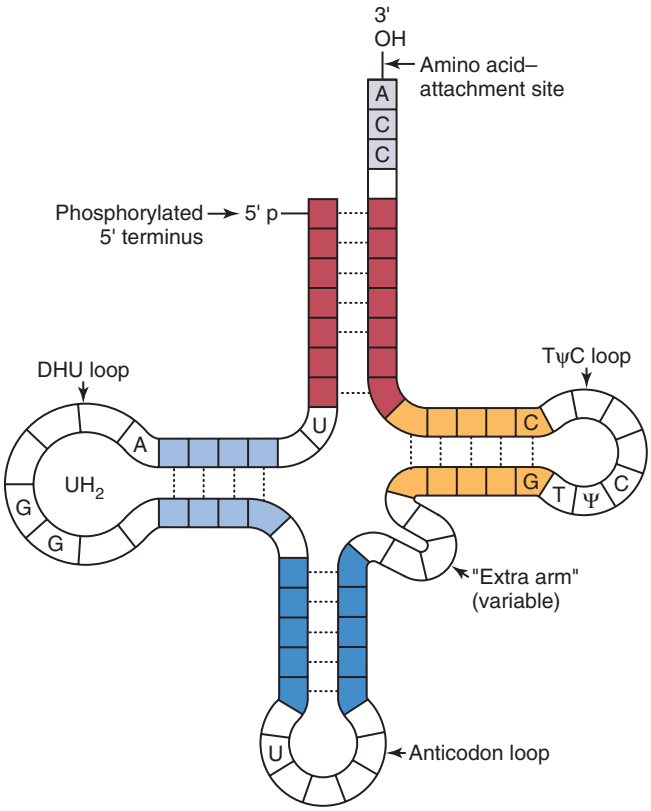

FIGURE 1-3 Secondary structure of transfer RNA (tRNA). The structure of each tRNA serves as an adapter molecule that recognizes a specific codon for the amino acid to be added to the polypeptide chain. About one half the hydrogen-bonded bases of the single chain of ribonucleotides are shown paired in double helices like a cloverleaf. The 5′ terminus is phosphorylated, and the 3′ terminus contains the hydroxyl group on an attached amino acid. The anticodon loop is typically located in the middle of the tRNA molecule. C, Cytocide; DHU, dihydroxyuridine; G, guanine; UH_2, dihydrouridine; ψ, pseudouridine; T, ribothymidine; U, uracil. (Data from Berg JM, Tymoczko JL, Strayer JL: Berg, Tymoczko, and Strayer's biochemistry, ed 5, New York, 2006, WH Freeman.)

number of available tRNA molecules, mitigates the chances of premature chain termination, and ameliorates the potential deleterious consequences of single-base mutations. The enzymatic activity of the ribosome then links amino acids through the synthesis of a peptide bond, releasing the tRNA in the process.

Consecutive linkage of amino acids in the growing polypeptide chain represents the terminal event in the conversion of information contained within the nuclear DNA sequence into mature protein (DNA → RNA → protein). Proteins are directly responsible for the form and function of an organism. Abnormalities in protein structure or function brought about by changes in primary amino acid sequence are the immediate precedent cause of changes in phenotype, adverse forms of which define a disease state.

Inhibition of RNA synthesis is a well-recognized mechanism of specific toxins and antibiotics. Toxicity from the ingestion of the poisonous mushroom *(Amanita phalloides)*, for example, leads to the release of the toxin α-amanitin, a cyclic octapeptide that inhibits the RNA polymerase II and blocks elongation of RNA synthesis. The antibiotic actinomycin D binds with high affinity to double-helical DNA and intercalates between base pairs, precluding access of DNA-dependent RNA polymerases and the selective inhibition of transcription. Several major antibiotics inhibit translation. For example, the aminoglycoside antibiotics disrupt the mRNA-tRNA codon-anticodon interaction, whereas erythromycin and chloramphenicol inhibit peptide bond formation.

CONTROL OF GENE EXPRESSION

Overview

The timing, duration, localization, and magnitude of gene expression are all important elements in the complex tapestry of cell form and function governed by the genome. Gene expression represents the flow of information from the DNA template into mRNA transcripts and the process of translation into mature protein.

Four levels of organization involving transcription factors, RNAs, chromatin structure, and epigenetic factors orchestrate gene expression in the mammalian genome. Transcriptional regulators bind to specific DNA motifs that positively or negatively control the expression of neighboring genes. The information contained in the genome must be transformed into functional units of RNA or protein products. How DNA is packed and modified represents additional modes of gene regulation by disrupting the access of transcription factors from DNA-binding motifs.

In the postgenomic era, the challenge is to understand the architecture by which the genome is organized, controlled, and modulated. Transcription factors, chromatin architecture, and modifications of nucleosomal organization make up the major mechanisms of gene regulation in the genome.

Transcriptional Regulation

The principal regulatory step in gene expression occurs at the level of gene transcription. A specific DNA-dependent RNA polymerase performs the transcription of information contained in genomic DNA into mRNA transcripts. Transcription begins at a proximal (i.e., toward the 5′ end of the gene) transcription start site containing nucleotide sequences that influence the rate and extent of the process (see Fig. 1-1). This *promoter region* of the gene often includes a sequence rich in adenine and thymine (i.e., TATA box) along with other sequence motifs within about 100 bases of the start site. These regions of DNA that regulate transcription are known as *cis*-acting regulatory elements. Some of these regulatory regions of promoter sequence bind proteins known as *trans*-acting factors (i.e., transcription factors), which are themselves encoded by other genes. The *cis*-acting regulatory sequences to which transcription factors bind are often referred to as *response elements*. Families of transcription factors have been identified and are often described by unique aspects of their predicted secondary protein structure, including helix-turn-helix motifs, zinc finger motifs, and leucine zipper motifs. Transcription factors make up an estimated 3% to 5% of the protein-coding products of the genome.

In addition to gene-promoter regions, enhancer sites are distinct from promoter sites in that they can exist at distances quite remote from the start site, either upstream or downstream (i.e., beyond the 3′ end of the gene), and without clear orientation