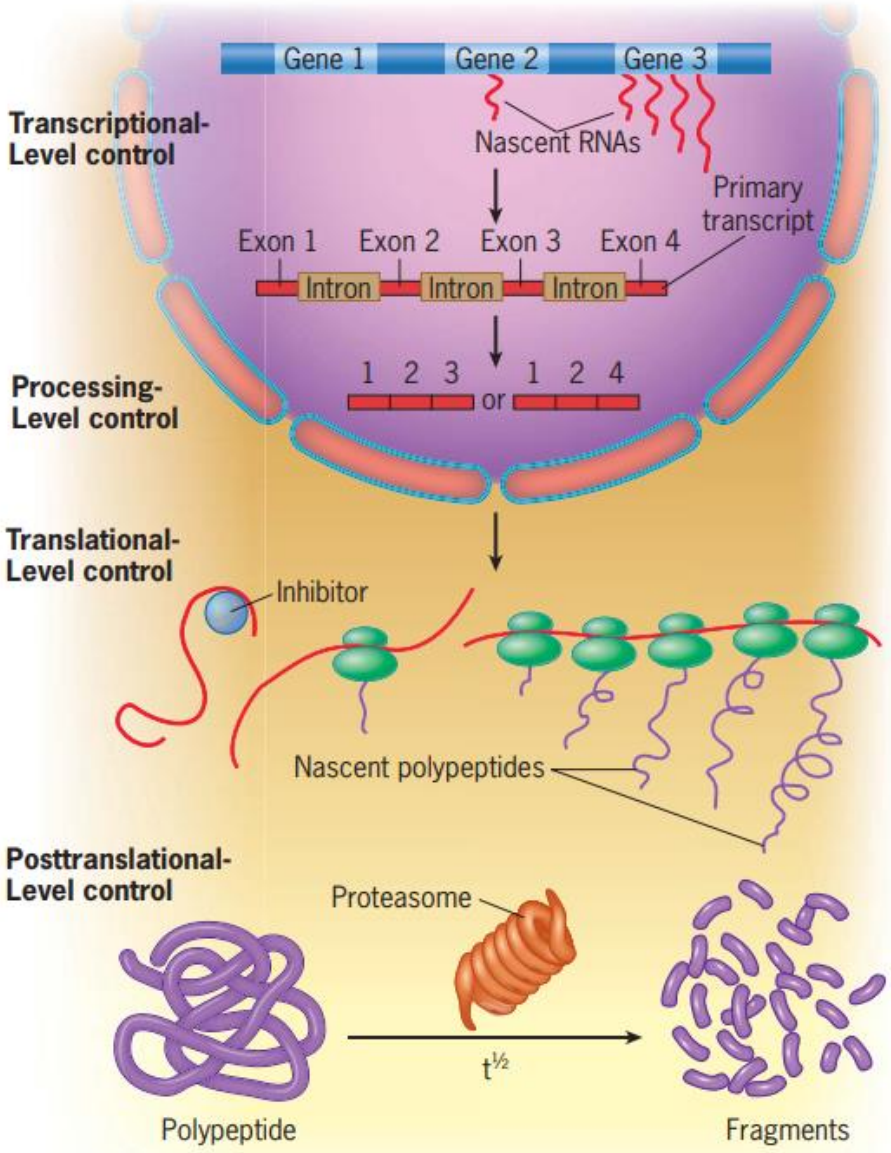
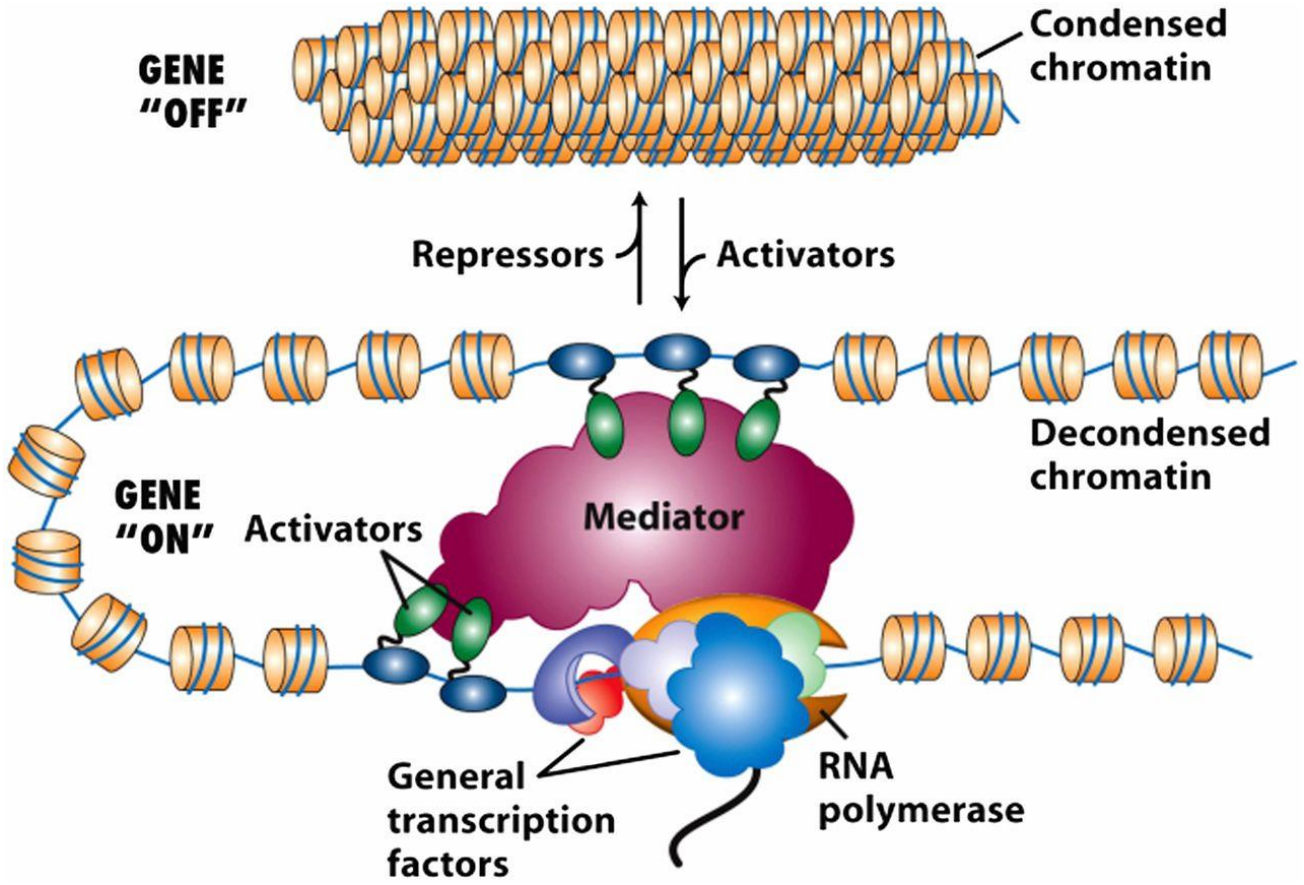
Eukaryotic gene regulation



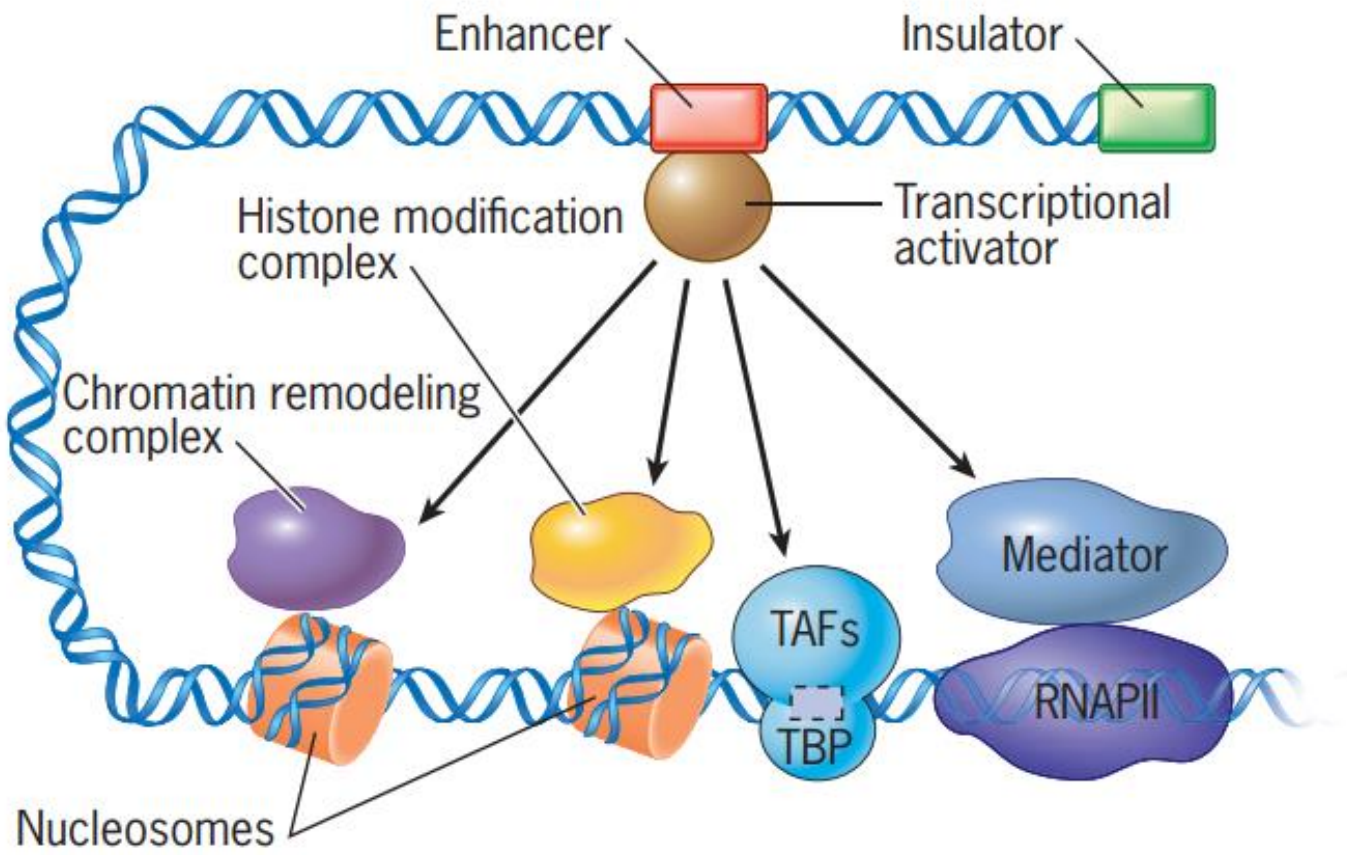
Eukaryotic gene regulation. Transcriptional-level controls operate by determining which genes are transcribed and how often; processing-level controls operate by determining which parts of the primary transcripts become part of the pool of cellular mRNAs; translational-level controls regulate whether a particular mRNA is translated and, if so, how often and for how long, and posttranslational-level controls determine the longevity of specific proteins.

Overview of eukaryotic transcription control



Activator proteins bind to specific DNA control elements in chromatin and interact with multiprotein co-activator machines, such as mediator, to decondense chromatin and assemble RNA polymerase and general transcription factors on promoters. Inactive genes are assembled into regions of condensed chromatin that inhibit RNA polymerase and their associated general transcription factors (GTFs) from interacting with promoters. Alternatively, repressor proteins bind to other control elements to inhibit initiation by RNA polymerase and interact with multiprotein co-repressor complexes to condense chromatin.

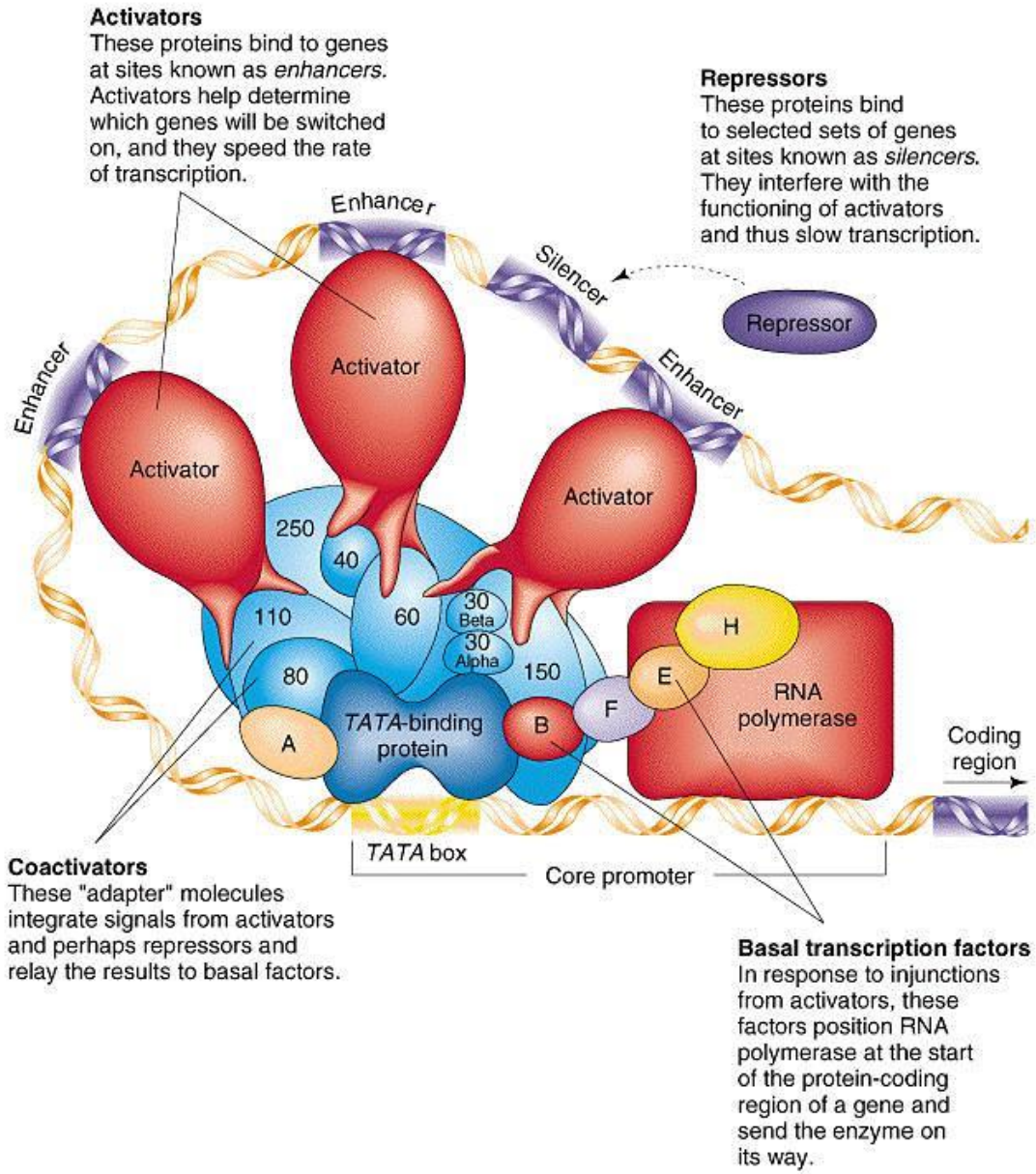
Transcriptional Activation: The Role of Enhancers, Promoters, and Coactivators

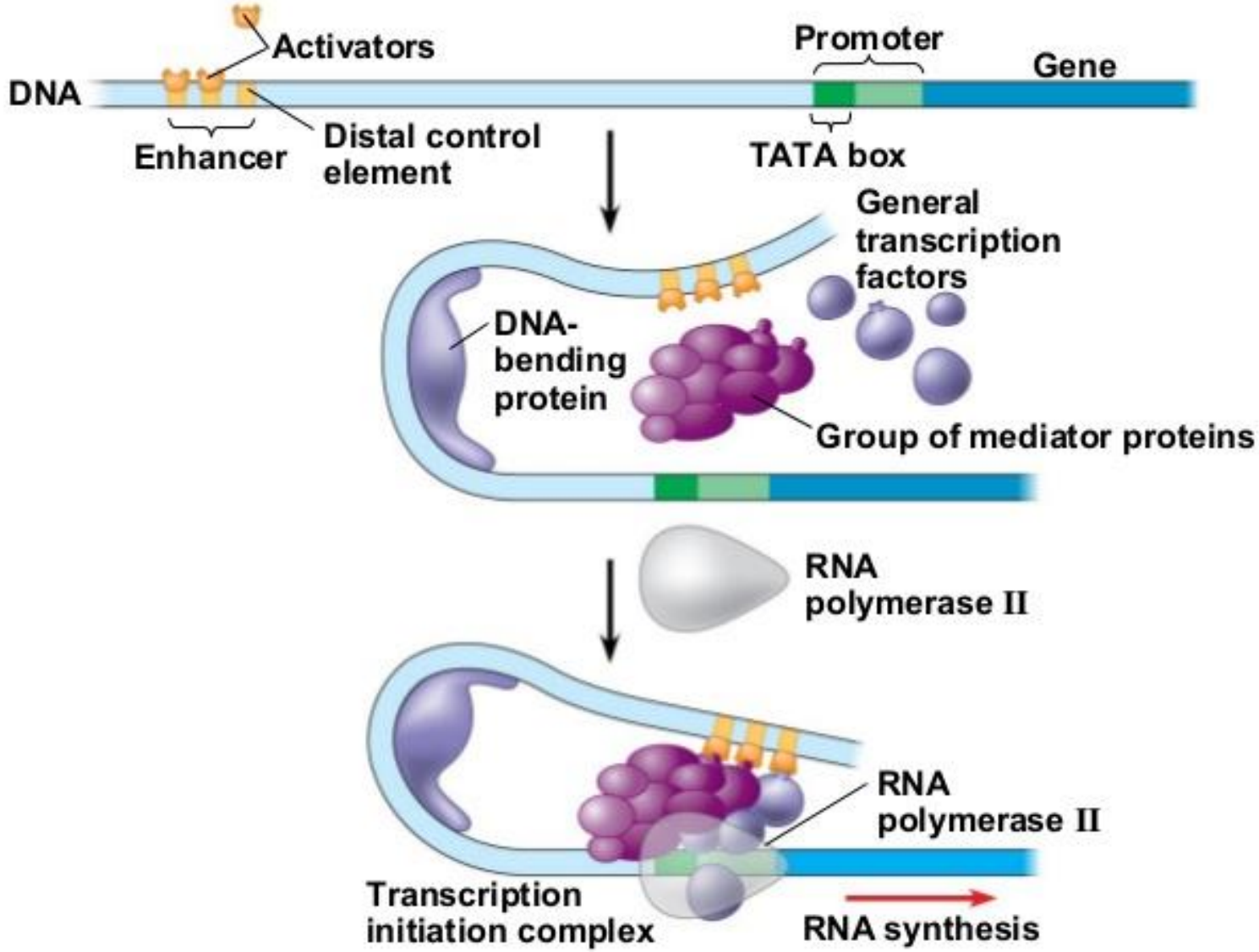


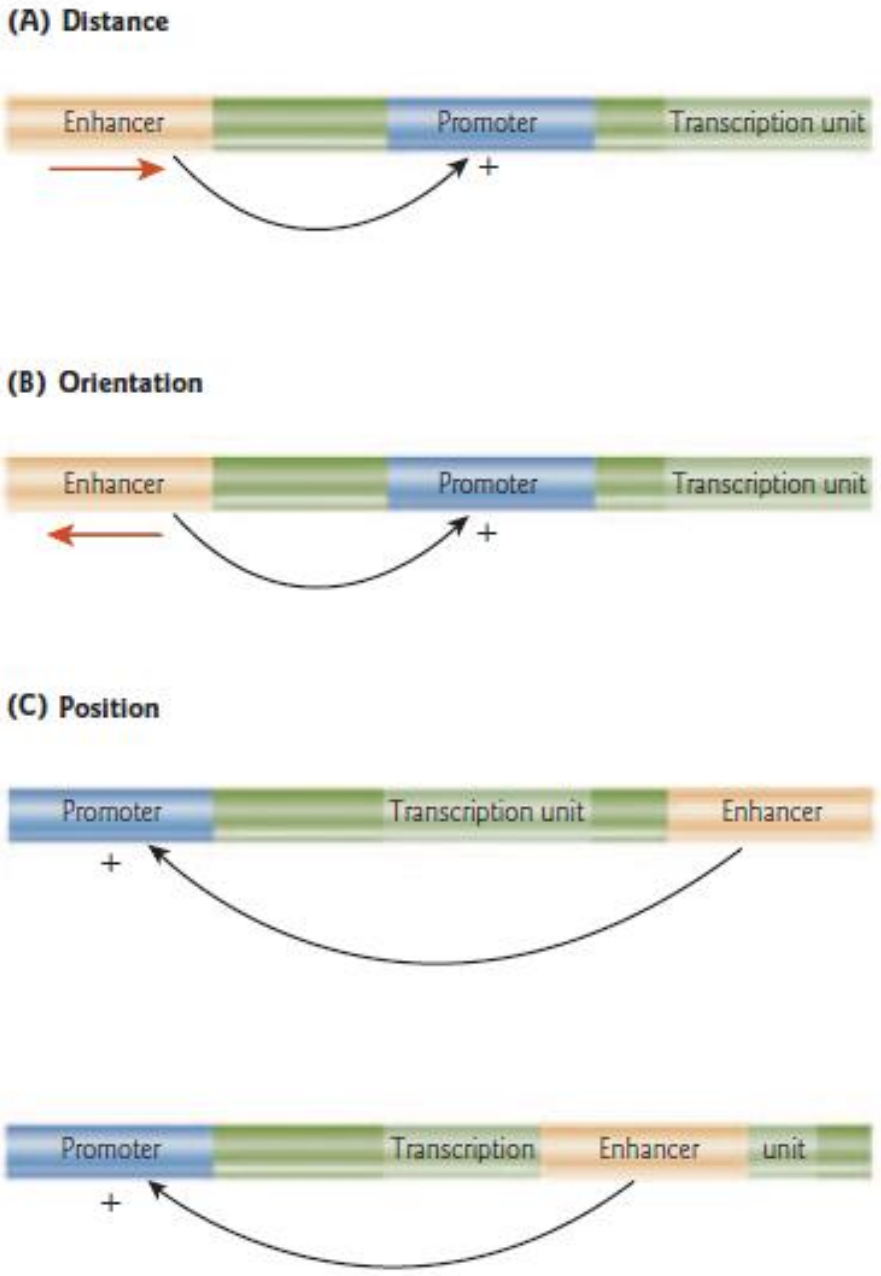
The mechanisms by which transcriptional activators bound at distant sites can influence gene expression. Transcriptional activators bound at upstream enhancers influence gene expression through interaction with coactivators. Four different types of coactivators are depicted here, two of them labeled “Histone modification complex” and “Chromatin remodeling complex” act by altering the structure of chromatin. Two others, labeled “TAFs” and “Mediator” act on components of the basal transcription machinery that assembles at the core promoter. These various types of coactivators are discussed in the following sections.

Activators and Repressors

- There are two different types of gene regulation: positive and negative. Activators (and sometimes inducers) instigate positive regulation, and repressors instigate negative regulation. When an activator or inducer binds to an operon, the transcription process either increases in rate or is allowed to continue. When a repressor binds to an operon, the transcription process is slowed or halted.
- Activators determine the frequency of transcription.
- Activators work by making protein-protein contacts with basal factors.
- Activators may work via coactivators.
- Repression is achieved by affecting chromatin structure or by binding to and masking activators.


Activators
These proteins bind to genes at sites known as enhancers. Activators help determine which genes will be switched on, and they speed the rate of transcription.
Repressors
These proteins bind to selected sets of genes at sites known as silencers. They interfere with the functioning of activators and thus slow transcription.
Enhancer
Silencer
Repressor
Enhancer
Enhancer
Activator
Activator
Activator
250
40
110
60
30 Beta
30 Alpha
150
80
A
TATA-binding protein
B
F
E
H
RNA polymerase
Coding region
TATA box
Core promoter
Coactivators
These "adapter" molecules integrate signals from activators and perhaps repressors and relay the results to basal factors.
Basal transcription factors
In response to injunctions from activators, these factors position RNA polymerase at the start of the protein-coding region of a gene and send the enzyme on its way.

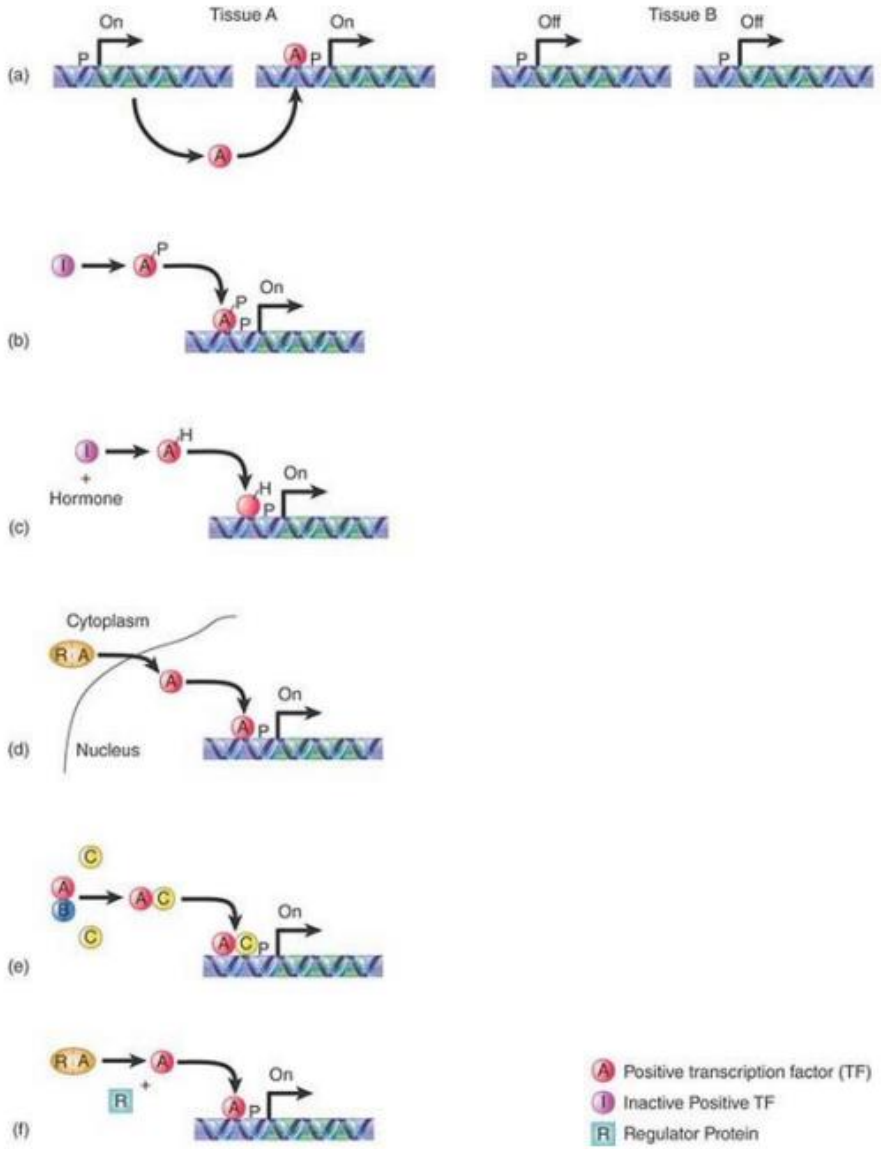

Activators
Promoter
Gene
DNA
Enhancer
Distal control element
TATA box
General transcription factors
DNA-bending protein
Group of mediator proteins
RNA polymerase II
RNA polymerase II
Transcription initiation complex
RNA synthesis



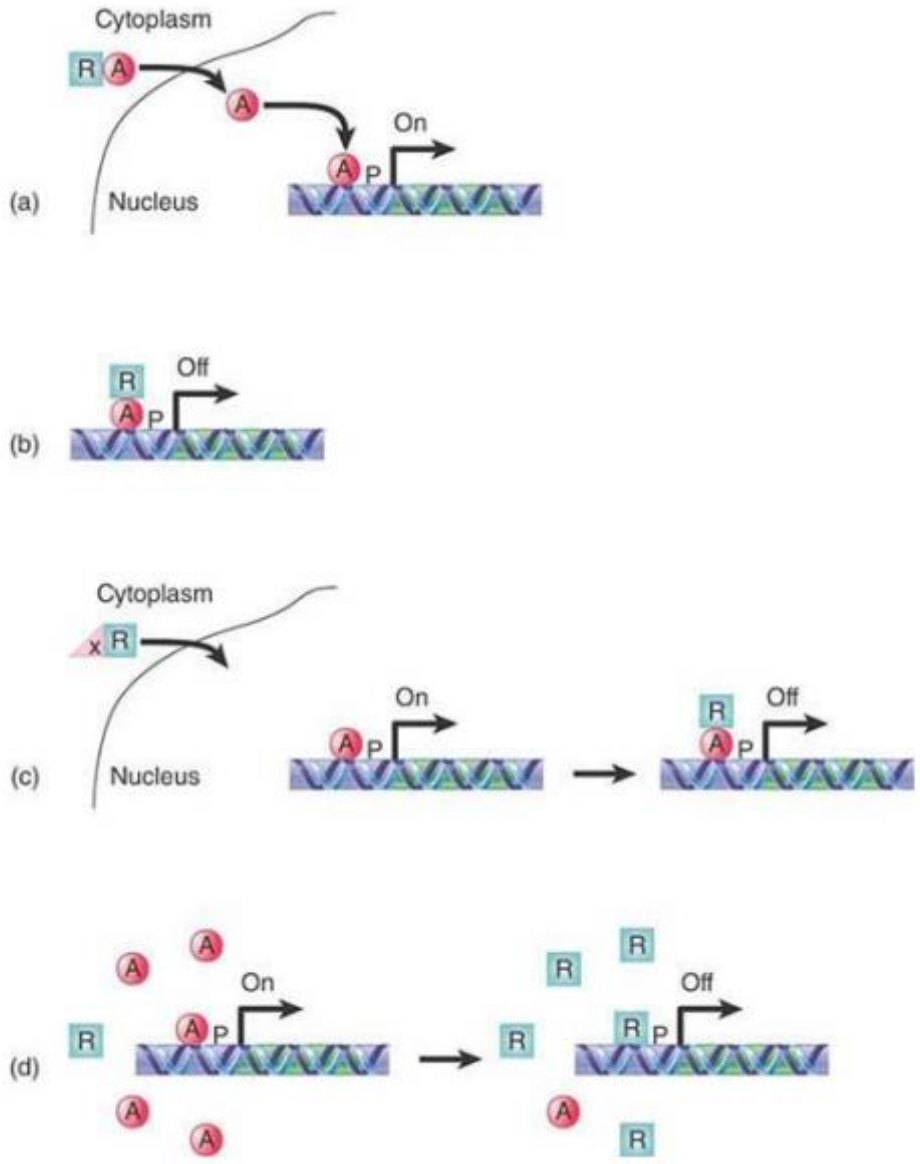
Three key characteristics of an enhancer element. An enhancer element can activate a promoter at a distance (A), in either orientation (B) or when positioned upstream, downstream, or within a transcription unit (C).

- In addition to the general transcription factors, other transcription factors can bind to the promoter to regulate gene transcription. These transcription factors bind to the promoters of a specific set of genes. They are not general transcription factors that bind to every promoter complex, but are recruited to a specific sequence on the promoter of a specific gene. There are hundreds of transcription factors in a cell that each bind specifically to a particular DNA sequence motif. When transcription factors bind to the promoter just upstream of the encoded gene, it is referred to as a cis-acting element, because it is on the same chromosome just next to the gene. The region that a particular transcription factor binds to is called the transcription factor binding site. Transcription factors respond to environmental stimuli that cause the proteins to find their binding sites and initiate transcription of the gene that is needed

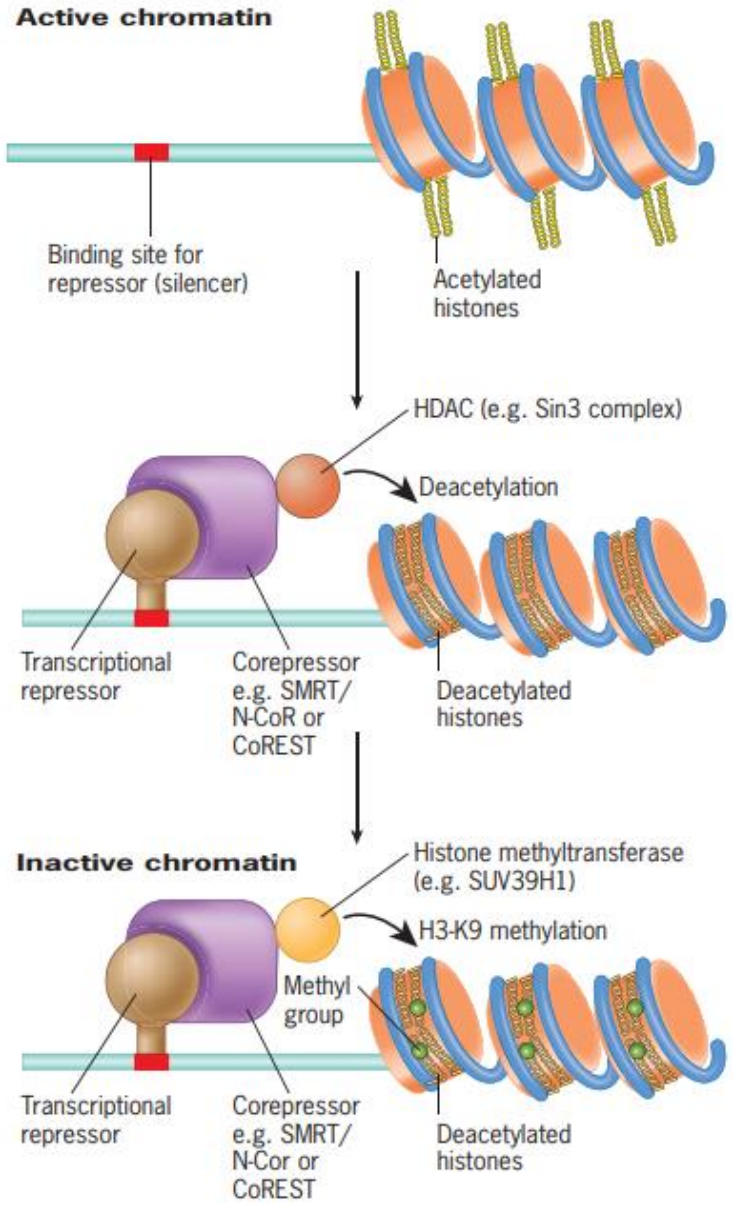
- Enhancers and Transcription • In some eukaryotic genes, there are regions that help increase or enhance transcription. These regions, called enhancers, are not necessarily close to the genes they enhance. They can be located upstream of a gene, within the coding region of the gene, downstream of a gene, or may be thousands of nucleotides away. • Enhancer regions are binding sequences, or sites, for transcription factors. When a DNA-bending protein binds, the shape of the DNA changes (Figure). This shape change allows for the interaction of the activators bound to the enhancers with the transcription factors bound to the promoter region and the RNA polymerase. Whereas DNA is generally depicted as a straight line in two dimensions, it is actually a three-dimensional object. Therefore, a nucleotide sequence thousands of nucleotides away can fold over and interact with a specific promoter. • Turning Genes Off: Transcriptional Repressors • Like prokaryotic cells, eukaryotic cells also have mechanisms to prevent transcription. Transcriptional repressors can bind to promoter or enhancer regions and block transcription. Like the transcriptional activators, repressors respond to external stimuli to prevent the binding of activating transcription factors.



The activity of a positive regulatory transcription factor may be controlled by (a) synthesis of protein, (b) covalent modification of protein, (c) ligand binding, or (d) binding of inhibitors that sequester the protein or affect its ability to bind to DNA (e) by the ability to select the correct binding partner for activation and (f) by cleavage from an inactive precursor.



A repressor may control transcription by (a) sequestering an activator in the cytoplasm, (b) by binding an activator and masking its activation domain, (c) by being held in the cytoplasm until it is needed, or (d) by competing with an activator for a binding site.

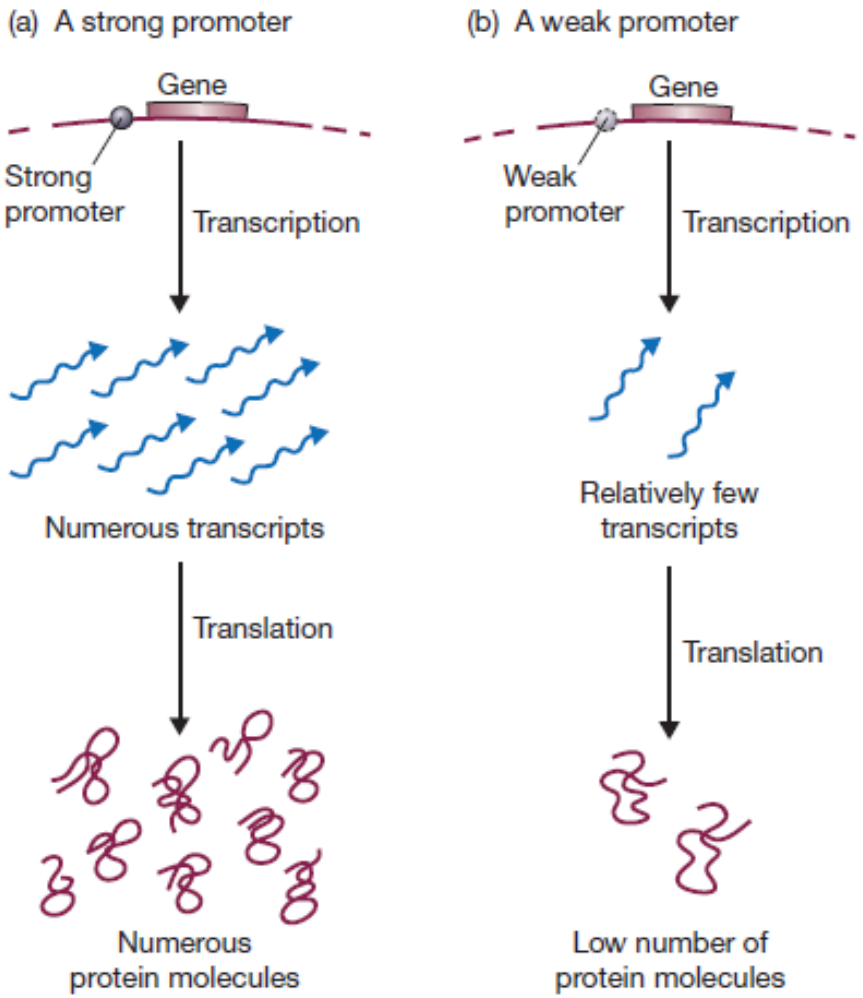


A model for transcriptional repression. Histone tails in the promoter regions of active chromatin are usually heavily acetylated. When a transcriptional repressor binds to its DNA binding site, it recruits a corepressor complex (e.g., SMRT/N-CoR or CoREST) and an associated HDAC activity. The HDAC removes acetyl groups from the histone tails. A separate protein containing histone methyltransferase activity adds methyl groups to the K9 residue of H3 histone tails. Together, the loss of acetyl groups and addition of methyl groups lead to chromatin inactivation and gene silencing.

Promoter

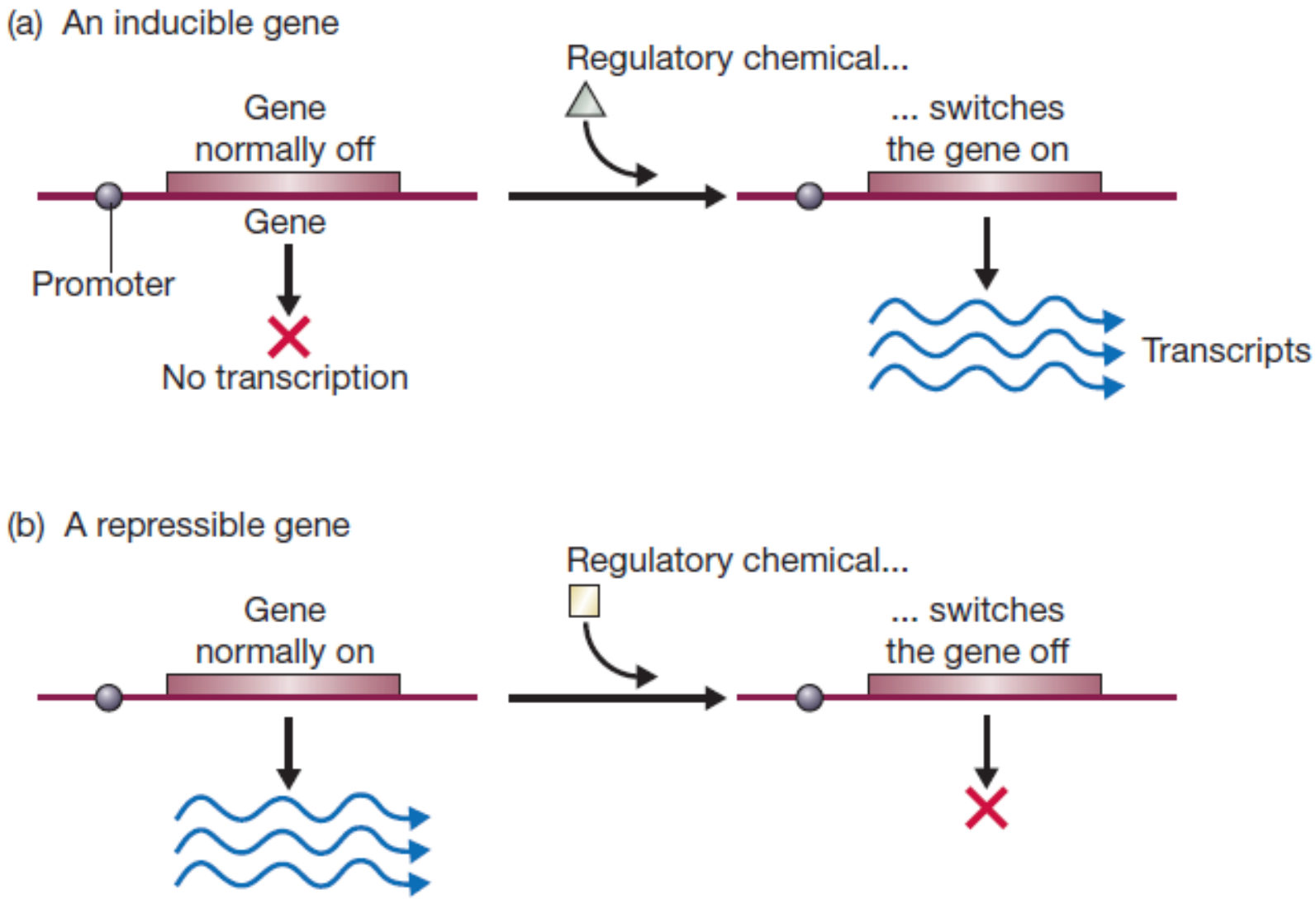
- Promoter sequences are DNA sequences that define where transcription of a gene by RNA polymerase begins. Promoter sequences are typically located directly upstream or at the 5' end of the transcription initiation site. RNA polymerase and the necessary transcription factors bind to the promoter sequence and initiate transcription. Promoter sequences define the direction of transcription and indicate which DNA strand will be transcribed; this strand is known as the sense strand.
- Many eukaryotic genes have a conserved promoter sequence called the TATA box, located 25 to 35 base pairs upstream of the transcription start site. Transcription factors bind to the TATA box and initiate the formation of the RNA polymerase transcription complex, which promotes transcription.

Promoter

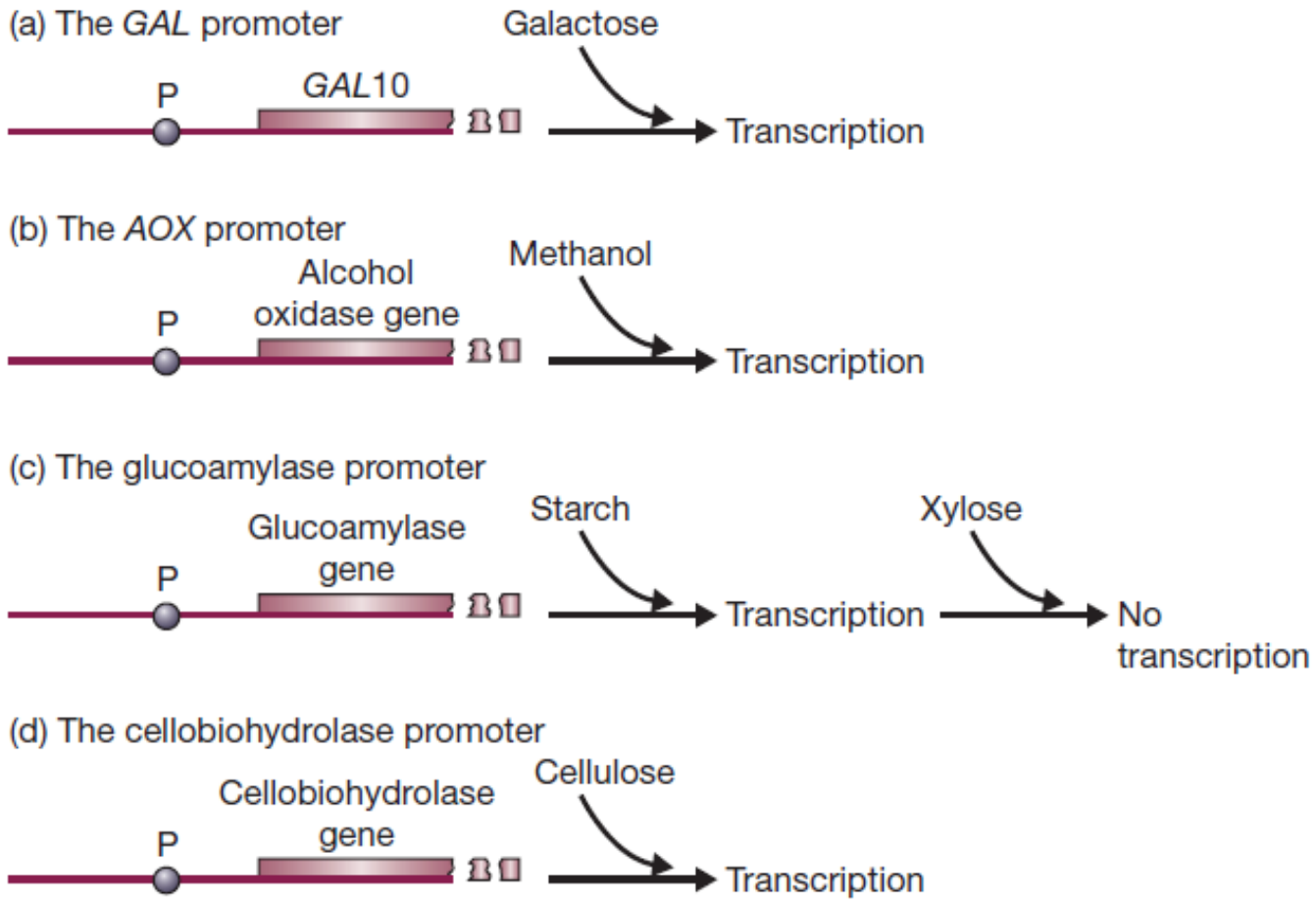

(a) A strong promoter
Gene
Strong promoter
Transcription
Numerous transcripts
Translation
Numerous protein molecules
(b) A weak promoter
Gene
Weak promoter
Transcription
Relatively few transcripts
Translation
Low number of protein molecules

Types of Promoters

- Constitutive promoters facilitate expression of the gene in all tissues regardless of the surrounding environment and development stage of the organism. Such promoters can turn on the gene in every living cell of the organism, all the time, throughout the organism's lifetime. These promoters can often be utilized across species. Examples of constitutive promoters that are commonly used for plants include Cauliflower mosaic virus (CaMV) 35S, opine promoters, plant ubiquitin (Ubi), rice actin 1 (Act-1) and maize alcohol dehydrogenase 1 (Adh-1). CaMV 35S is the most commonly used constitutive promoter for high levels of gene expression in dicot plants. Maize Ubi and rice Act-1 are the currently the most commonly used constitutive promoters for monocots.
- Tissue-specific or development-stage-specific promoters facilitate expression of a gene in specific tissue(s) or at certain stages of development while leaving the rest of the organism unmodified. In the case of plants, such promoters might specifically influence expression of genes in the roots, fruits, or seeds, or during the vegetative, flowering, or seed-setting stage. If the developer wants a gene of interest to be expressed in more than one tissue type for example the root, anthers and egg sac, then multiple tissue-specific promoters may have to be included in the gene construct.
- Effective gene expression in specific plant parts or development stages often has been observed when promoters from closely related species are used. There are many promoters in this category because they have different tissue and developmental specificities. An example of a tissue-specific promoter is the phosphoenolpyruvate (PEP) carboxylase promoter which induces gene expression only in cells that are actively involved in photosynthesis. In plant genetic engineering, this promoter is used for traits desired in the shoot, leaves and sometimes the stem. Expression of genes controlled by this promoter is reduced later in the growing season as the plant approaches senescence.
- Inducible promoters are activated by exogenous (i.e., external) factors. Exogenous factors may be abiotic such as heat, water, salinity, chemical, or biotic like pathogen or insect attack. Promoters that react to abiotic factors are the most commonly used in plant genetic engineering because these can easily be manipulated. Such promoters respond to chemical compounds such as antibiotics, herbicides or changes in temperature or light. Inducible promoters can also be tissue or development stage specific.
- Promoters can be derived directly from naturally occurring genes, or may be synthesized to combine regulatory sequences from different promoter regions. The promoters interact with other regulatory sequences (enhancers or silencers) and regulatory proteins (transcription factors) to influence the amount of gene transcription/expression.


(a) An inducible gene
Regulatory chemical...
Gene
normally off
... switches
the gene on
Gene
Promoter
No transcription
Transcripts
(b) A repressible gene
Regulatory chemical...
Gene
normally on
... switches
the gene off

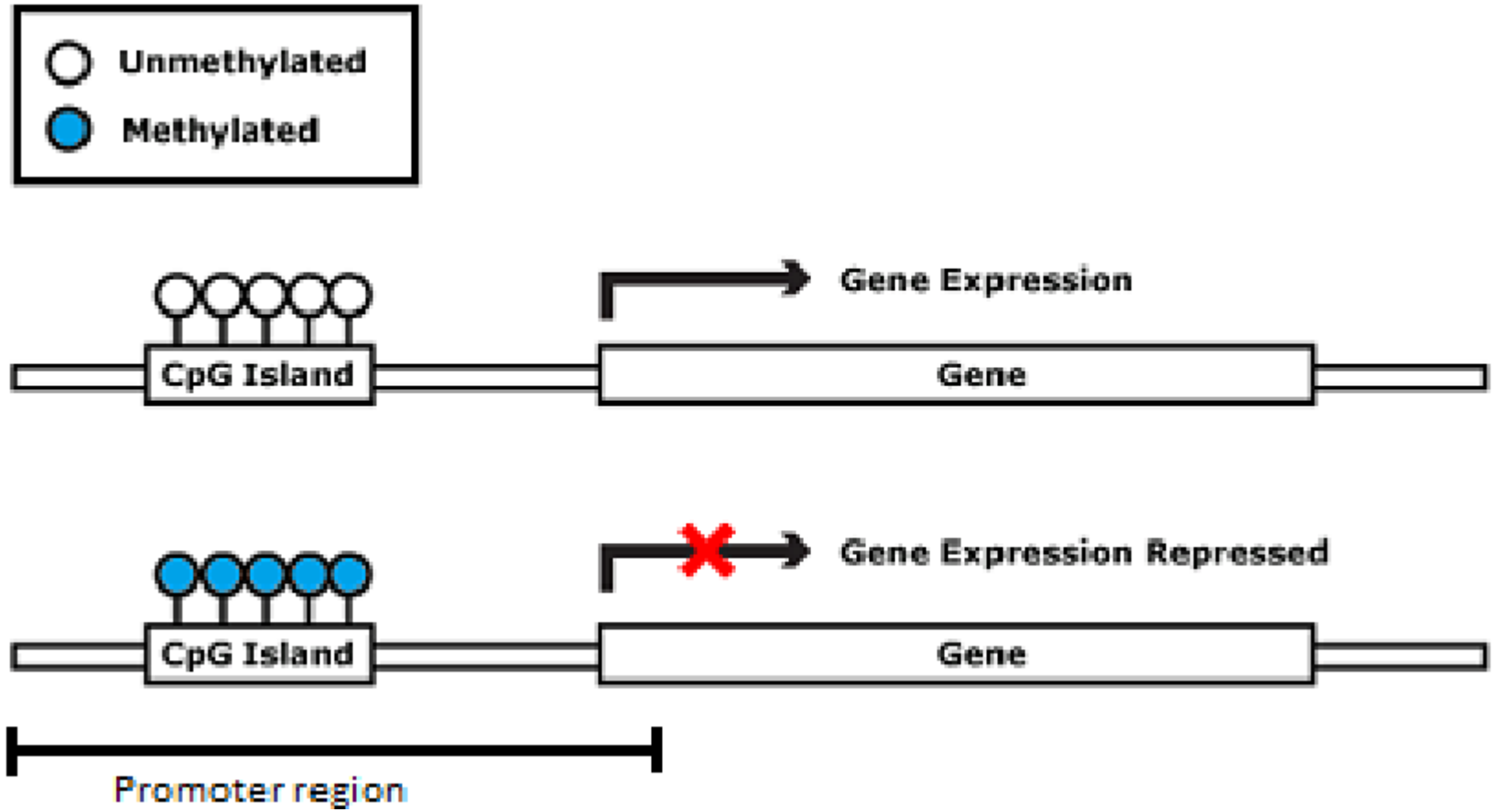
Four promoters frequently used in expression vectors for microbial eukaryotes.



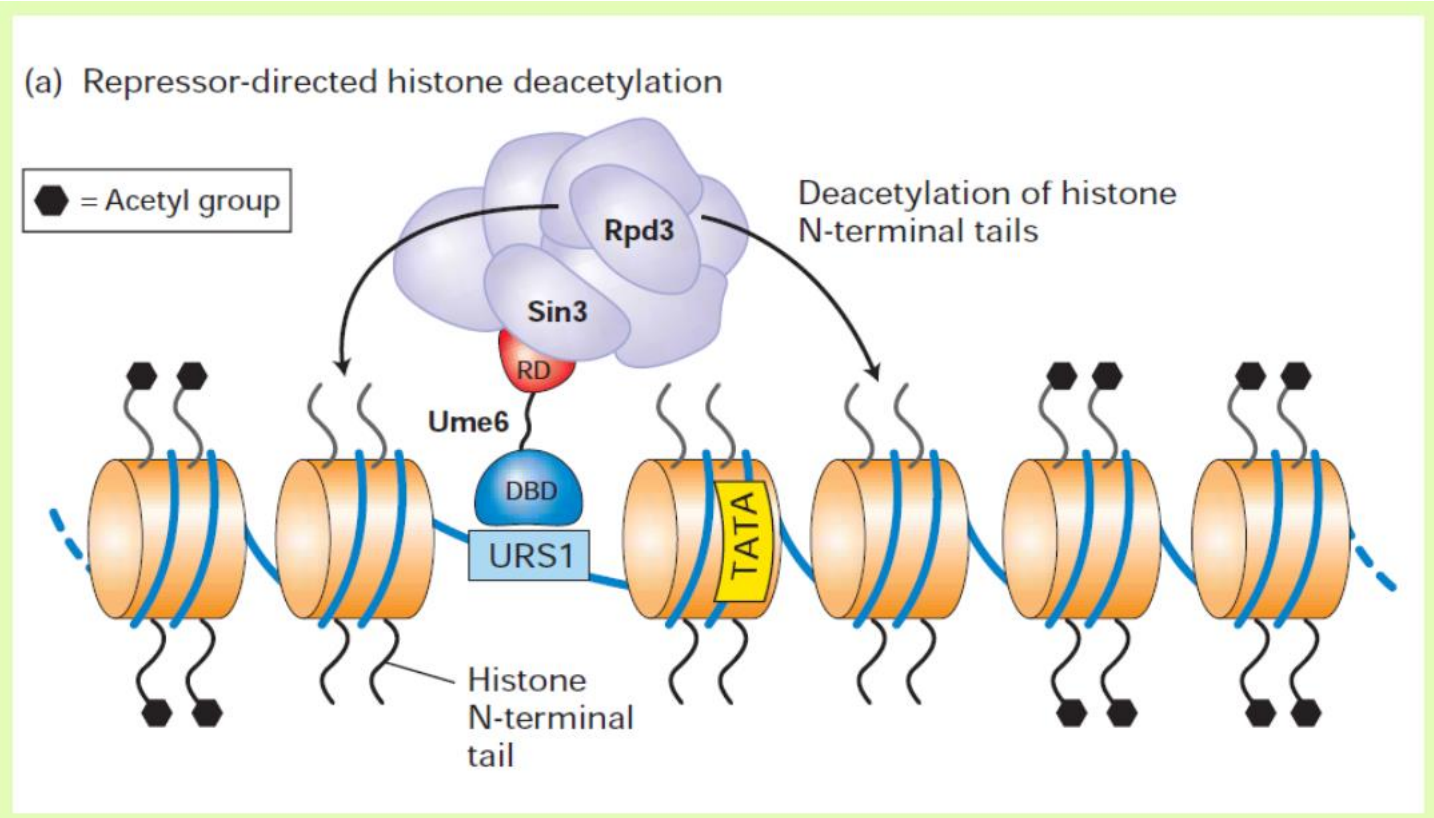
CpG islands and the regulation of transcription

- Vertebrate CpG islands (CGIs) are short interspersed DNA sequences that deviate significantly from the average genomic pattern by being GC-rich, CpG-rich, and predominantly nonmethylated.
- Most, perhaps all, CGIs are sites of transcription initiation, including thousands that are remote from currently annotated promoters. Shared DNA sequence features adapt CGIs for promoter function by destabilizing nucleosomes and attracting proteins that create a transcriptionally permissive chromatin state.
- Silencing of CGI promoters is achieved through dense CpG methylation or polycomb recruitment, again using their distinctive DNA sequence composition.
- CGIs are therefore generically equipped to influence local chromatin structure and simplify regulation of gene activity.

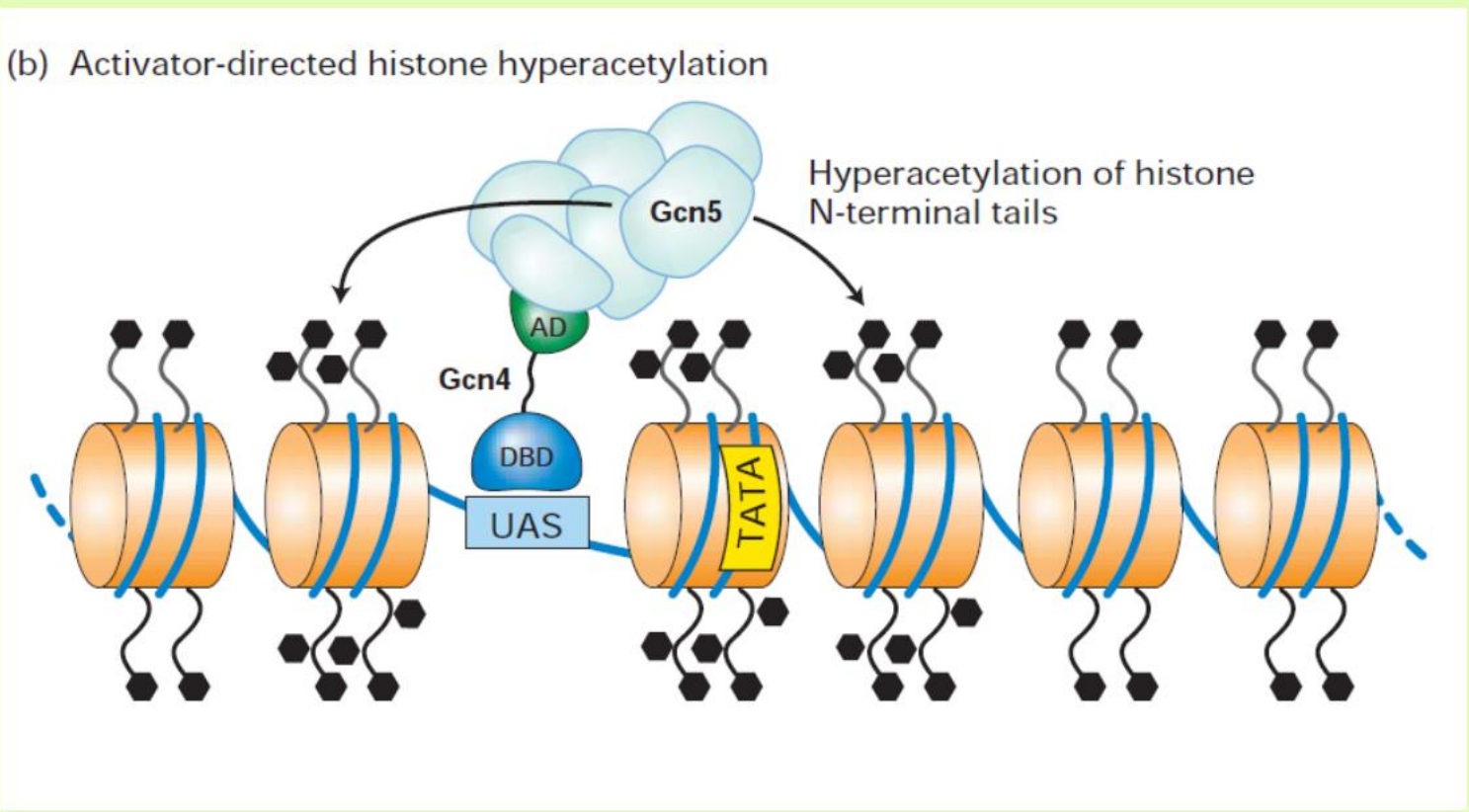
CpG islands regulate expression of nearby genes



Proposed mechanism of histone deacetylation and hyperacetylation in yeast transcription control

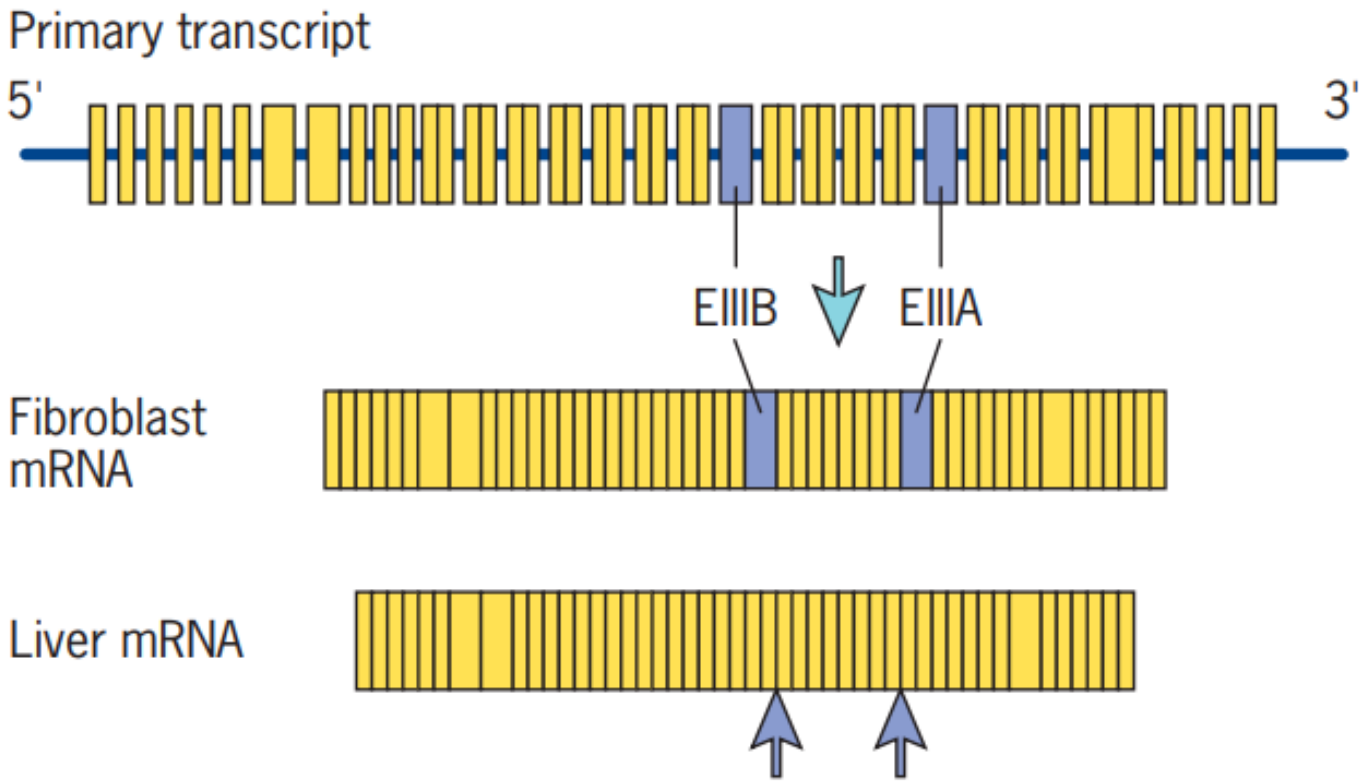


(a) Repressor-directed deacetylation of histone N-terminal tails. The DNA binding domain (DBD) of the repressor UME6 interacts with a specific upstream control element (URS1) of the genes it regulates. The UME6 repression domain (RD) binds SIN3, a subunit of a multiprotein complex that includes RPD3, a histone deacetylase. Deacetylation of histone N-terminal tails on nucleosomes in the region of the UME6- binding site inhibits binding of general transcription factors at the TATA box, thereby repressing gene expression



(b) Activator directed hyper acetylation of histone N-terminal tails. The DNA binding domain of the activator GCN4 interacts with specific upstream activating sequences (UAS) of the genes it regulates. The GCN4 activation domain (AD) then interacts with a multiprotein histone acetylase complex that includes the GCN5 catalytic subunit. Subsequent hyper acetylation of histone N terminal tails on nucleosomes in the vicinity of the GCN4-binding site facilitates access of the general transcription factors required for initiation. Repression and activation of many genes in higher eukaryotes occurs by similar mechanisms

RNA Processing Control



Alternative splicing of the fibronectin gene. The fibronectin gene consists of a number of exons shown in the top drawing (the introns shown in black are not drawn to scale). Two of these exons encode portions of the polypeptide called EIIIA and EIIIB, which are included in the protein produced by fibroblasts, but which are excluded from the protein produced in the liver. The difference is due to alternative splicing; those portions of the pre-mRNA that encode these two exons are excised from the transcript in liver cells. The sites of the missing exons are indicated by the arrows in the liver mRNA.

RNA editing

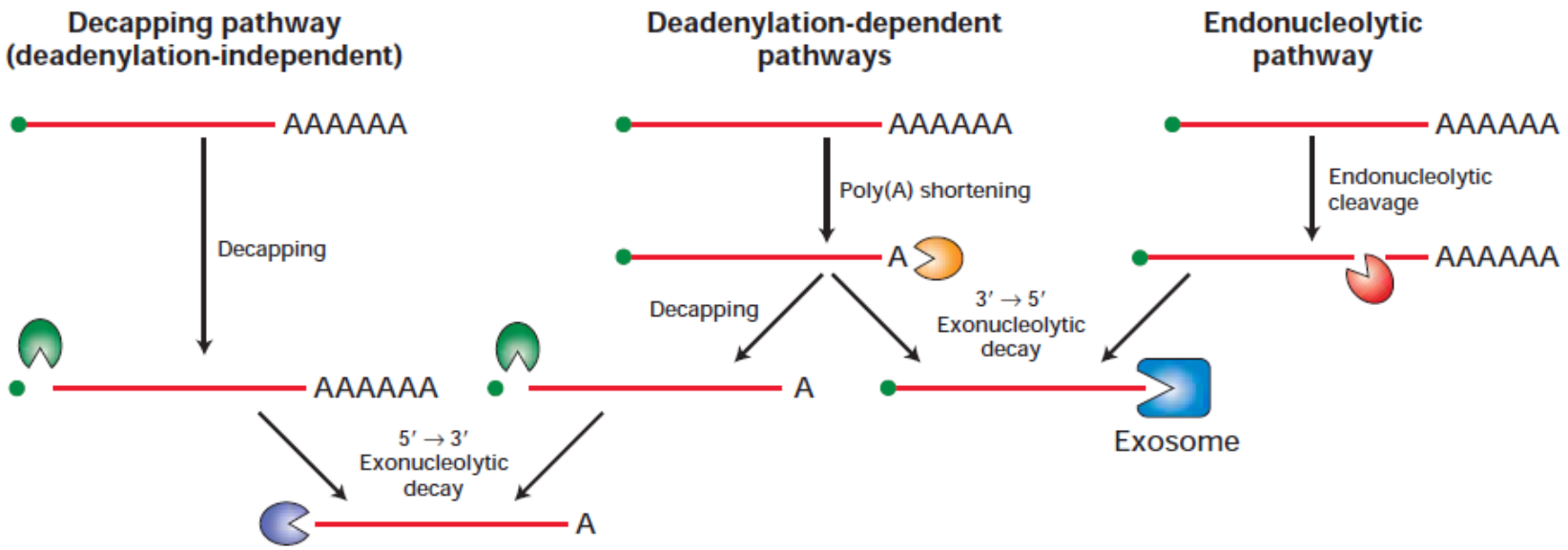
- Another way in which gene expression can be regulated at the posttranscriptional level is by RNA editing , in which specific nucleotides are converted to other nucleotides after the RNA has been transcribed. RNA editing can create new splice sites, generate stop codons, or lead to amino acid substitutions.
- Although not nearly as widespread as alternative splicing, RNA editing is particularly important in the nervous system, where a significant number of messages appear to have one or more adenines (A) converted to inosines (I). This modification involves the enzymatic removal of an amino group from the nucleotide. I is subsequently read as a G by the translational machinery. The glutamate receptor, which mediates excitatory synaptic transmission in the brain, is a product of RNA editing.
- In this case, an A-to-I modification generates a glutamate receptor whose internal channel is impermeable to Ca 2+ ions. Genetically engineered mice that are unable to carry out this specific RNA-editing step develop severe epileptic seizures and die within weeks after birth.

Pathways for degradation of eukaryotic mRNAs.

Cytoplasmic mRNAs are degraded by one of the pathways shown in Figure. For most mRNAs, the length of the poly(A) tail gradually decreases with time through the action of a deadenylating nuclease. When it is shortened sufficiently, PABPI molecules can no longer bind and stabilize interaction of the 5 cap and initiation factors (see Figure). The exposed cap then is removed by a decapping enzyme and the unprotected mRNA is degraded by a 5 → 3 exonuclease. Removal of the poly(A) tail also makes mRNAs susceptible to degradation by cytoplasmic exosomes containing 3 → 5 exonucleases. The 5 → 3 exonucleases predominate in yeast, and the 3 → 5 exosome apparently predominates in mammalian cells. For mRNAs degraded in these deadenylation-dependent pathways, the rate at which they are deadenylated controls the rate at which they are degraded. The rate of deadenylation varies inversely with the frequency of translation initiation for an mRNA: the higher the frequency of initiation, the slower the rate of deadenylation. This relation probably is due to the reciprocal interactions between initiation factors and PABPI that stabilize the binding of PABPI to the poly(A) tail, thereby protecting it from the deadenylation exonuclease.

Many short-lived mRNAs in mammalian cells contain multiple, sometimes overlapping, copies of the sequence AUUUA in their 3 untranslated region. Specific RNA-binding Recent experiments suggest that the bound proteins interact with a deadenylating enzyme and with the exosome, thereby promoting the rapid deadenylation and subsequent 3 → 5 degradation of these mRNAs. In this mechanism, the rate of mRNA degradation is uncoupled from the frequency of translation. Thus mRNAs containing the AUUUA sequence can be translated at high frequency, yet also degraded rapidly, allowing the encoded proteins to be expressed in short bursts. As shown in Figure, some mRNAs are degraded in pathways that do not involve significant deadenylation. In one of these, mRNAs are decapped before the poly(A) tail is shortened extensively. It appears that certain mRNA sequences make the cap sensitive to the decapping enzyme, but the precise mechanism is unclear. In the other alternative pathway, mRNAs first are cleaved internally by endonucleases. The RNA-induced silencing complex (RISC) discussed earlier is an example of such an endonuclease (see Figure). The fragments generated by internal cleavage then are degraded by exonucleases.

Pathways for degradation of eukaryotic mRNAs.

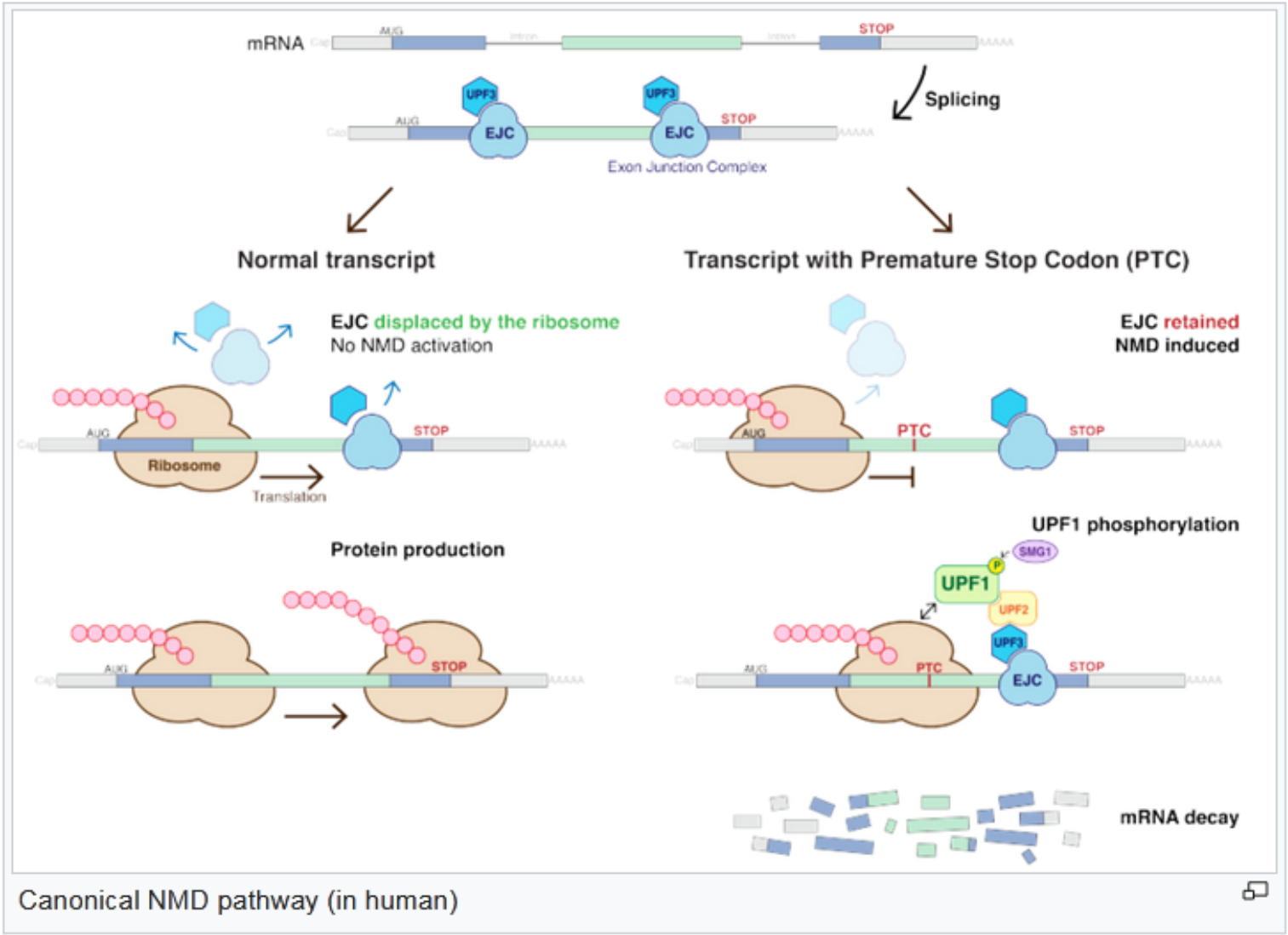


In the deadenylation-dependent (*middle*) pathways, the poly(A) tail is progressively shortened by a deadenylase (orange) until it reaches a length of 20 or fewer A residues at which the interaction with PABPI is destabilized, leading to weakened interactions between the 5 cap and translation initiation factors. The deadenylated mRNA then may either (1) be decapped and degraded by a 5 → 3 exonuclease or (2) be degraded by a 3 → 5 exonuclease in cytoplasmic exosomes. Some mRNAs (*right*) are cleaved internally by an endonuclease, and the fragments degraded by an exosome. Other mRNAs (*left*) are decapped before they are deadenylated, and then degraded by a 5 → 3 exonuclease. [Adapted from M. Tucker and R. Parker, 2000, *Ann. Rev. Biochem.* **69**:571.]

NMD Pathway

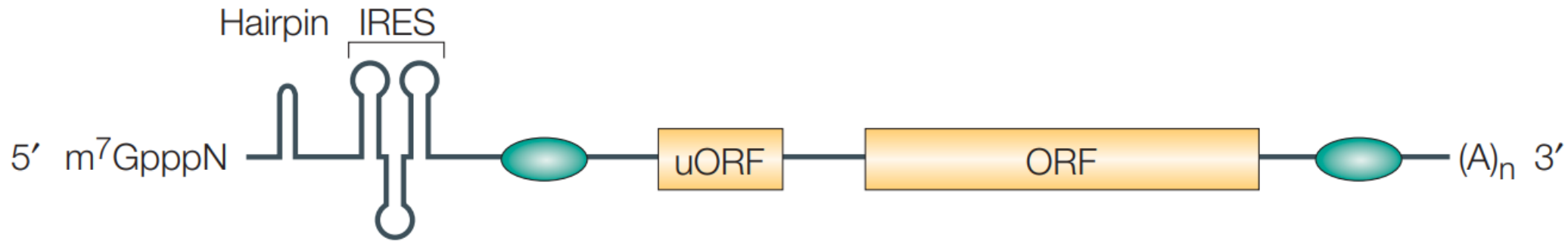
- **Nonsense-mediated mRNA decay** (**NMD**) is a surveillance pathway that exists in all eukaryotes. Its main function is to reduce errors in gene expression by eliminating mRNA transcripts that contain premature Termination Codons (PTCs). Translation of these aberrant mRNAs could, in some cases, lead to deleterious gain-of-function or dominant-negative activity of the resulting proteins.
- The phenomenon of NMD was first described in human cells and in yeast almost simultaneously in 1979. This suggested broad phylogenetic conservation and an important biological role of this intriguing mechanism. NMD was discovered when it was realized that cells often contain unexpectedly low concentrations of mRNAs that are transcribed from alleles carrying nonsense mutations. Nonsense mutations code for a premature stop codon which causes the protein to be shortened. The truncated protein may or may not be functional, depending on the severity of what is not translated. In human genetics, NMD has the possibility to not only limit the translation of abnormal proteins, but it can occasionally cause detrimental effects in specific genetic mutations.

NMD Pathway



Canonical NMD pathway (in human)

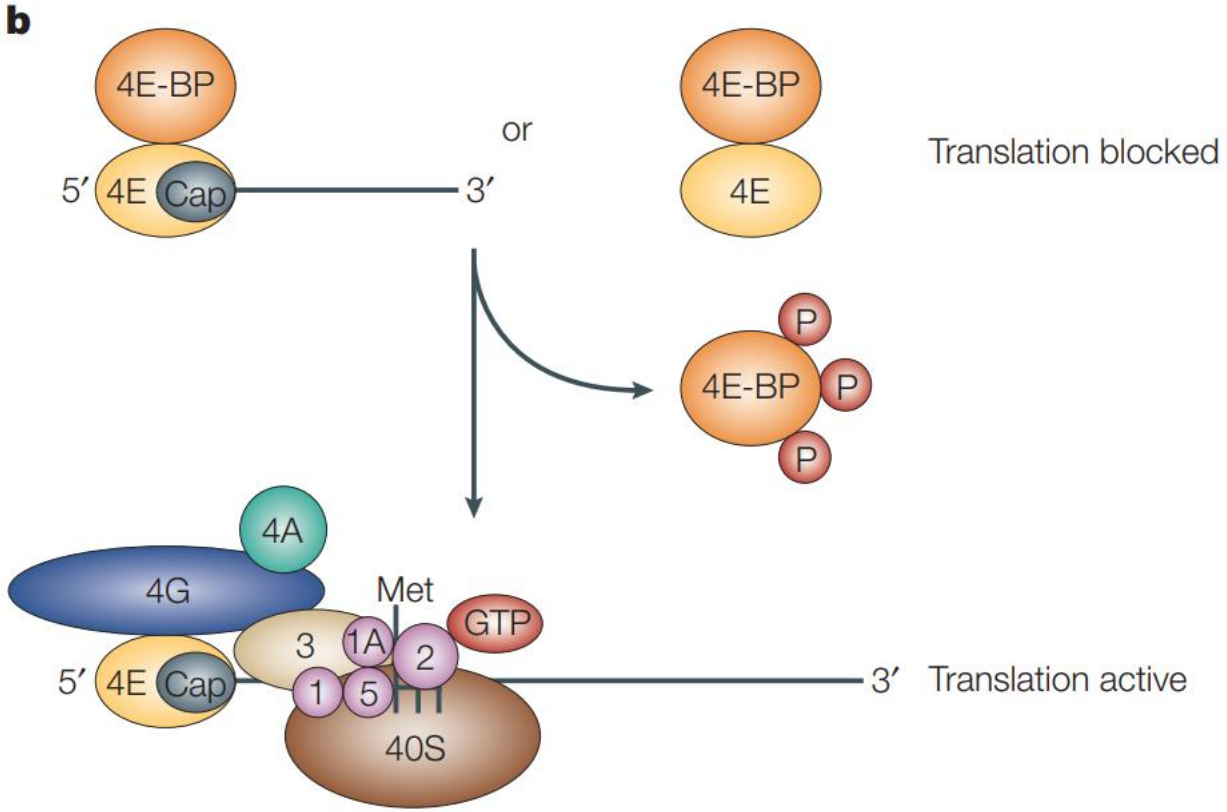
- While many of the proteins involved in NMD are not conserved between species, in *Saccharomyces cerevisiae* (yeast), there are three main factors in NMD: UPF1, UPF2 and UPF3 (UPF3A and UPF3B in humans), that make up the conserved core of the NMD pathway. All three of these factors are trans-acting elements called up-frameshift (UPF) proteins. In mammals, UPF2 and UPF3 are part of the exon-exon junction complex (EJC) bound to mRNA after splicing along with other proteins, eIF4AIII, MLN51, and the Y14/MAGOH heterodimer, which also function in NMD. UPF1 phosphorylation is controlled by the proteins SMG-1, SMG-5, SMG-6 and SMG-7.
- The process of detecting aberrant transcripts occurs during translation of the mRNA. A popular model for the detection of aberrant transcripts in mammals suggests that during the first round of translation, the ribosome removes the exon-exon junction complexes bound to the mRNA after splicing occurs. If after this first round of translation, any of these proteins remain bound to the mRNA, NMD is activated. Exon-exon junction complexes located downstream of a stop codon are not removed from the transcript because the ribosome is released before reaching them. Termination of translation leads to the assembly of a complex composed of UPF1, SMG1 and the release factors, eRF1 and eRF3, on the mRNA. If an EJC is left on the mRNA because the transcript contains a premature stop codon, then UPF1 comes into contact with UPF2 and UPF3, triggering the phosphorylation of UPF1. In vertebrates, the location of the last exon-junction complex relative to the termination codon usually determines whether the transcript will be subjected to NMD or not. If the termination codon is downstream of or within about 50 nucleotides of the final exon-junction complex then the transcript is translated normally. However, if the termination codon is further than about 50 nucleotides upstream of any exon-junction complexes, then the transcript is down regulated by NMD. The phosphorylated UPF1 then interacts with SMG-5, SMG-6 and SMG-7, which promote the dephosphorylation of UPF1. SMG-7 is thought to be the terminating effector in NMD, as it accumulates in P-bodies, which are cytoplasmic sites for mRNA decay. In both yeast and human cells, the major pathway for mRNA decay is initiated by the removal of the 5’ cap followed by degradation by XRN1, an exoribonuclease enzyme. The other pathway by which mRNA is degraded is by deadenylation from 3’-5'.
- In addition to the well recognized role of NMD in removing aberrant transcripts, there are transcripts that contain introns within their 3'UTRs. These messages are predicted to be NMD-targets yet they (ex. activity-regulated cytoskeleton-associated protein, known as Arc) can play crucial biologic functions suggesting that NMD may have physiologically relevant roles.



Elements that influence translation of mRNA. The m7 GpppN cap structure at the 5′ end of the mRNA, and the poly(A) tail ((A)n in the figure) at the 3′ end, are canonical motifs that strongly promote translation initiation. Secondary structures, such as hairpins, block translation. Internal ribosome entry sequences (IRESs) mediate cap-independent translation. Upstream open reading frames (uORFs) normally function as negative regulators by reducing translation from the main ORF. Green ovals symbolize binding sites for proteins and/or RNA regulators, which usually inhibit, but occasionally promote, translation.

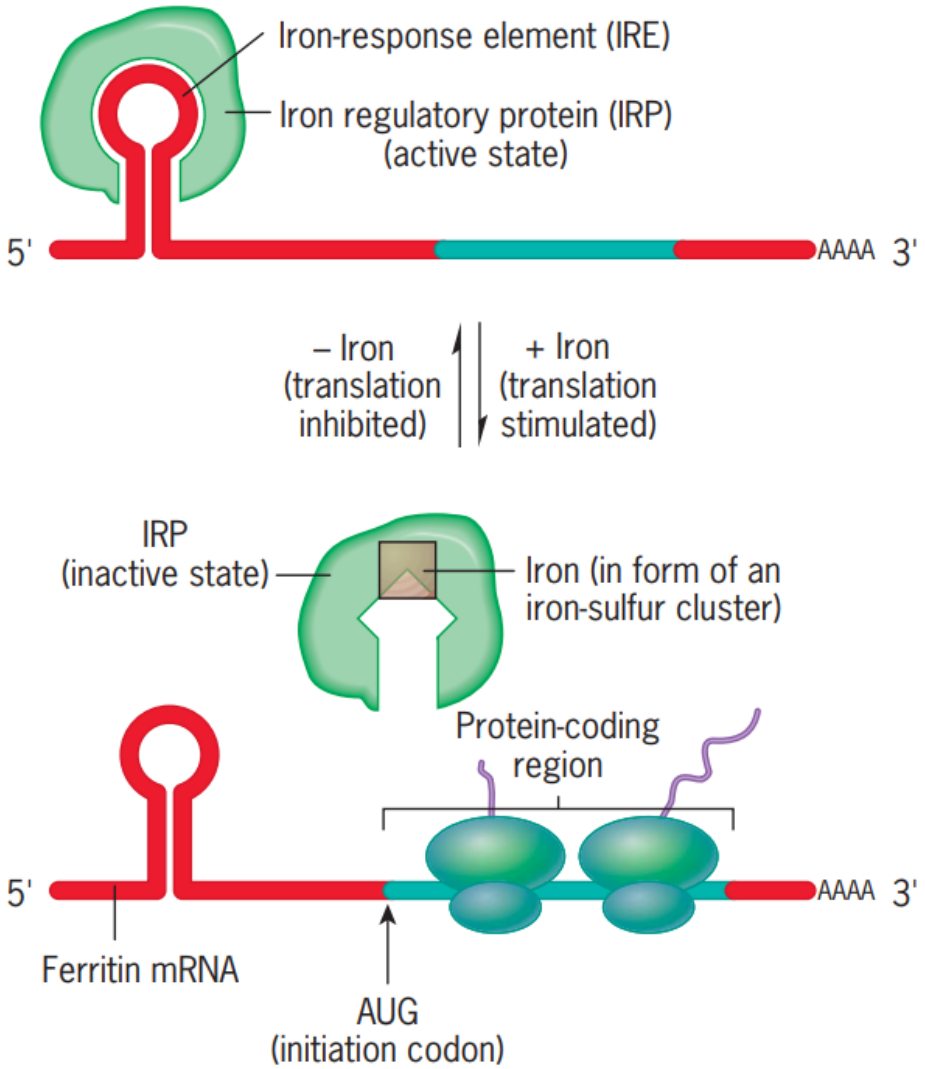
Translational Control

Global control of protein synthesis

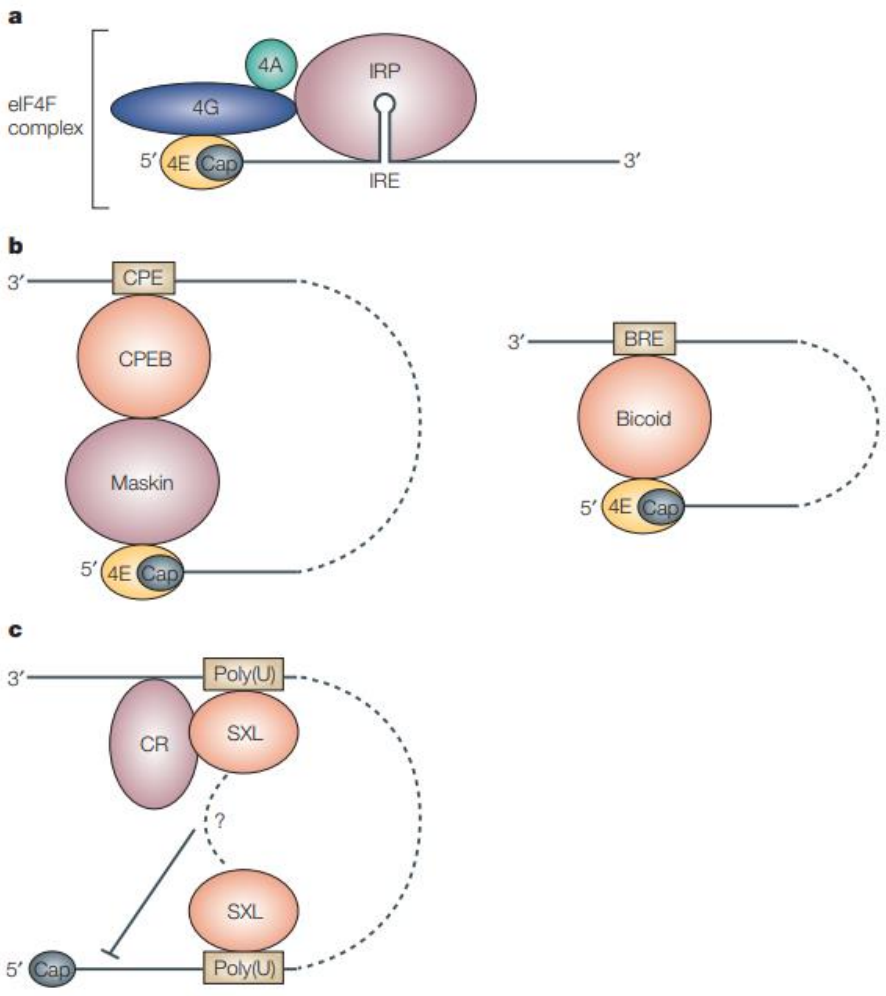


Function of eIF4E-binding proteins (4E-BPs). 4E-BPs bind to eIF4E, thereby preventing its interaction with eIF4G and so inhibiting translation. Phosphorylation of 4E-BP molecules releases the 4E-BPs from eIF4E, which allows their interaction with eIF4G, and thereby allows translation to proceed.

Translational Control: mRNA specific

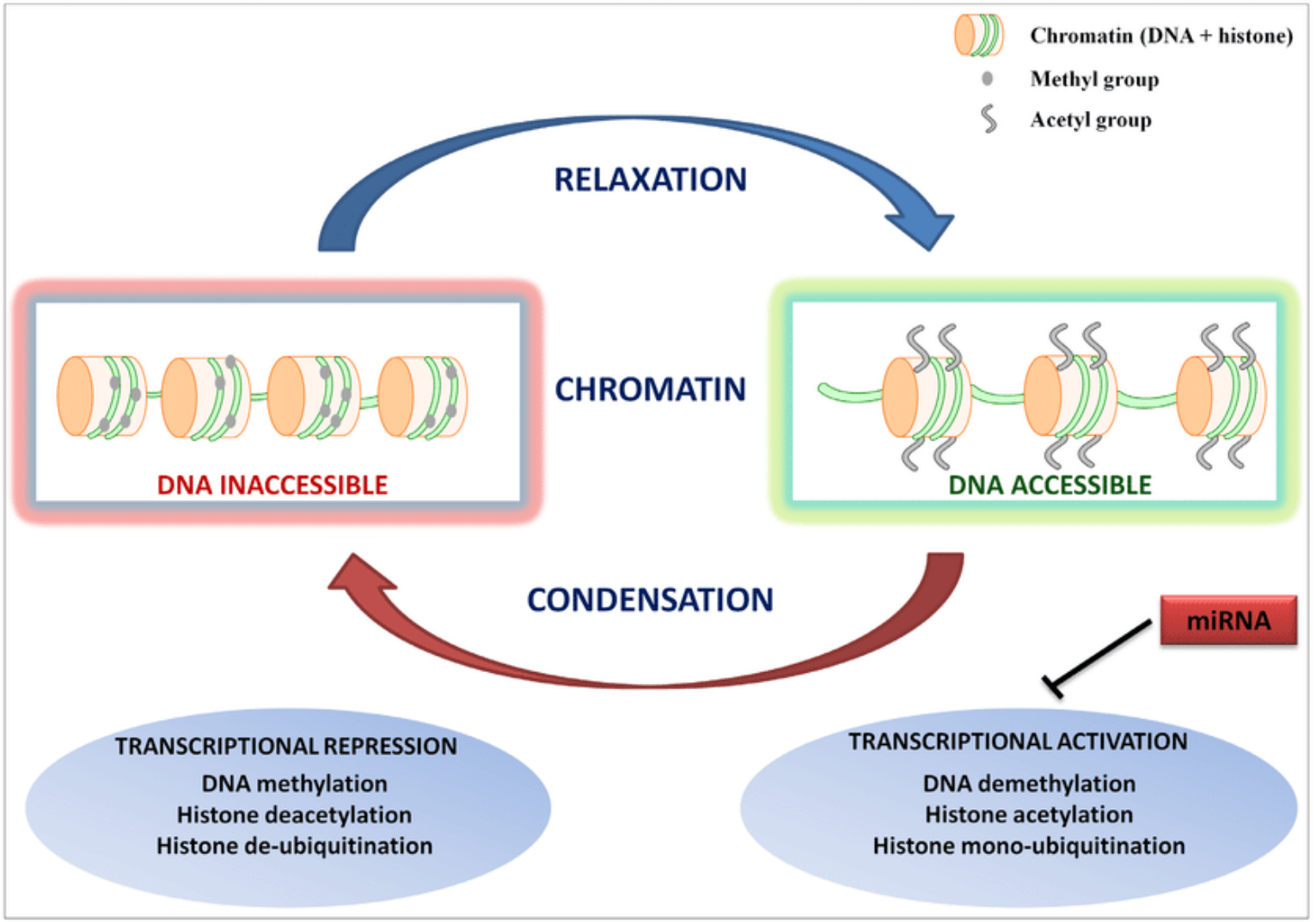


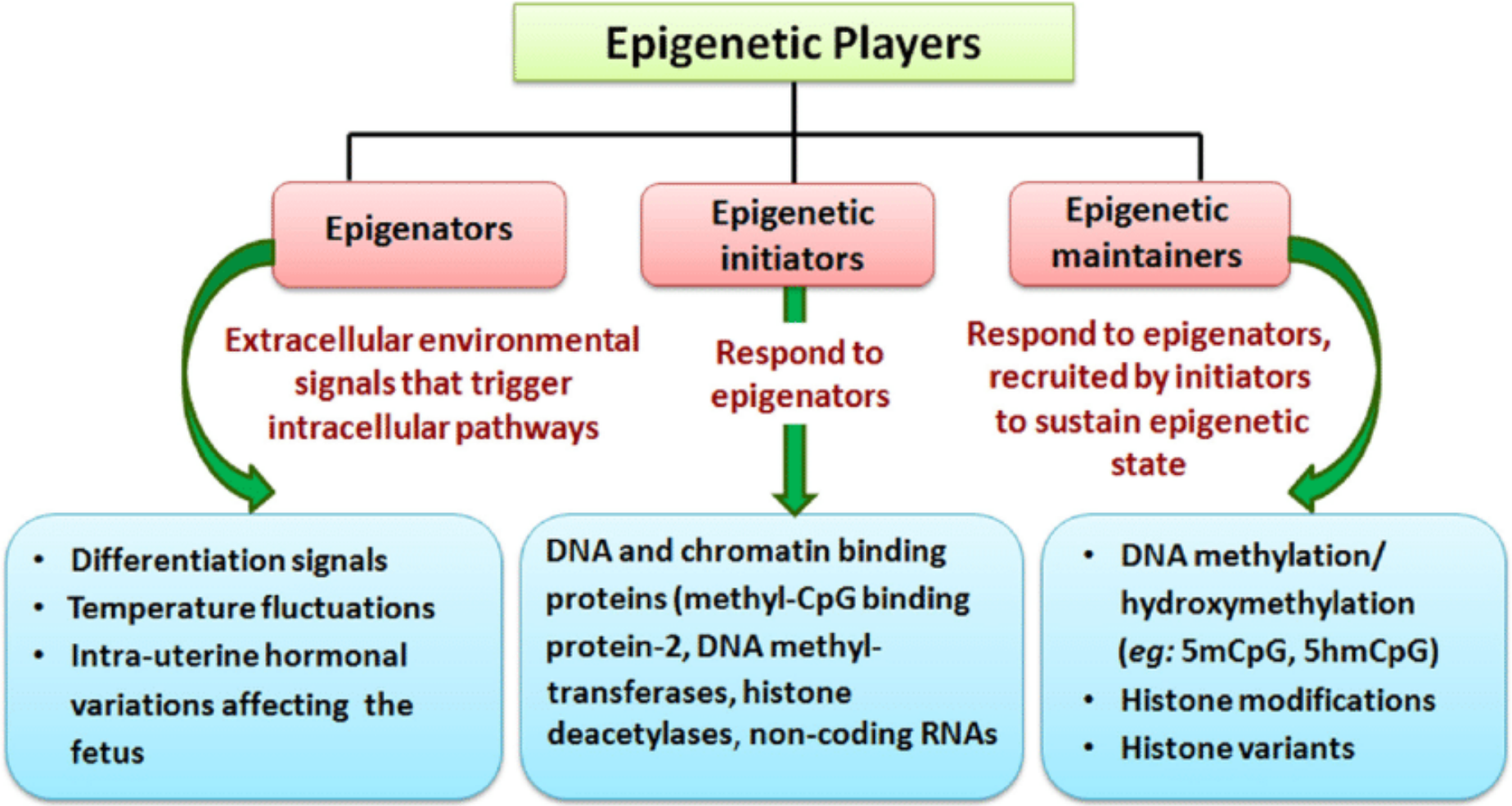
5’ UTR control of ferritin mRNA translation. When iron concentrations are low, an iron-binding repressor protein, called the iron regulatory protein (IRP), binds to a specific sequence in the 5 ’ UTR of the ferritin mRNA, called the iron-response element (IRE), which is folded into a hairpin loop. When iron becomes available, it binds to the IRP, changing its conformation and causing it to dissociate from the IRE, allowing translation of the mRNA to form ferritin.



Mechanisms of mRNA-specific regulation of 40S ribosomal subunit association. a | Steric blockage. The iron regulatory proteins (IRPs) 1 or 2 bind to the ironresponsive element (IRE) and prevent the recruitment of the 43S pre-initiation complex to the mRNA-bound eukaryotic initiation factor (eIF)4F complex by steric hindrance. b | Interference with the eIF4F complex. The mRNA-specific eIF4E-binding proteins Maskin and Bicoid interact with eIF4E, thereby preventing its interaction with eIF4G. Maskin is targeted to the mRNA through the cytoplasmic-polyadenylation-element-binding protein (CPEB) that recognizes the cytoplasmic polyadenylation element (CPE) that is located at the 3′ untranslated region (UTR), whereas Bicoid directly binds to the mRNA at the Bicoid response element (BRE). c | Capindependent inhibition. Binding of Sex-lethal (SXL) to uridine-rich sequences (Poly(U) in the figure) at both the 5′ and 3′ UTRs assists the recruitment of a co-repressor complex (CR) to inhibit translation, possibly by interference with ribosome scanning from the cap structure.

Epigenetic regulation of gene expression



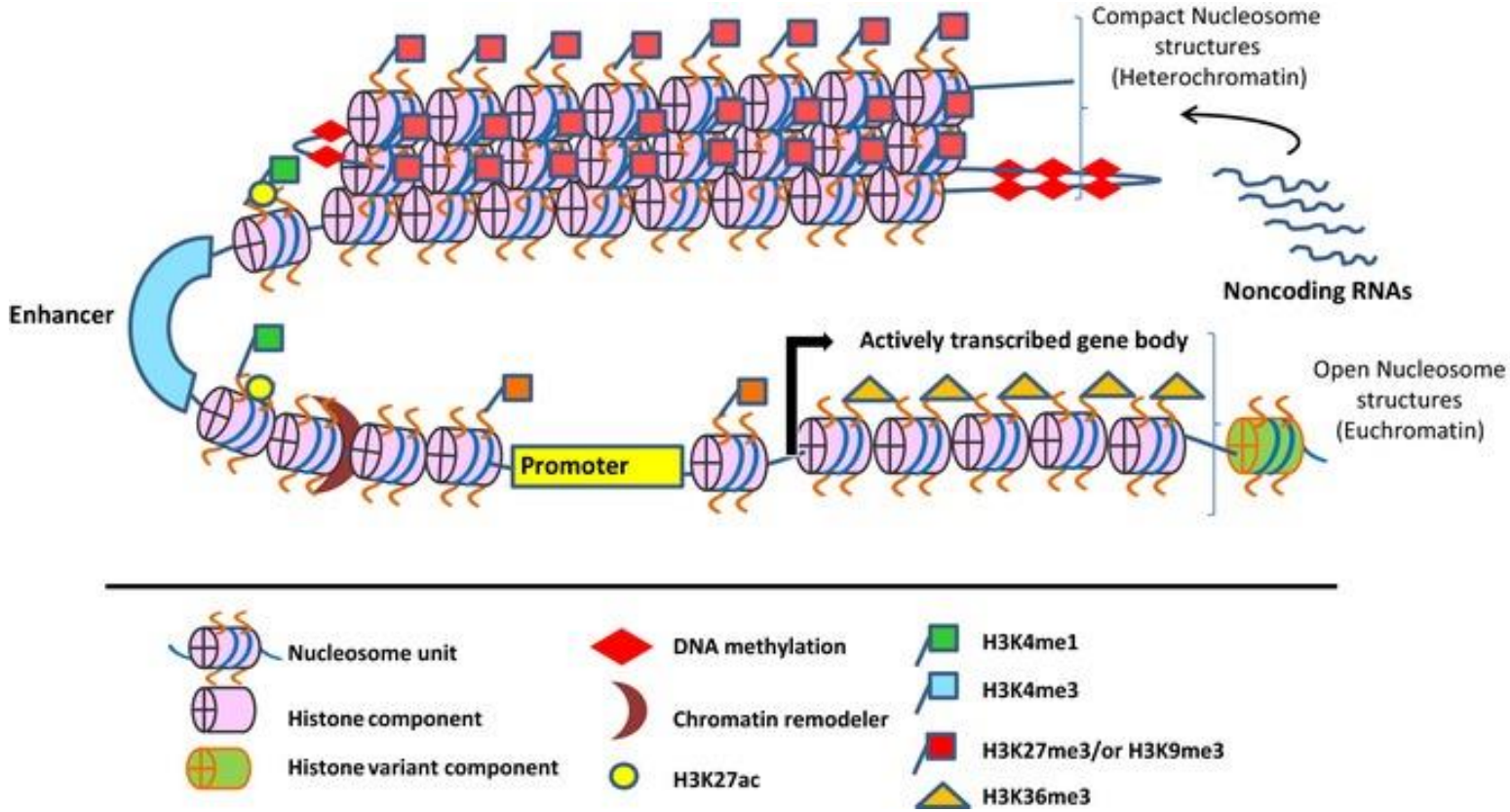


Schematic showing the interaction between different epigenetic components and their actions that lead to altered gene expression profiles in an individual. 5mCpG, 5'-methylcytosine-phosphodiester-guanine-3';5hmCpG, 5'-hydroxymethylcytosine-phosphodiester-guanine-3'.

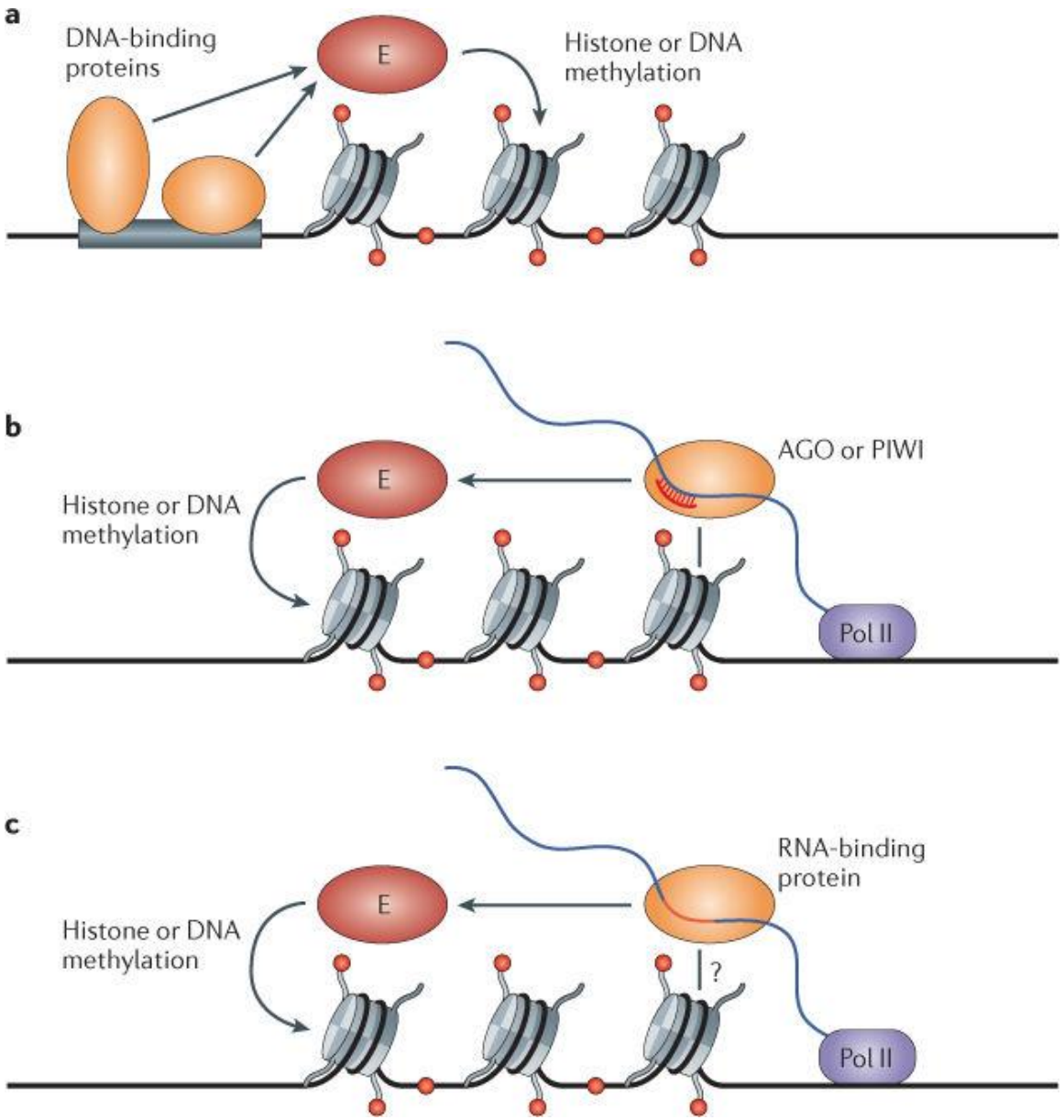
Epigenetic regulation of gene expression

Molecular basis

- Epigenetic changes modify the activation of certain genes, but not the genetic code sequence of DNA.
- The microstructure (not code) of DNA itself or the associated chromatin proteins may be modified, causing activation or silencing. This mechanism enables differentiated cells in a multicellular organism to express only the genes that are necessary for their own activity.
- Epigenetic changes are preserved when cells divide. Most epigenetic changes only occur within the course of one individual organism's lifetime; however, these epigenetic changes can be transmitted to the organism's offspring through a process called transgenerational epigenetic inheritance. Moreover, if gene inactivation occurs in a sperm or egg cell that results in fertilization, this epigenetic modification may also be transferred to the next generation.
- Specific epigenetic processes include paramutation, bookmarking, imprinting, gene silencing, X chromosom inactivation, position effect, DNA methylation reprogramming, transvection, maternal effects, the progress of carcinogenesis, many effects of teratogens, regulation of histone modifications and heterochromatin, and technical limitations affecting parthenogenesis and cloning.



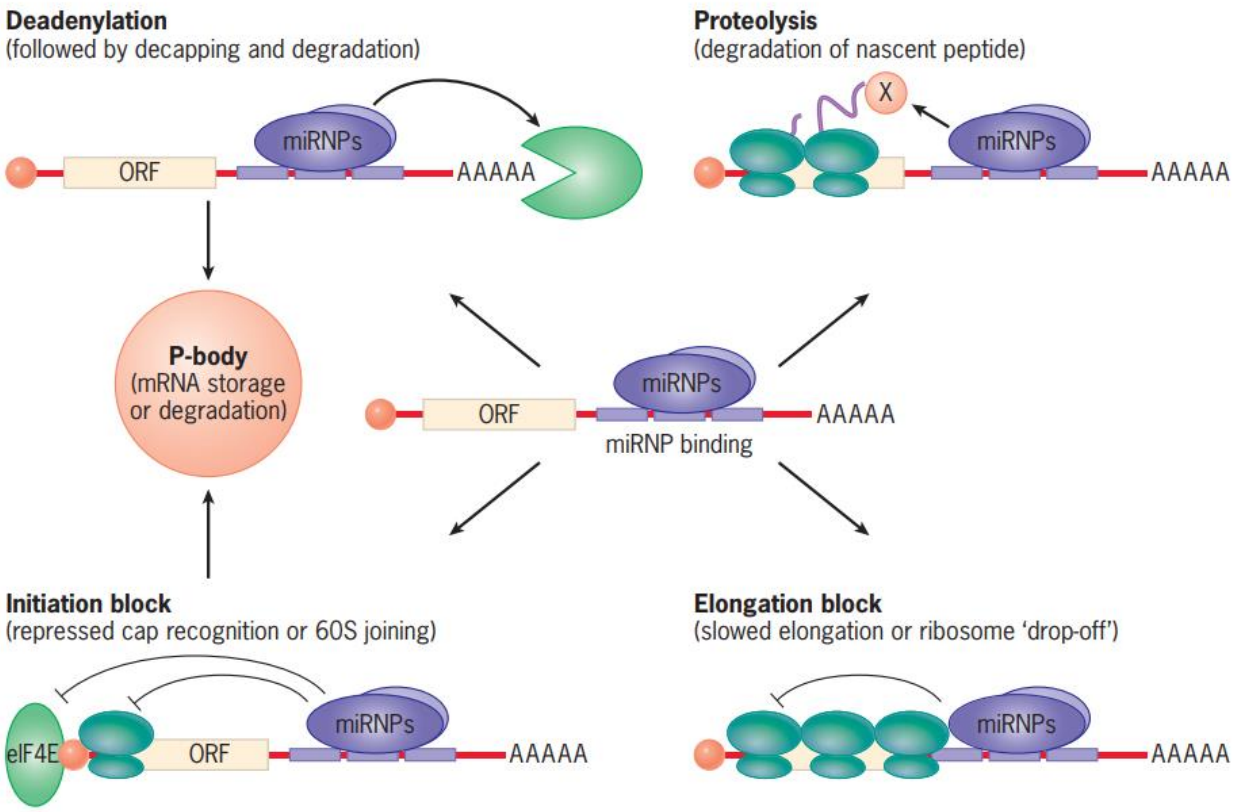
Epigenetic mechanisms in the regulation of gene expression. Epigenetic mechanisms maintain chromatin structure either in a transcriptionally silent 'heterochromatin' or open and active 'euchromatin' states. Both heterochromatin and euchromatin structures are marked with distinct epigenetic modifications such as DNA methylation and or histone modification. Non-coding RNAs also contribute to epigenetic regulation of gene expression.



RNAs, both short and long, represent an alternative to DNA-binding proteins as specificity determinants for epigenetic regulation of gene expression

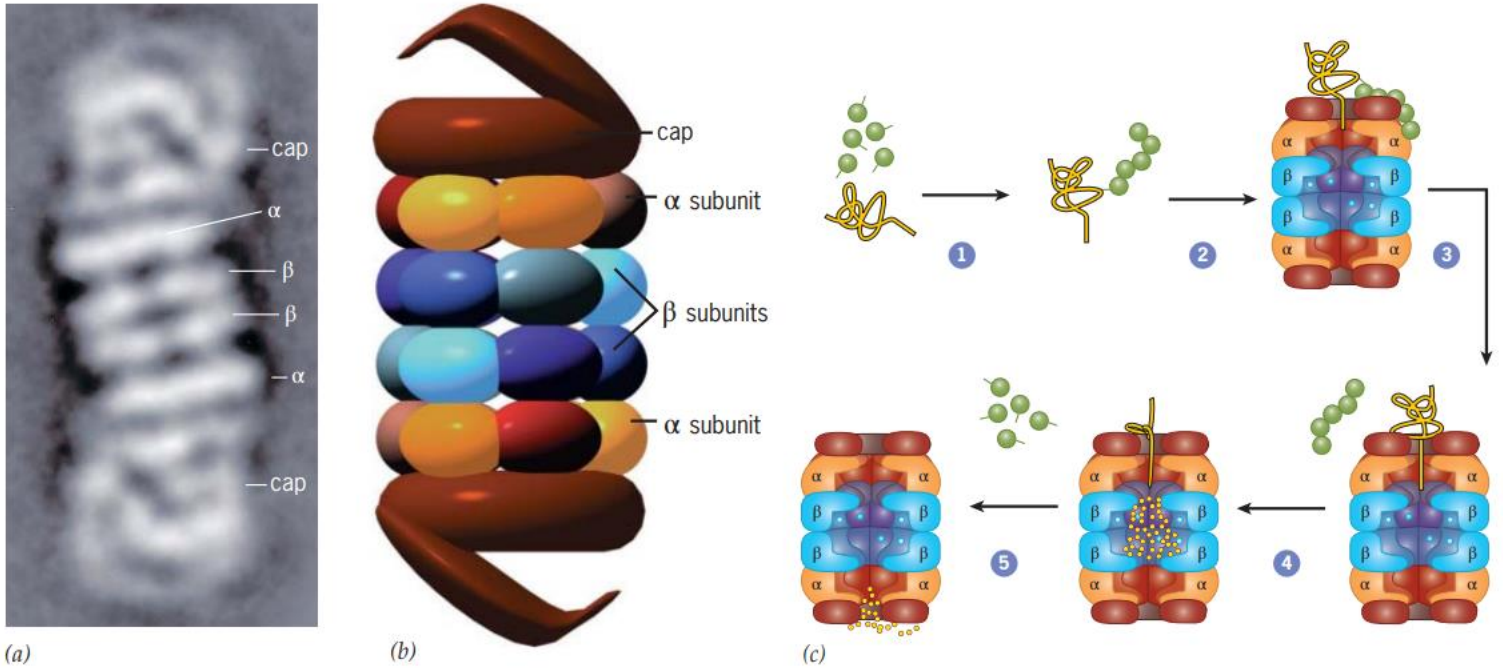
Enzymes (E) that catalyse methylation of histone tails or cytosine bases in DNA are recruited to chromatin by distinct mechanisms. **a** | Sequence-specific DNA-binding proteins recruit histone- or DNA-modifying enzymes to chromatin. **b** | Small RNAs target an Argonaute (AGO) or PIWI protein to a nascent transcript through base-pairing interactions to recruit modifying enzymes. **c** | Long RNAs act as scaffolds for RNA-binding proteins to recruit chromatin-modifying complexes. In all cases, the binding of the enzyme or the recruiting factors (for example, AGO–PIWI complexes in part **b** and RNA-binding protein complexes in part **c**) to chromatin may be enhanced by interactions with pre-existing modifications, which self-reinforce the epigenetic state. Pol II, RNA polymerase II.

The Role of MicroRNAs in Translational Control



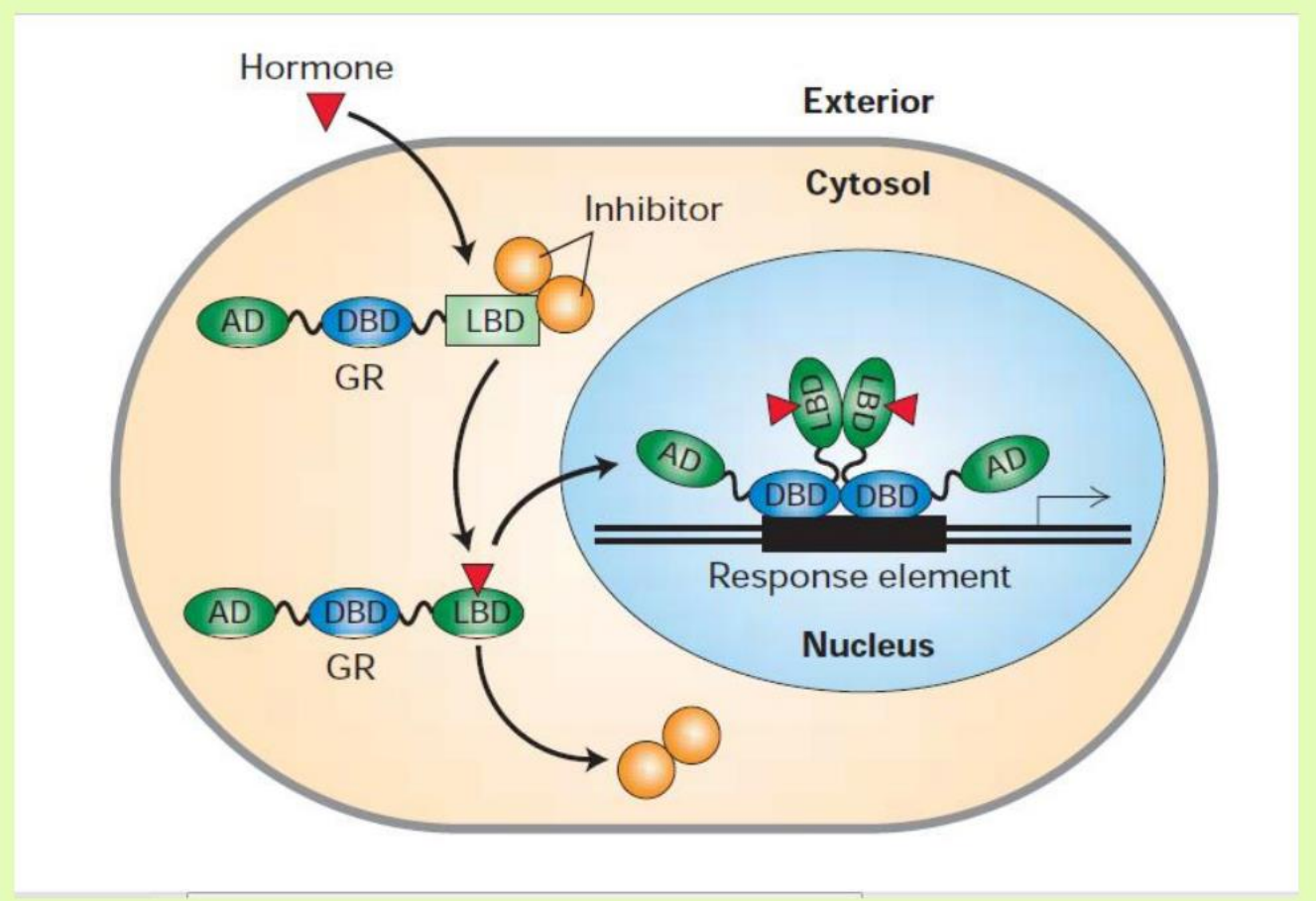
miRNA mediated gene silencing. miRNAs, as part of an miRNP protein complex as illustrated in Figure 11.35, pair with sequence elements in the 3 ′ UTR of target mRNAs. They suppress gene expression posttranscriptionally by either promoting mRNA deadenylation and degradation (upper left), inhibiting the initiation of translation (lower left), inhibiting translation elongation (lower right), or possibly activating degradation of nascent peptides (upper right). Some mRNA: miRNA pairs may be stored in cytoplasmic P-bodies and, upon depression by removal of miRNAs, exit P-bodies and resume translation. ORF (open reading frame) corresponds to the amino acid coding segment of the mRNA. SOURCE: W. Filipowicz , et al., Nat. Revs. Gen. 9 , 109 , 2008 , Fig. 3. Nature Reviews Genetics by Nature Publishing Group . Reproduced with permission of Nature Publishing Group in the format reuse in a book/textbook via Copyright Clearance Center.

Post Translational Control

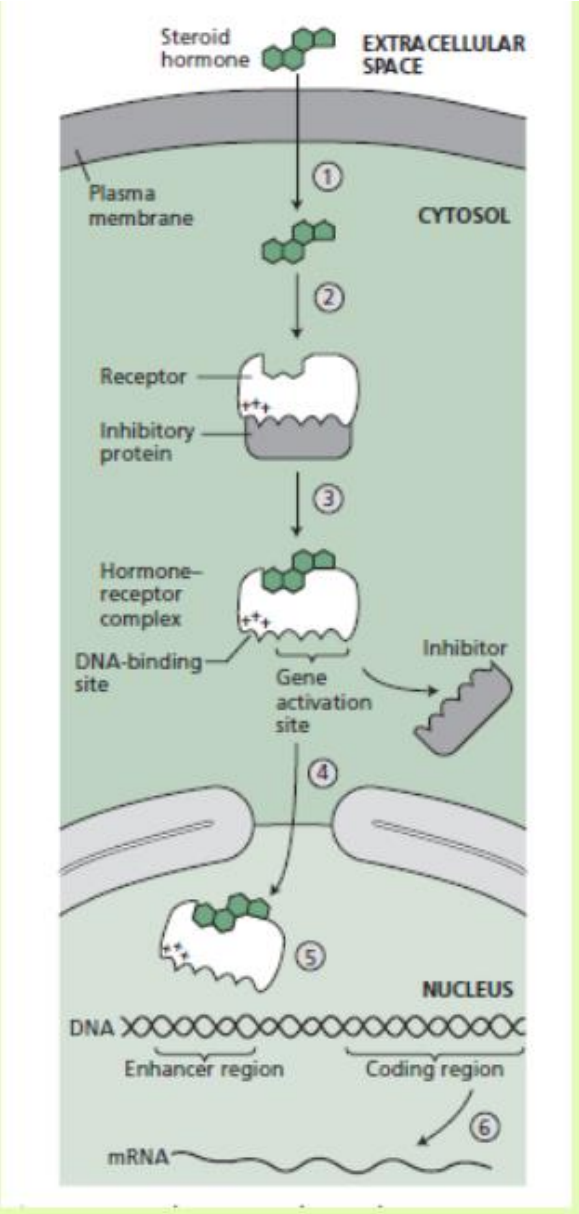


Proteasome structure and function. (a) High-resolution electron micrograph of an isolated Drosophila proteasome. (b) Model of a proteasome based on high-resolution electron microscopy and X-ray crystallography. Each proteasome consists of two multisubunit caps (or regulatory particles) on either end of a tunnel-shaped cylinder (or core particle) that is formed by a stack of four rings. Each ring consists of seven subunits that are divided into two classes, α-type and β-type. The two inner rings are composed of β subunits, which surround a central chamber. The subunits are drawn in different shades of color because they are similar, but not identical, polypeptides. Three of the seven β subunits in each ring possess proteolytic activity; the other four are inactive in eukaryotic cells. The two outer rings are composed of enzymatically inactive α subunits that form a narrow opening (approximately 13 Å) through which unfolded polypeptide substrates are threaded to reach the central chamber, where they are degraded. (c) Steps in the degradation of proteins by a proteasome. In step 1, the protein to be degraded is linked covalently to a string of ubiquitin molecules. Ubiquitin attachment requires the participation of three distinct enzymes (E1, E2, and E3) in a process that is not discussed in the text. In step 2, the polyubiquitinated target protein binds to the cap of the proteasome. The ubiquitin chain is then removed, and the unfolded polypeptide is threaded into the central chamber of the proteasome (step 3), where it is degraded by the catalytic activity of the β subunits (steps 4 and 5).

Model of hormone-dependent gene activation by a homodimeric nuclear receptor.

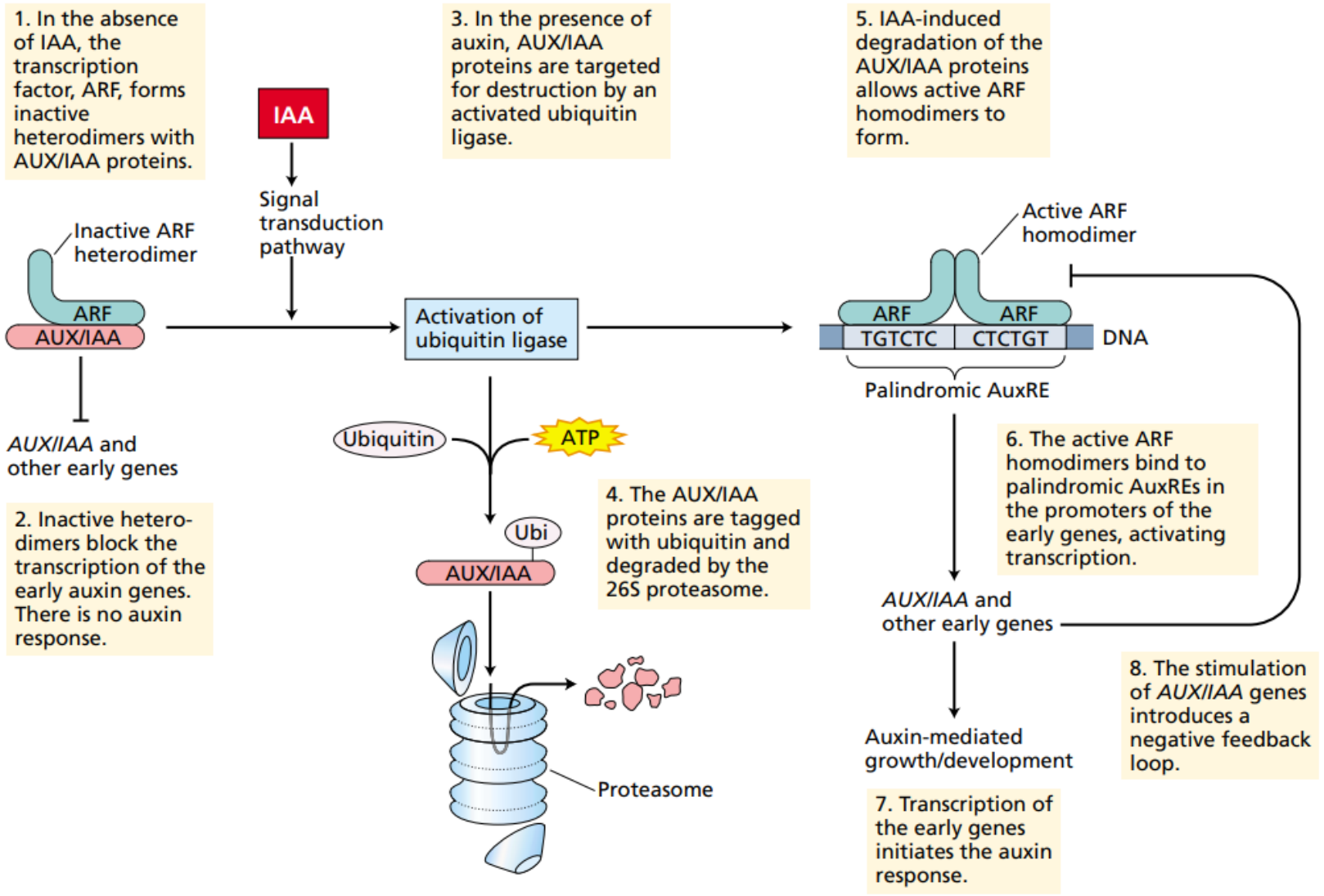


In the absence of hormone, the receptor is kept in the cytoplasm by interaction between its ligand-binding domain (LBD) and inhibitor proteins. When hormone is present, it diffuses through the plasma membrane and binds to the ligand binding domain, causing a conformational change that releases the receptor from the inhibitor proteins. The receptor with bound ligand is then translocated into the nucleus, where its DNA-binding domain (DBD) binds to response elements, allowing the ligandbinding domain and an additional activation domain (AD) at the N-terminus to stimulate transcription of target genes

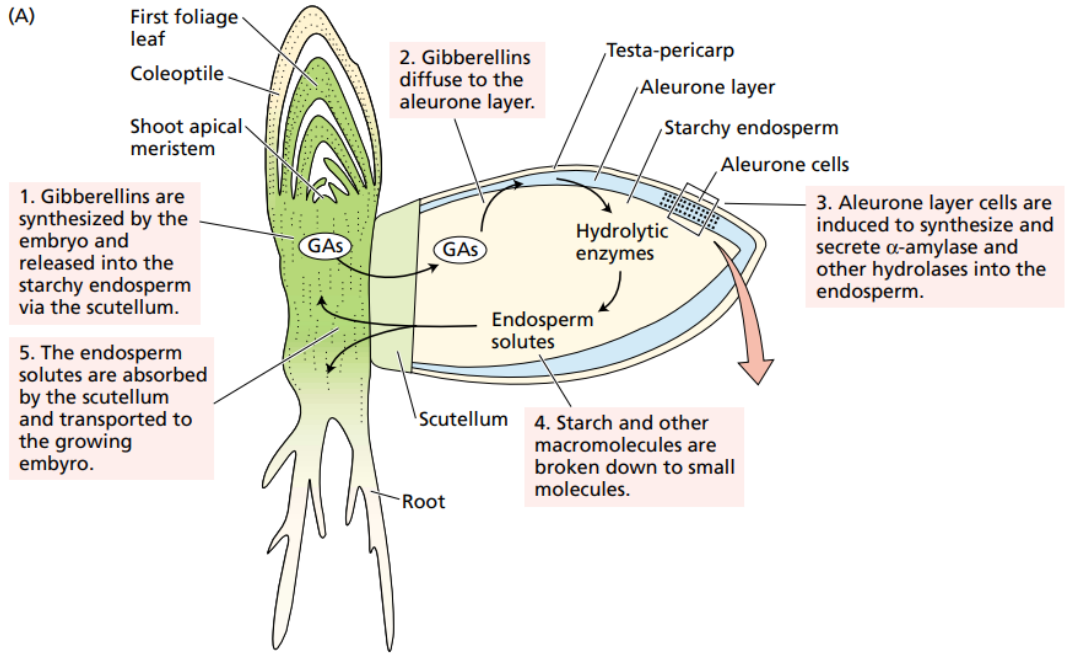


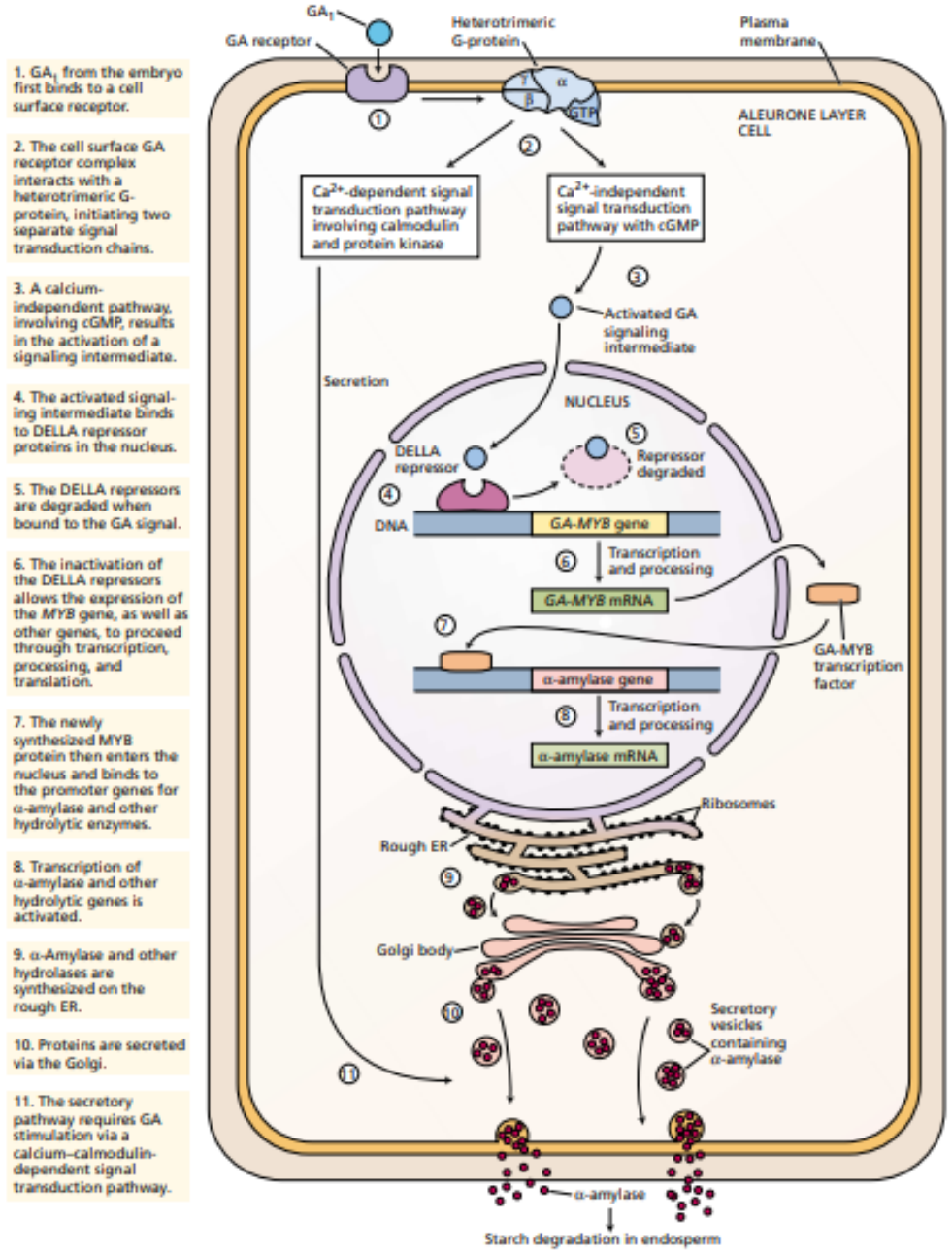
Glucocorticoid steroid receptors are transcription factors. (1) Glucocorticoid hormone is lipophilic and diffuses readily through the membrane to the cytosol. (2) Once in the cytosol, the hormone binds to its cytosolic receptor, (3) causing the release of an inhibitory protein from the receptor. (4) The activated receptor then diffuses into the nucleus. (5) In the nucleus, the receptor–hormone complex binds to the enhancer regions of steroid-regulated genes. (6) Transcription of the genes is stimulated. (From Becker et al. 1996.)

Auxin mediated gene regulation



GA mediated gene regulation





References

MOLECULAR MECHANISMS OF TRANSLATIONAL CONTROL

Fátima Gebauer and Matthias W. Hentze‡*

Abstract | Translational control is widely used to regulate gene expression. This mode of regulation is especially relevant in situations where transcription is silent or when local control over protein accumulation is required. Although many examples of translational regulation have been described, only a few are beginning to be mechanistically understood. Instead of providing a comprehensive account of the examples that are known at present, we discuss instructive cases that serve as paradigms for different modes of translational control.

REVIEW

CpG islands and the regulation of transcription

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Lodish et al., Molecular Cell Biology, 6th edition, W.H.Freeman & Co.Ltd.