

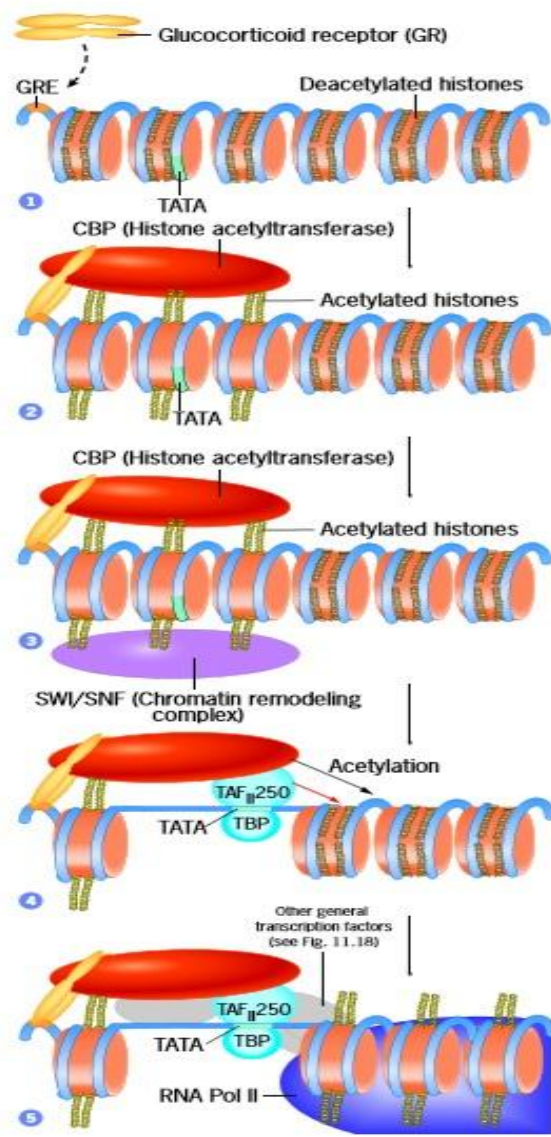
Mechanism of Action of GR and GRE in Gene Expression

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- The complexity inherent in the control of gene
 - expression can be illustrated by examining the
 - DNA in and around a single gene.
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- The level of synthesis of mRNA from a gene is
 - controlled by a variety of different transcription
 - factors.

- Transcription factors, such as the glucocorticoid receptor (GR), bind to the DNA and recruit coactivators, which facilitate the assembly of the transcription preinitiation complex.
- The twofold nature of a GRE is important because pairs of GR polypeptides bind to the DNA as dimers in which each subunit of the dimer binds to one-half of the DNA sequence.

- Step 1 of the figure shown in the
- next slide depicts a region of a
- chromosome that is in a repressed
- state because of the association of its
- DNA with deacetylated histones.



In step 2, the GR is bound to the GRE, and the coactivator CBP has been recruited. CBP contains a subunit that has histone acetyltransferase (HAT) activity. These enzymes transfer acetyl groups from an acetyl CoA donor to the amino groups of specific lysine residues on histone proteins. As a result, histones of the nucleosome core particles in the regions both upstream and downstream from the TATA box become acetylated.

In step 3, the acetylated histones recruit SWI/SNF, which is a chromatin remodeling complex. Together, the two coactivators CBP and SWI/SNF change the structure of the chromatin to a more open, accessible state.

- In step 4, TFIID binds to the open region of the
- DNA. One of the subunits of TFIID (called
- TAFII250 or TAF1) also possesses histone
- acetyltransferase activity as indicated by the
- red arrow. Together, CBP and TAFII250 modify
- additional nucleosomes to allow transcription
- initiation.

- In step 5, the remaining nucleosomes
- of the promoter have been acetylated,
- RNA polymerase II is bound to the
- promoter, and transcription is set to begin.

The keys to understanding the regulation of gene expression lie in :

- Unraveling the functions of the numerous DNA regulatory sequences that reside upstream from the gene.
- Identifying the transcription factors that bind these sequences.
- Elucidating the signaling pathways that activate the machinery responsible for selective gene expression.

- Secretion of glucocorticoids is highest during
- periods of stress

- For a cell to respond to glucocorticoids, it must
- possess a specific *glucocorticoid receptor (GR)*
- capable of binding the hormone.

- When a glucocorticoid hormone enters a
- target cell, it binds to a glucocorticoid
- receptor protein in the cytosol, changing
- the conformation of the protein.

- Conformation change exposes a nuclear
- localization signal of the receptor which
- facilitates its translocation into the nucleus.
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- The ligand-bound receptor binds to a specific
- DNA sequence, called a *glucocorticoid response*
- *element (GRE)*.

• THANK YOU