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Molecular Basis of Human Disease

Ivor J. Benjamin

INTRODUCTION

Medicine has evolved dramatically during the past century—from a healing art in which standards of practice were established on the basis of personal experience passed on from one practitioner to the next to a rigorous intellectual discipline reliably steeped in the scientific method. This process tests the validity of a hypothesis or prediction through experimentation, the foundation of current advances in the fields of physiology, microbiology, biochemistry, and pharmacology.

These advances have served as the basis for new diagnostic and therapeutic approaches to illness and disease while challenging providers and practitioners to adopt their use at an accelerated pace in 21st century. Since the 1980s, for example, understanding of the molecular basis of genetics has expanded dramatically, and advances in this field have identified new and exciting dimensions for defining the basis of conventional genetic diseases (e.g., sickle cell disease) and complex genetic traits (e.g., hypertension). Insights into the interactions between genes and environment that independently influence the noncoding genome laid the foundation for the field of epigenetics.

Armed with a variety of sensitive and specific molecular techniques, contemporary medicinal practice seeks to provide the molecular underpinning of complex pathobiologic processes and identify individuals at risk for common diseases. To fully exploit modern medicine, clinical teams are increasingly relying on a detailed understanding of cellular mechanisms and on precision drugs that disrupt the fine-structural targets underlying the molecular basis of disease. The outcomes of large clinical trials that yield mean responses to therapy will likely evolve into personalized medicine, defining more effective treatments for specific patient subpopulations. This introductory chapter offers an overview of these complex and rapidly evolving topics and summarizes the principles of molecular medicine that are highlighted in specific sections throughout this text.

DEOXYRIBONUCLEIC ACID AND THE GENOME

All organisms possess a scheme to transmit the essential information containing the genetic makeup of the species through successive generations. Human cells have 23 pairs of chromosomes, and each pair contains a unique sequence of genetic information. In the human genome, about 6×10^9 nucleotides, or 3×10^9 pairs of nucleotides, associate in the double helix. The specificity of DNA is determined by the base sequence that is stored in complementary form in the double-helical structure. It facilitates correction of sequence errors and provides a mechanistic basis for replication of information during cell division. Each DNA strand provides a template for replication, which is accomplished by the action of DNA-dependent polymerases that unwind the double-helical DNA and copy each single strand with remarkable fidelity.

Except for gametocytes, all cells contain the duplicate, diploid number of genetic units, one half of which is referred to as the *haploid number*. The genetic information contained in chromosomes is separated into discrete functional elements known as *genes*. A gene is a unit of base sequences that (with rare exception) encodes a specific polypeptide sequence. New evidence suggests that small, noncoding RNAs play critical roles in the expression of this essential information. An estimated 30,000 genes constitute the human haploid genome, and they are interspersed among sequence regions that do not code for protein and whose function is as yet unknown. For example, noncoding RNAs (e.g., transfer RNAs [tRNAs], ribosomal RNAs [rRNAs], other small RNAs) are components of enzyme complexes such as the ribosome and spliceosome. The average chromosome contains 3000 to 5000 genes, which range in size from about 1 kilobase (kb) to 2 megabases (Mb).

RIBONUCLEIC ACID SYNTHESIS

Transcription, or RNA synthesis, is the process of transferring information contained in nuclear DNA to an intermediate molecular species known as messenger RNA (mRNA). Two biochemical differences distinguish RNA from DNA. The polymeric backbone is made up of ribose rather than deoxyribose sugars linked by phosphodiester bonds, and the base composition is different in that uracil is substituted for thymine.

RNA synthesis from a DNA template is performed by three types of DNA-dependent RNA polymerases, each a multisubunit complex with distinct nuclear location and substrate specificity. RNA polymerase I, located in the nucleolus, directs the transcription of genes encoding the 18S, 5.8S, and 28S ribosomal RNAs, forming a molecular scaffold with catalytic and structural functions within the ribosome. RNA polymerase II, which is located in the nucleoplasm instead of the nucleoli, primarily transcribes precursor mRNA transcripts and small RNA molecules. The carboxyl terminus of RNA polymerase II is uniquely modified with a 220-kD protein domain, which is the site of enzymatic regulation by protein phosphorylation of critical serine and threonine