Hormonal Regulation of Gene Expression

- describe the key elements present in the region of a gene involved in gene transcription
- define promoters, response elements, transcription factors and co-activators
- explain how a hydrophobic hormone receptor is a transcription factor
- describe the basic organisation of a steroid receptor molecule
- describe how hydrophobic hormones regulate gene expression

Types of Hormones and Their Actions:

1. **Hydrophilic Hormones**:
   - Cannot pass through the plasma membrane.
   - Bind to cell surface receptors and exert their effects via second messengers.
2. **Hydrophobic Hormones**:
   - Lipophilic hormones, such as steroid hormones, can diffuse through the cell membrane.
   - Bind to intracellular receptors, which then act as transcription factors.

Nuclear Receptor Superfamily:

1. Nuclear receptors are highly conserved proteins, particularly in their DNA-binding and ligand-binding domains.
2. There are three receptor families:
   - **Family I**: Non-steroid receptors (e.g., thyroid and vitamin D receptors) that bind to tandem repeat response elements as heterodimers with RXR.
   - **Family II**: Orphan receptors that often lack known ligands, with RXR as the exception.
   - **Family III**: Classic steroid hormone receptors (e.g., glucocorticoid, androgen, and oestrogen receptors) that bind to palindromic response elements as homodimers.

Hormone Response Elements (HREs):

- HREs are specific DNA sequences that interact with hormone-receptor complexes to regulate transcription.
- Examples:
  - Oestrogen response element: 5′-GGTCA...TGACC-3′
  - Glucocorticoid response element: 5′-AGAACA...TGTTCT-3′
- A gene can have multiple HREs, allowing complex regulation of transcription.

Regulation Through RXR Heterodimers:

1. **Heterodimer Activation**: RXR can pair with various receptors (e.g., thyroid hormone receptor, peroxisome proliferator-activated receptors) to form heterodimers.
2. **Permissive vs. Non-permissive Heterodimers**:
   - Permissive heterodimers are activated by ligands of RXR or its partner receptor.
   - Non-permissive heterodimers respond only to the partner receptor's ligand.

Selective Estrogen Receptor Modulators (SERMs):

1. SERMs (e.g., tamoxifen, raloxifene) selectively block or activate oestrogen receptors in different tissues.
2. Example: Tamoxifen blocks oestrogen in breast tissue but can activate it in bones and the uterus, making it highly targeted.

Therapeutic Potential of Nuclear Receptors:

1. Nuclear receptors have significant therapeutic applications due to their roles in transcriptional regulation and cell signaling.
2. Targeted modulation (e.g., rexinoids for RXR heterodimers or SERMs) offers promising treatment options for various diseases, including cancers, metabolic disorders, and inflammation.

Cellular Localization of Nuclear Receptors:

1. Most nuclear receptors are synthesized in the cytoplasm and require a nuclear localization signal (NLS) to translocate to the nucleus.
2. Some receptors, such as glucocorticoid receptors, require hormone binding to expose their NLS, allowing nuclear import.
3. A small fraction (~5%) of steroid receptors are localized to the plasma membrane, where they mediate rapid non-genomic signaling.

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Key Elements of a Gene Involved in Transcription:

1. **Promoters**: Specific DNA sequences that serve as binding sites for transcription machinery, initiating transcription.
2. **Hormone Response Elements (HREs)**: DNA sequences that specific hormone-receptor complexes bind to, regulating transcription. They often consist of inverted repeats separated by a few nucleotides.
3. **Transcription Factors**: Proteins that bind to promoters or response elements to regulate gene expression.
4. **Co-activators**: Proteins that enhance transcription by interacting with transcription factors and modifying chromatin to make it accessible.

Definitions:

1. **Promoters**: DNA regions upstream of genes where RNA polymerase and transcription factors assemble.
2. **Response Elements**: Specific DNA sequences (e.g., HREs) that bind transcription factors or hormone-receptor complexes to control transcription.
3. **Transcription Factors**: Proteins that regulate transcription by binding to DNA at promoters or response elements.
4. **Co-activators**: Proteins that interact with transcription factors to enhance gene transcription, often by altering chromatin structure.

Hydrophobic Hormone Receptors as Transcription Factors:

- Hydrophobic hormones (e.g., steroid hormones) diffuse across cell membranes and bind to intracellular receptors.
- These hormone-receptor complexes function as transcription factors by binding to HREs in the DNA and modulating transcription.

Basic Organisation of a Steroid Receptor Molecule:

1. **DNA-Binding Domain (DBD)**: Contains zinc fingers that bind to specific DNA sequences (HREs).
2. **Ligand-Binding Domain (LBD)**: Binds hormones and facilitates receptor dimerisation. It also interacts with coactivators and corepressors.
3. **Activation Functions (AF-1 and AF-2)**:
    1. AF-1 (ligand-independent) is located in the N-terminal region.
    2. AF-2 (ligand-dependent) is in the LBD and activates transcription when the ligand is bound.
4. **Nuclear Localisation Signal (NLS)**: Directs the receptor to the nucleus.
5. **Flexible Hinge Region**: Connects the DBD and LBD, aiding in nuclear localisation and receptor flexibility.

Regulation of Gene Expression by Hydrophobic Hormones:

1. **Hormone Diffusion**: Hormones passively diffuse through the plasma membrane.
2. **Receptor Binding**: Hormones bind to intracellular receptors in the cytoplasm or nucleus.
3. **Dimerisation and DNA Binding**: Hormone-receptor complexes form homodimers or heterodimers, then bind to HREs.
4. **Transcriptional Regulation**: Bound receptors recruit coactivators, enhancing transcription of target genes.
5. **Outcome**: Changes in mRNA expression lead to altered protein levels and cellular responses.