CONTROL OF GENE EXPRESSION

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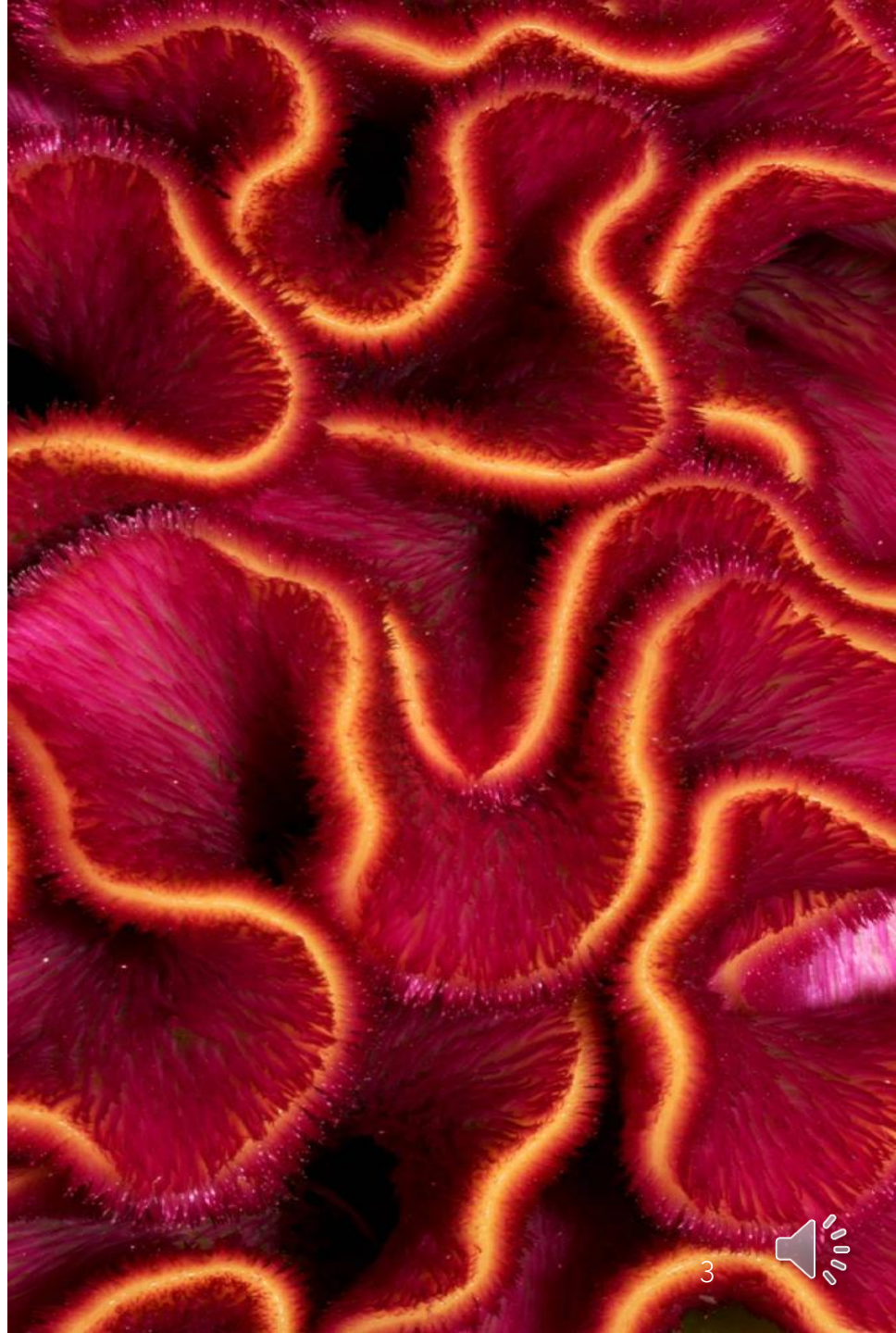
OUTLINE

- Introduction
- Overview of Gene Expression
- How Transcriptional Switch Work

INTRODUCTION

- Control of gene expression is essential to all organisms.
- In bacteria, it allows the cell to take advantage of changing environmental conditions.
- In multicellular organisms, it is critical for directing development and maintaining homeostasis.
- But how do cells coordinate and control such an intricate process—and how does an individual cell specify which of its genes to express?



THE DIFFERENT CELL TYPES OF A MULTICELLULAR ORGANISM CONTAIN THE SAME DNA

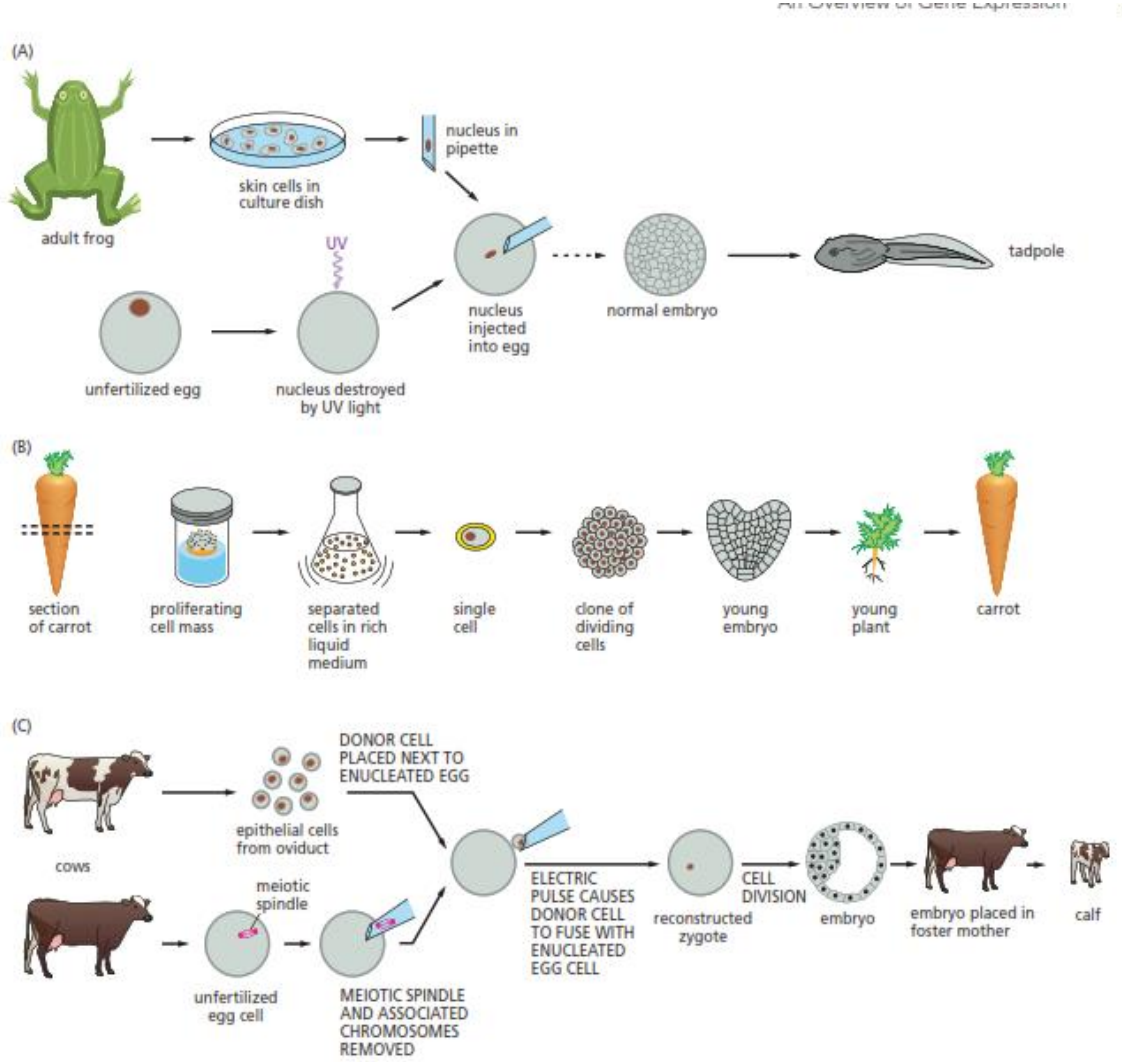


Figure 8–2 Differentiated cells contain all the genetic instructions necessary to direct the formation of a complete organism. (A) The nucleus of a skin cell from an adult frog transplanted into an egg whose nucleus has been destroyed can give rise to an entire tadpole. The broken arrow indicates that to give the transplanted genome time to adjust to an embryonic environment, a further transfer step is required in which one of the nuclei is taken from the early embryo that begins to develop and is put back into a second enucleated egg. (B) In many types of plants, differentiated cells retain the ability to "de-differentiate," so that a single cell can proliferate to form a clone of progeny cells that later give rise to an entire plant. (C) A nucleus removed from a differentiated cell from an adult cow can be introduced into an enucleated egg from a different cow to give rise to a calf. Different calves produced from the same differentiated cell donor are all clones of the donor and are therefore genetically identical. (A, modified from J.B. Gurdon, *Sci. Am.* 219:24–35, 1968, with permission from the Estate of Bunji Tagawa.)

DIFFERENT CELL TYPES PRODUCE DIFFERENT SETS OF PROTEINS

- The extent of the differences in gene expression between different cell types may be roughly gauged by comparing the protein composition of cells in liver, heart, brain, and so on.
- Gene expression can also be studied by cataloging a cell's RNAs, including the mRNAs that encode protein.
- at any one time, a typical differentiated human cell expresses perhaps 5000–15,000 protein-coding genes from a total of about 21,000.
- It is the expression of a different collection of genes in each cell type that causes the large variations seen in the size, shape, behavior, and function of differentiated cells.

GENE EXPRESSION CAN BE REGULATED AT VARIOUS STEPS FROM DNA TO RNA TO PROTEIN

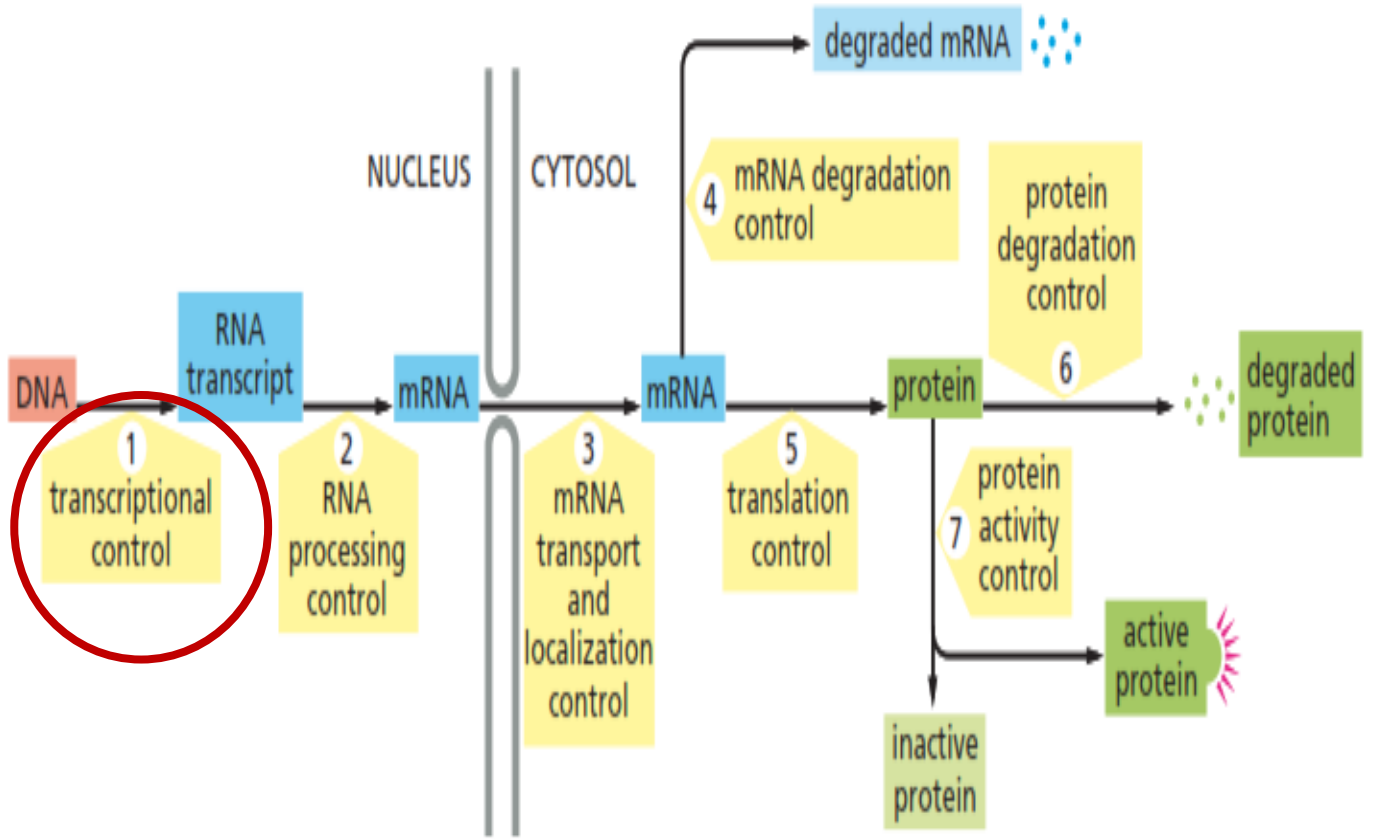
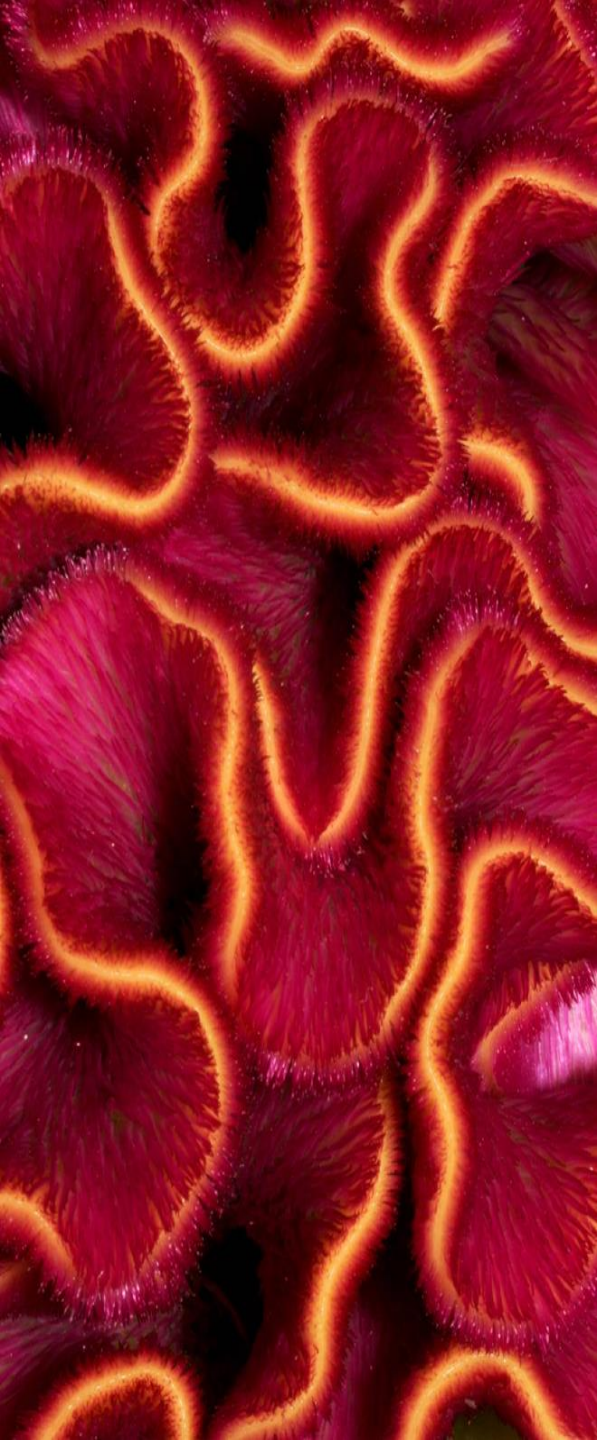


Figure 8–3 Gene expression in eukaryotic cells can be controlled at various steps. Examples of regulation at each of these steps are known, although for most genes the main site of control is step 1—transcription of a DNA sequence into RNA.

HOW TRANSCRIPTIONAL SWITCHES WORK

- This concept was a major advance, and it came originally from studies of how E. coli bacteria adapt to changes in the composition of their growth medium.
- The enormous complexity of gene regulation in higher organisms, combined with the packaging of their DNA into chromatin
- The discussion begin with **the transcription regulators** → proteins that bind to DNA and control gene transcription.



TRANSCRIPTION REGULATORS BIND TO REGULATORY DNA SEQUENCES

- Control of transcription is usually exerted at the step at which the process is initiated → Promotor regions of gene
- Promotor regions include a transcription initiation site and proteins that associate with the active polymerase–sigma factor in bacteria or general transcription factors in eukaryotes
- In addition to the promoter, nearly all genes, whether bacterial or eukaryotic, have regulatory DNA sequences that are used to switch the gene on or off.
- Some regulatory DNA sequences are as short as 10 nucleotide (bacteria), and more than 10,000 nucleotide pairs (eukaryotes)
- Regulatory DNA sequences do not work by themselves. To have any effect, these sequences must be recognized by proteins called transcription regulators.
- The binding of a transcription regulator to a regulatory DNA sequence that acts as the switch to control transcription.

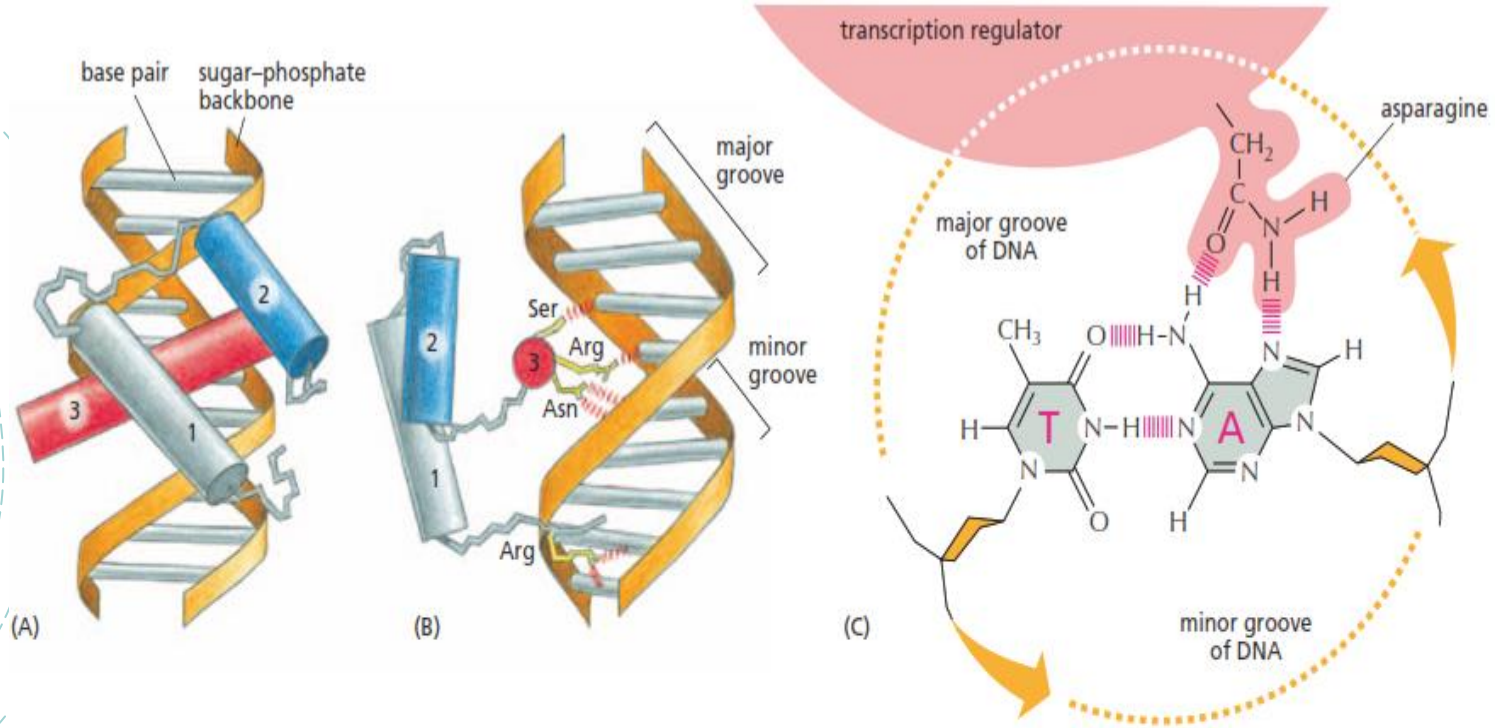


Figure 8–4 A transcription regulator interacts with the major groove of a DNA double helix. (A) This regulator recognizes DNA via three α helices, shown as numbered cylinders, which allow the protein to fit into the major groove and form tight associations with the base pairs in a short stretch of DNA. This particular structural motif, called a *homeodomain*, is found in many eukaryotic DNA-binding proteins (Movie 8.1). (B) Most of the contacts with the DNA bases are made by helix 3 (*red*), which is shown here end-on. The protein interacts with the edges of the nucleotides without disrupting the hydrogen bonds that hold the base pairs together. (C) An asparagine residue from helix 3 forms two hydrogen bonds with the adenine in an A-T base pair. The view is end-on looking down the DNA double helix, and the protein contacts the base pair from the major groove side. For simplicity, only one amino acid–base contact is shown; in reality, transcription regulators form hydrogen bonds (as shown here), ionic bonds, and hydrophobic interactions with individual bases in the major groove. Typically, the protein–DNA interface would consist of 10–20 such contacts, each involving a different amino acid and each contributing to the overall strength of the protein–DNA interaction.

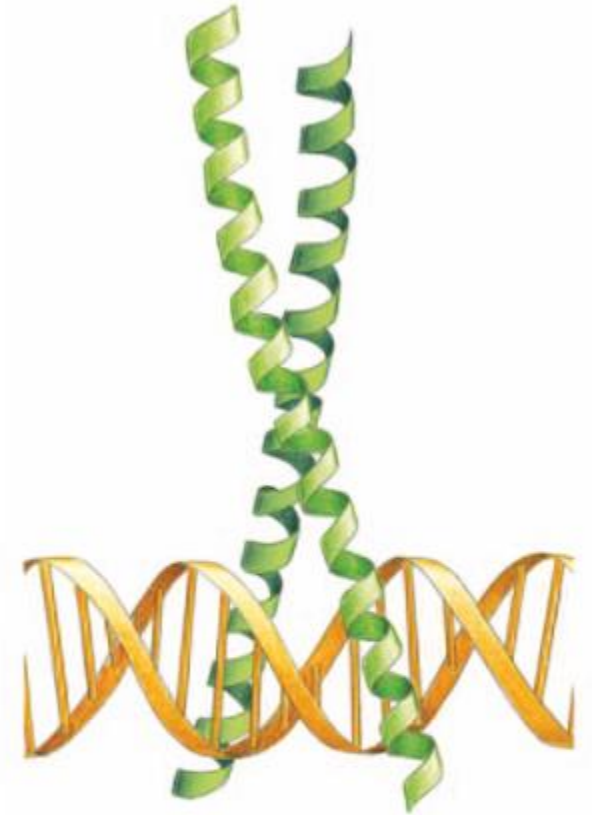


Figure 8–5 Many transcription regulators bind to DNA as dimers. This transcription regulator contains a *leucine zipper* motif, which is formed by two α helices, each contributed by a different protein subunit. Leucine zipper proteins thus bind to DNA as dimers, gripping the double helix like a clothespin on a clothesline (Movie 8.2).

TRANSCRIPTION CONTROL IN BACTERIAL GENE (E.COLI)

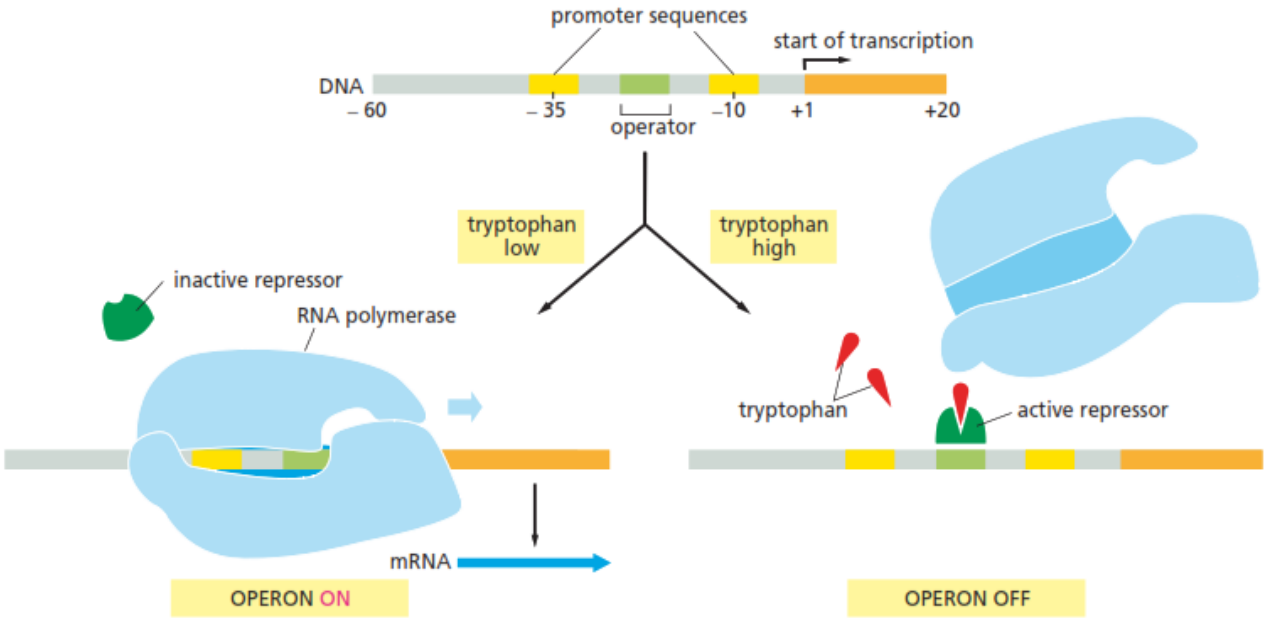


Figure 8–7 Genes can be switched off by repressor proteins. If the concentration of tryptophan inside a bacterium is low (*left*), RNA polymerase (*blue*) binds to the promoter and transcribes the five genes of the tryptophan operon. However, if the concentration of tryptophan is high (*right*), the repressor protein (*dark green*) becomes active and binds to the operator (*light green*), where it blocks the binding of RNA polymerase to the promoter. Whenever the concentration of intracellular tryptophan drops, the repressor falls off the DNA, allowing the polymerase to again transcribe the operon. The promoter contains two key blocks of DNA sequence information, the –35 and –10 regions, highlighted in *yellow*, which are recognized by RNA polymerase (see Figure 7–10). The complete operon is shown in Figure 8–6.

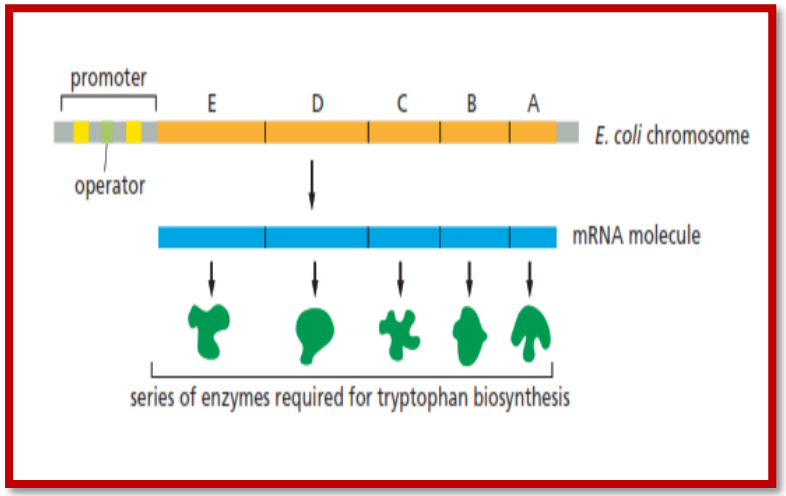


Figure 8–6 A cluster of bacterial genes can be transcribed from a single promoter. Each of these five genes encodes a different enzyme; all of the enzymes are needed to synthesize the amino acid tryptophan. The genes are transcribed as a single mRNA molecule, a feature that allows their expression to be coordinated. Clusters of genes transcribed as a single mRNA molecule are common in bacteria. Each of these clusters is called an *operon* because its expression is controlled by a regulatory DNA sequence called the *operator* (*green*), situated within the promoter. The *yellow* blocks in the promoter represent DNA sequences that bind RNA polymerase.

TRANSCRIPTION CONTROL IN BACTERIAL GENE (E.COLI)

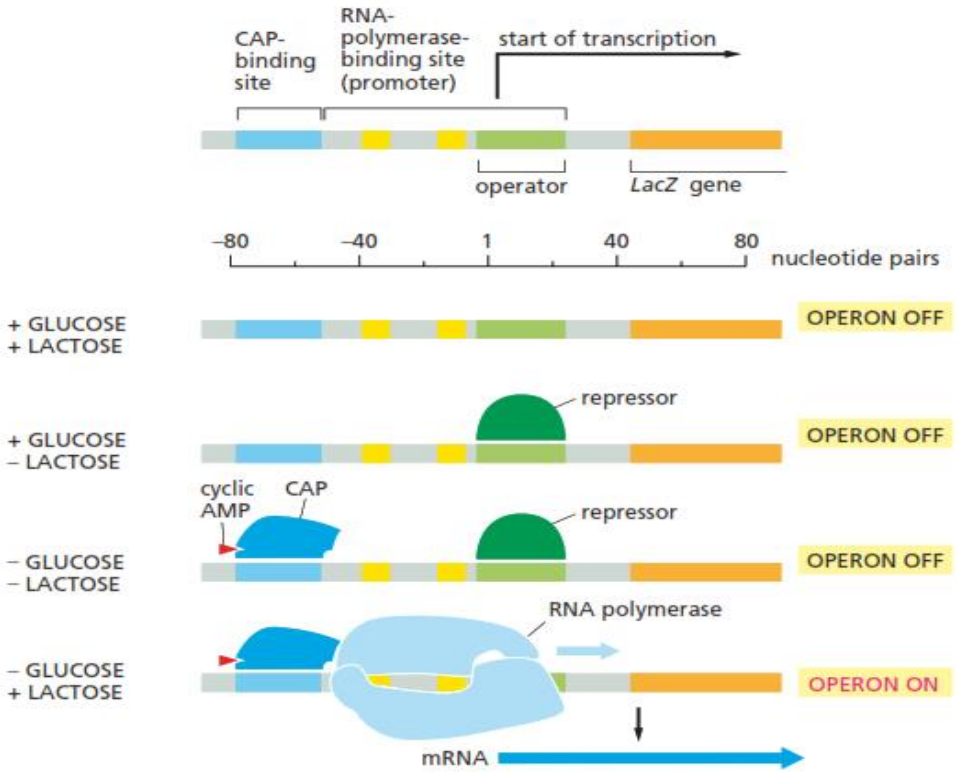


Figure 8–9 The *Lac* operon is controlled by two transcription regulators, the Lac repressor and CAP. When lactose is absent, the Lac repressor binds to the *Lac* operator and shuts off expression of the operon. Addition of lactose increases the intracellular concentration of a related compound, allolactose; allolactose binds to the Lac repressor, causing it to undergo a conformational change that releases its grip on the operator DNA (not shown). When glucose is absent, cyclic AMP (*red* triangle) is produced by the cell, and CAP binds to DNA. *LacZ*, the first gene of the operon, encodes the enzyme β-galactosidase, which breaks down lactose to galactose and glucose.

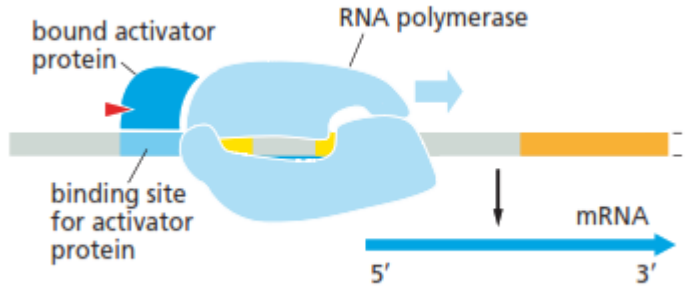


Figure 8–8 Genes can be switched on by activator proteins. An activator protein binds to a regulatory sequence on the DNA and then interacts with the RNA polymerase to help it initiate transcription. Without the activator, the promoter fails to initiate transcription efficiently. In bacteria, the binding of the activator to DNA is often controlled by the interaction of a metabolite or other small molecule (*red* triangle) with the activator protein. The *Lac* operon works in this manner, as we discuss shortly.

TRANSCRIPTION CONTROL IN EUKARYOTES

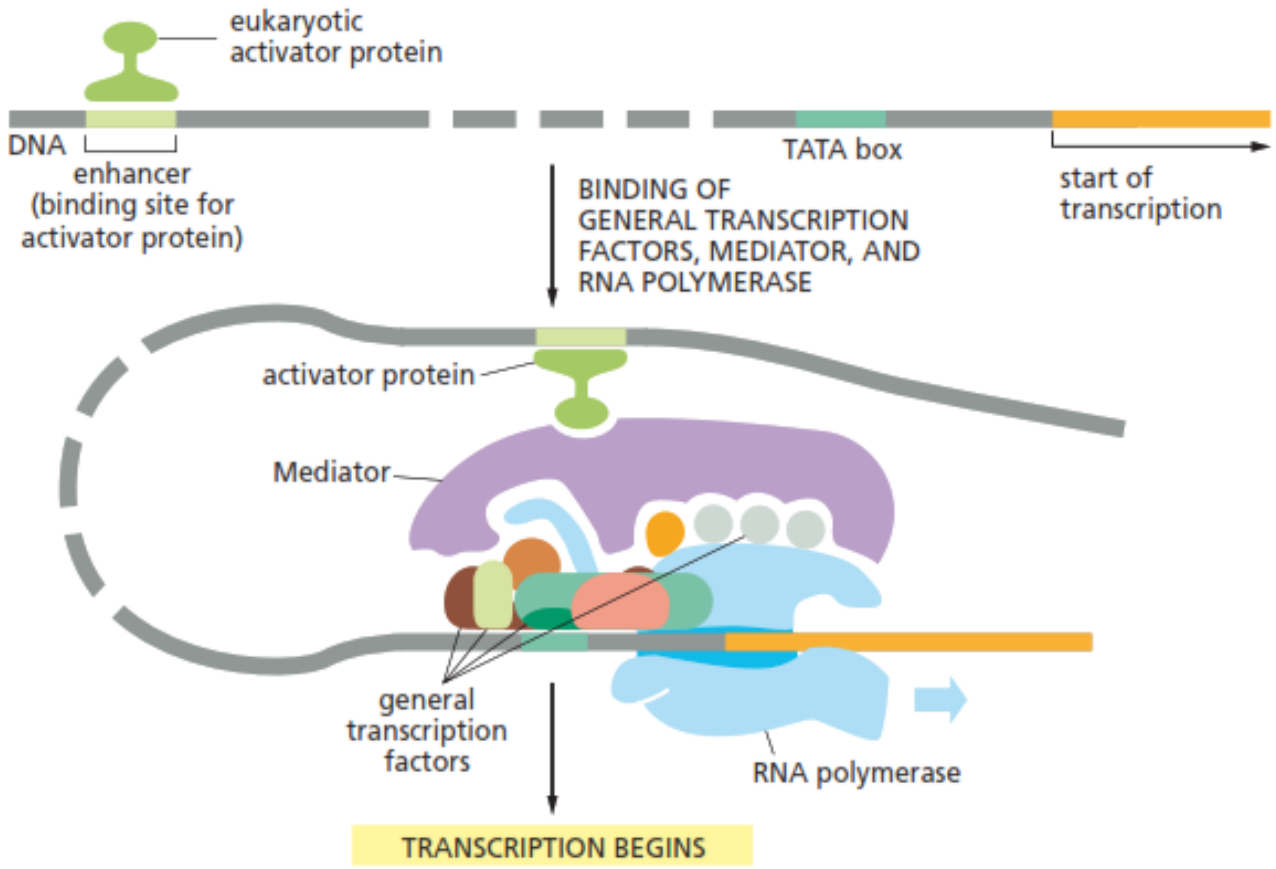


Figure 8–10 In eukaryotes, gene activation can occur at a distance. An activator protein bound to a distant enhancer attracts RNA polymerase and general transcription factors to the promoter. Looping of the intervening DNA permits contact between the activator and the transcription initiation complex bound to the promoter. In the case shown here, a large protein complex called Mediator serves as a go-between. The broken stretch of DNA signifies that the length of DNA between the enhancer and the start of transcription varies, sometimes reaching tens of thousands of nucleotide pairs in length. The TATA box is a DNA recognition sequence for the first general transcription factor that binds to the promoter (see Figure 7–12).

TRANSCRIPTION CONTROL IN EUKARYOTES

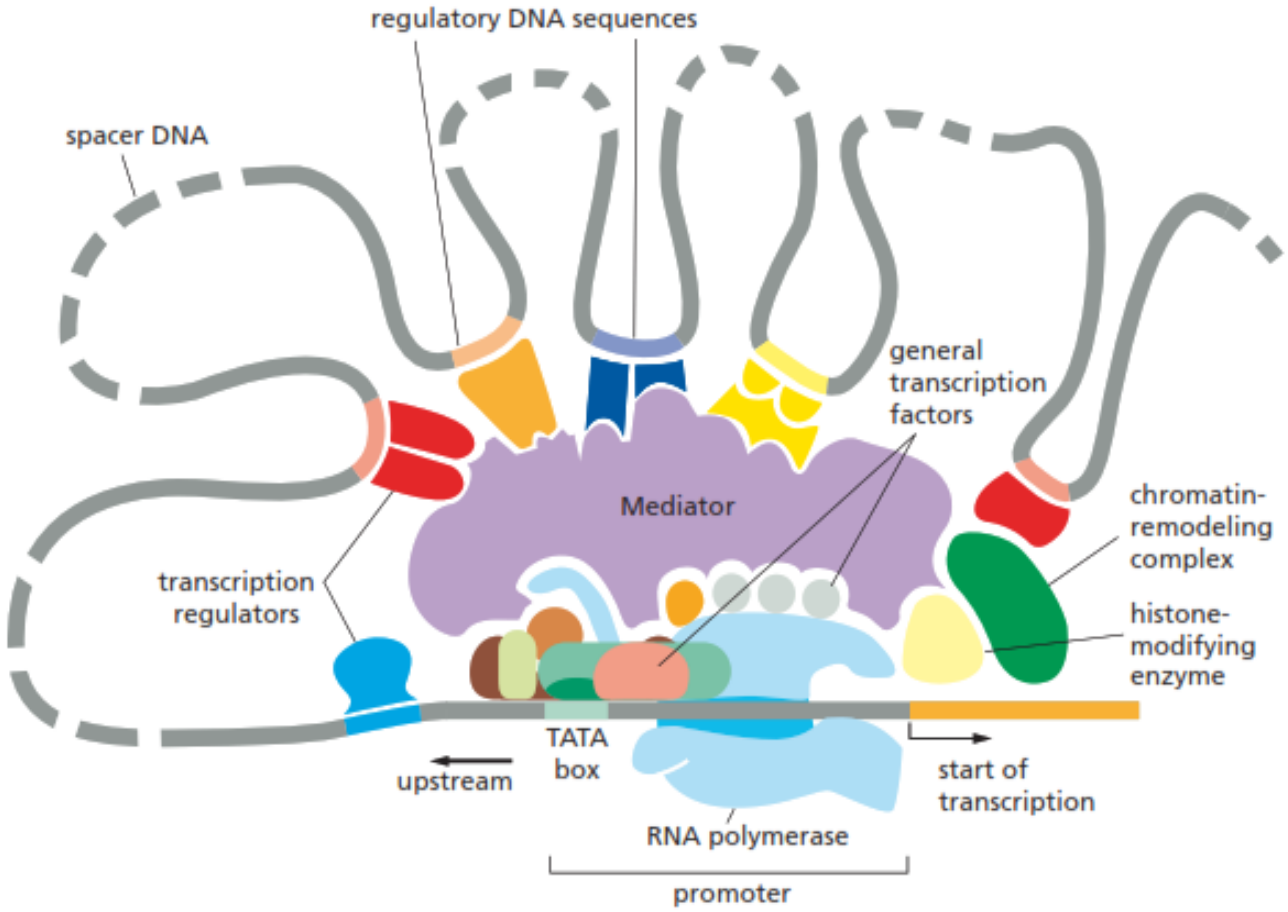


Figure 8–12 Transcription regulators work together as a "committee" to control the expression of a eukaryotic gene. Whereas the general transcription factors that assemble at the promoter are the same for all genes transcribed by RNA polymerase (see Figure 7–12), the transcription regulators and the locations of their DNA binding sites relative to the promoters are different for different genes. These regulators, along with chromatin-modifying proteins, are assembled at the promoter by the Mediator. The effects of multiple transcription regulators combine to determine the final rate of transcription initiation.

TRANSCRIPTION CONTROL IN EUKARYOTES

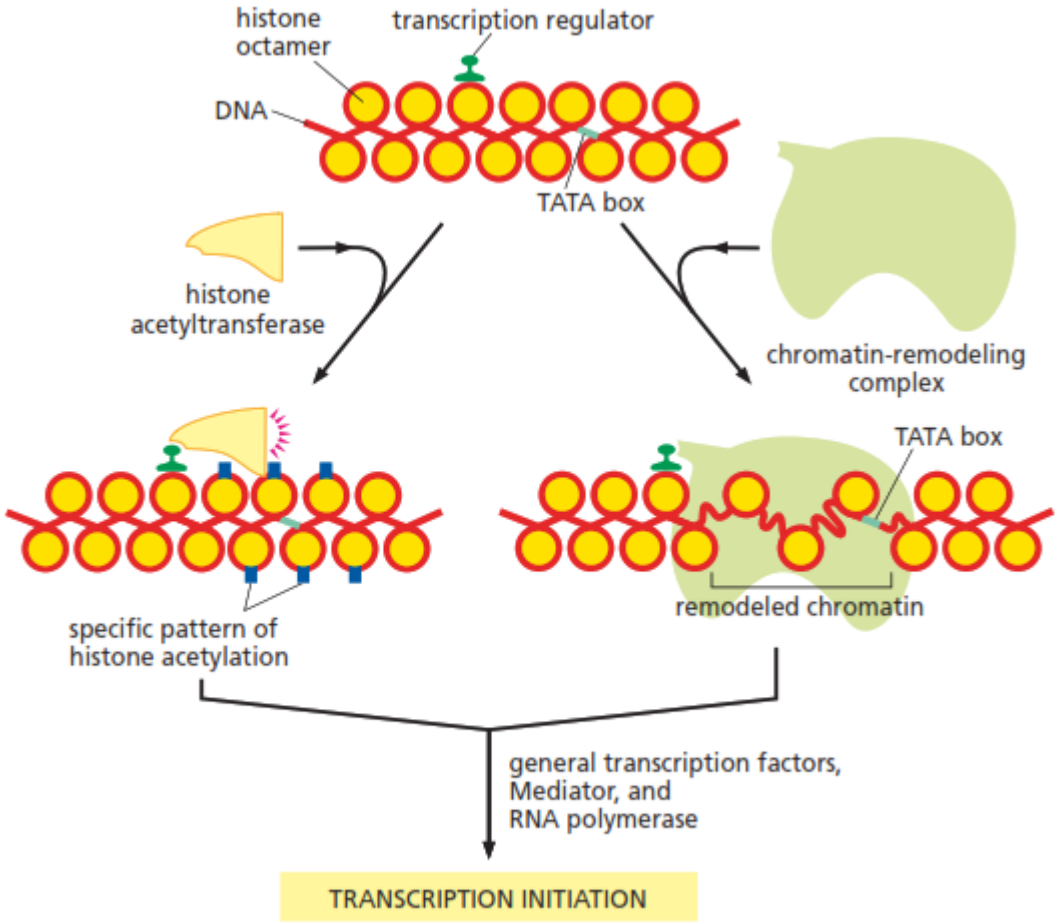


Figure 8–11 Eukaryotic transcriptional activators can recruit chromatin-modifying proteins to help initiate gene transcription. On the right, chromatin-remodeling complexes render the DNA packaged in chromatin more accessible to other proteins in the cell, including those required for transcription initiation; notice, for example, the increased exposure of the TATA box. On the left, the recruitment of histone-modifying enzymes such as histone acetyltransferases adds acetyl groups to specific histones, which can then serve as binding sites for proteins that stimulate transcription initiation (not shown).

THANK YOU