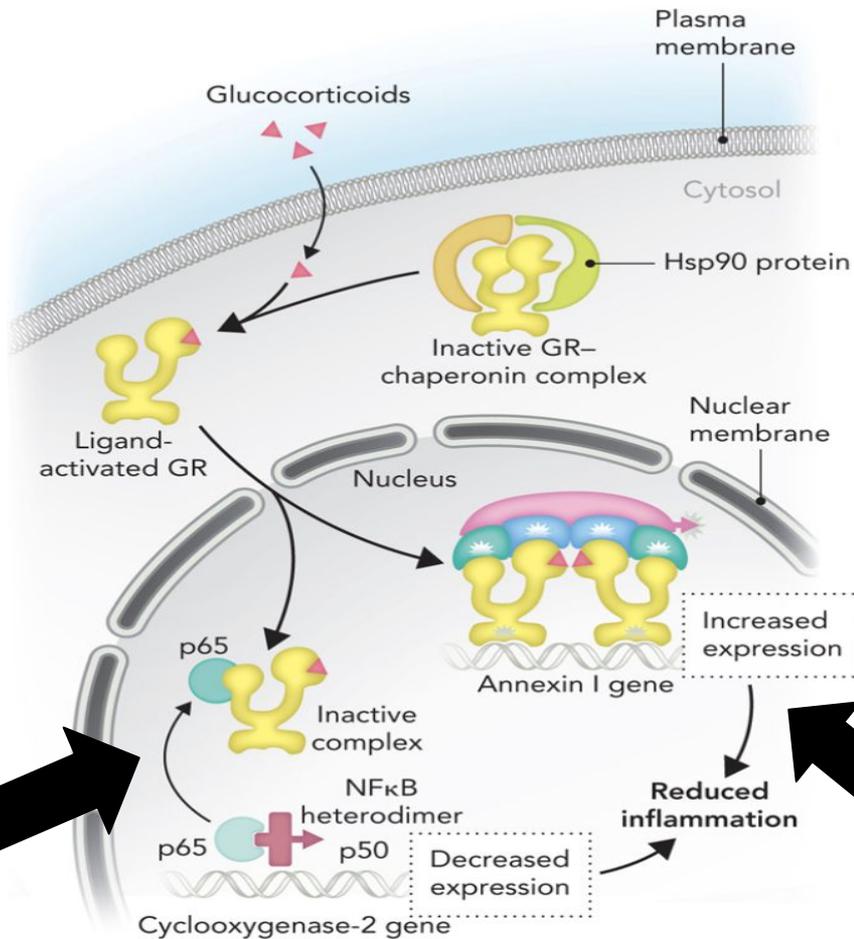
- **Fluticasone furoate:**
 - Asthma drug derivative**
- **Coregulatory binding site is on the surface of the GR ligand-binding domain**
 - **Is in direct contact with two α helices that extend into hydrophobic pockets**
- **Fluticasone:**
 - **Potent anti-inflammatory drug**
 - **Higher affinity for GR than physiologic glucocorticoid cortisol**
 - **Making it highly effective for clinical use**

Homodimer of GR ligand-binding domain in a complex with synthetic anti-inflammatory corticosteroid fluticasone furoate and an LXXLL motif-containing peptide



How do pharmaceutical glucocorticoids function as anti-inflammatory drugs?

- By directly or indirectly regulating the expression of genes encoding proteins that regulate the inflammatory response.



Indirectly

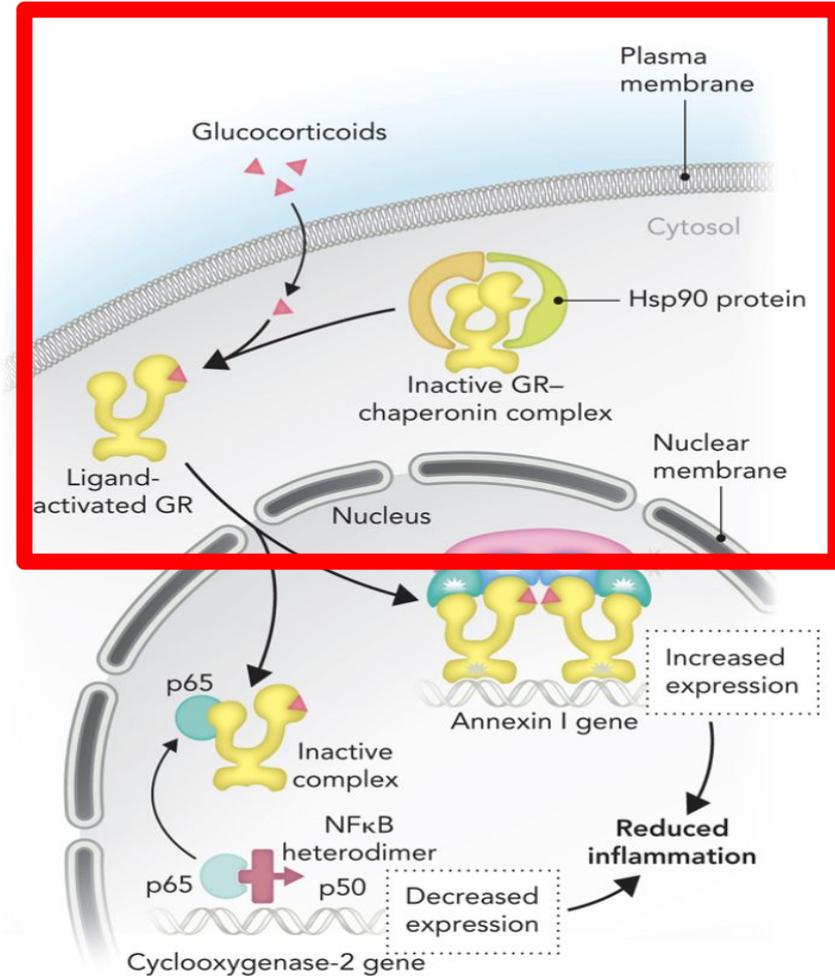


Directly

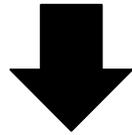
Useful Abbreviations, Protein Names, and Their Functions in Nuclear Signal Transduction Systems

Abbreviation	Protein Name	Function
GR	Glucocorticoid Receptor	Nuclear receptor that binds steroid hormones
GRE	Glucocorticoid Response Element	DNA sequence where glucocorticoid receptors bind
Hsp90	Heat shock protein 90	Chaperonin protein that assist protein folding

1. **Glucocorticoids cross the plasma membrane and bind to the unliganded GR protein. The unliganded GR protein resides in the cytoplasm.**
 - a. **The unliganded GR protein forms part of a large inactive complex containing chaperonin proteins.**
 - b. **Hsp90 (heat shock protein 90) is one of the most abundant chaperonin proteins in cells.**
2. **Ligand binding to GR results in disassembly of the GR-chaperonin protein complex**
3. **Translocation of GR into the nucleus.**

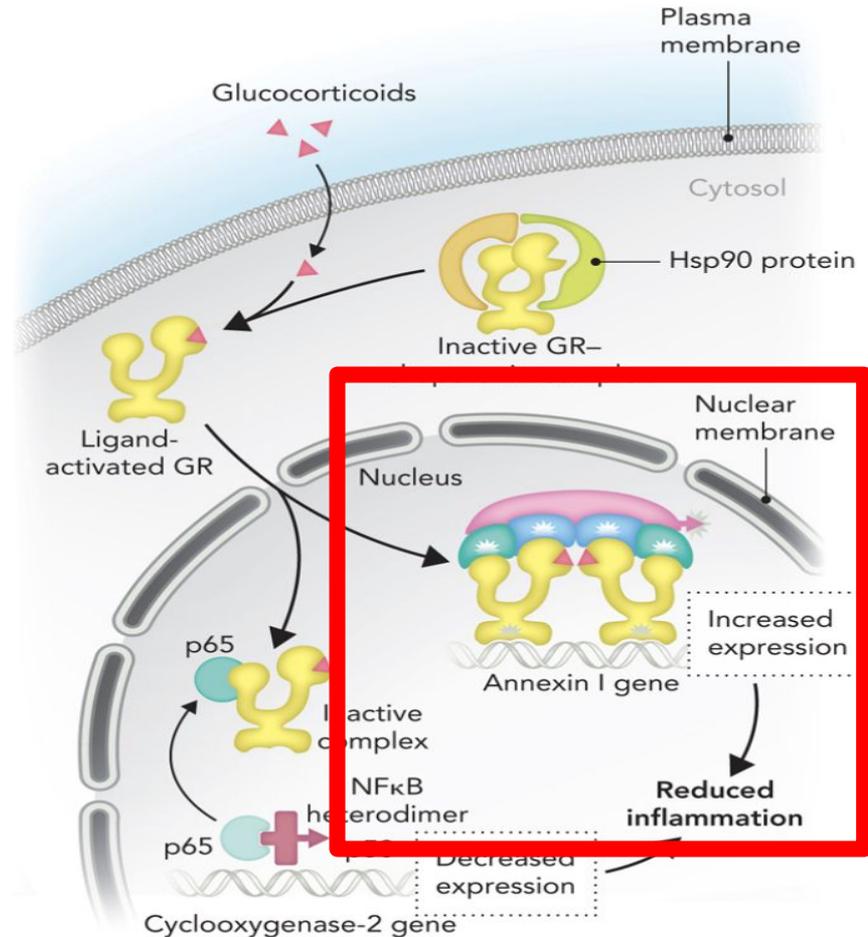


- In the nucleus: Ligand-activated GR homodimers bind to DNA sequences called glucocorticoid response elements (GREs) in the regulatory region of the Annexin I gene.
- GR directly induces the expression of Annexin I
 - Annexin I gene: Anti-inflammatory protein that functions to inhibit prostaglandin synthesis
 - Prostaglandins are pro-inflammatory molecules.

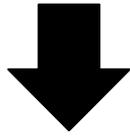


Net Result:

Reduced Inflammation!



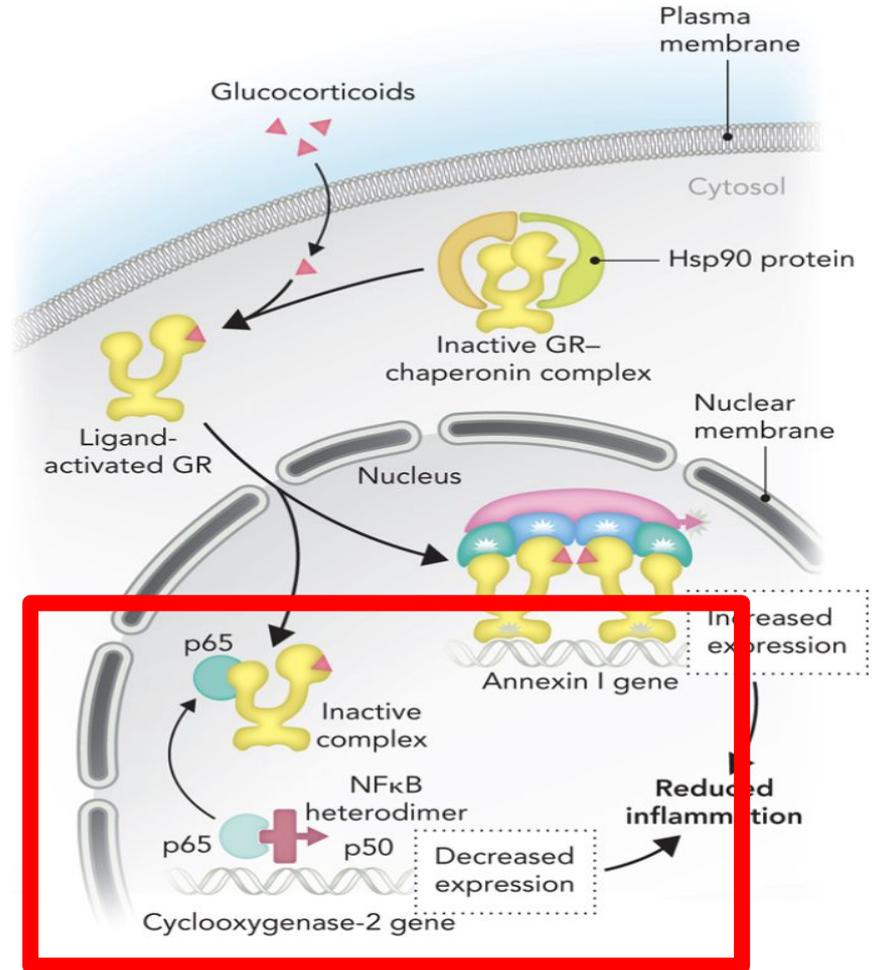
- In the nucleus: Ligand-activated GR binds to the P65 subunit of NF_κB heterodimer.
- GR sequesters the P65 subunit away from the cyclooxygenase-2 gene promoter (NF_κB)
- This blocks the transcription regulatory functions of NF_κB through protein-protein interactions, leading to reduced expression of cyclooxygenase-2
 - Cyclooxygenase-2: Pro-inflammatory gene



Net Result:

Reduced Inflammation!

- ** Studies show that monomers of ligand activated GR, rather than homodimers, bind to the P65 subunit of NF_κB



References

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