

Chapter 2

Principles of Molecular Biology

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The rapid development of molecular biology in recent decades has dramatically changed the way we practice medicine. With the help of an impressive arsenal of new technologies, including high-throughput sequencing and microarrays, we are now well-equipped to probe into the molecular nature of diseases. Which set of genes are involved? What are the genetic and epigenetic alterations associated with these genes? In this chapter, we will describe the basic concepts of molecular biology, including genes, types of mutations, and gene expression.

DNA

DNA (deoxyribonucleic acid) is the genetic material of cells. It is composed of individual units called nucleotides. A nucleotide is composed of three subunits: a five-carbon sugar (deoxyribose), a phosphate group, and a base. There are four types of bases in DNA: adenine (A), guanine (G), thymine (T), and cytosine (C). Adenine and guanine are purines, and thymine and cytosine are pyrimidines. A polynucleotide chain is formed by linking the adjacent nucleotides via 5'→3' phosphodiester bonds. In 1953, Watson and Crick solved the structure of DNA – demonstrating that a DNA molecule is composed of two complementary polynucleotide chains forming the double-helix structure [1]. The double-helix chains are stabilized by hydrogen bonds formed between the opposing A–T and C–G bases on the two complementary polynucleotide chains (Fig. 2.1).

RNA

In contrast to DNA, RNA (ribonucleic acid) contains the sugar ribose instead of deoxyribose, and uracil (U) instead of thymine (T). An RNA molecule is single-stranded and less stable than a DNA molecule. Cellular RNA serves diverse functions, carried out by different families of RNA molecules, including messenger RNA (mRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), small interfering RNA (siRNA), and microRNA (miRNA). Ribozymes are RNA molecules with catalytic

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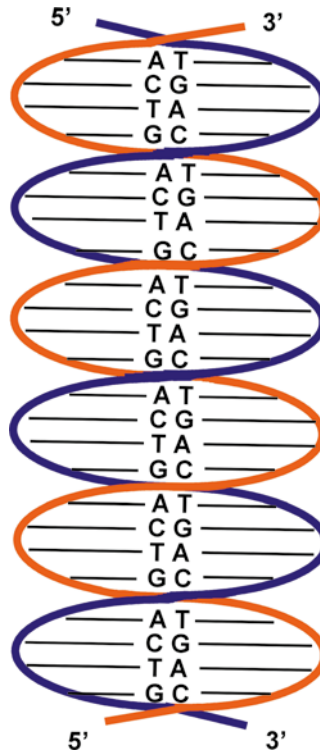


Fig. 2.1 Double-helix structure of DNA. The double-helix structure of DNA is stabilized by the hydrogen bonds formed between A–T and C–G bases on the two antiparallel complementary strands. *A* adenine, *T* thymine, *G* guanine, *C* cytosine

functions. Because RNA molecules have diverse functions, proponents of the “RNA world” theory suggest that RNA may have preceded DNA and protein in life’s long evolutionary journey [2, 3].

The Human Genome

The human genome is composed of slightly more than three billion base pairs of DNA, organized into 46 chromosomes (22 pairs of autosomes and 2 sex chromosomes). The Human Genome Project (HGP) has taught us that there are approximately 20,000–25,000 protein-coding genes, representing only ~1.5% of the entire genome size [4]. The remainder of the human genome includes regulatory sequences, RNA genes, pseudogenes, repeat sequences, and other sequences for which no known functions are currently understood.

Repeat DNA Sequences in the Genome

Much of the so-called “junk DNA” (noncoding DNA) in the human genome contains repeat sequences. There are two types of repeat sequences: (a) tandem repeat and (b) interspersed repeat.

Tandem repeats are two or more nucleotides repeated as a unit one after another in the same orientation. Examples of tandem repeats include microsatellites (2–6 nucleotides long) and minisatellites (longer than microsatellites, but shorter than 60 nucleotides in length). Microsatellites are useful markers for identity testing, bone marrow chimerism study, microsatellite instability (MSI) testing, and gene dosage studies, such as loss of heterozygosity (LOH) or gene duplication analyses.

Interspersed repetitive DNA sequences, also known as retrotransposons, are repeat elements characterized by RNA intermediates [5]. In mammals, interspersed repetitive DNA constitutes approximately half of the genome. There are two types of interspersed repeat: (a) LTR (long terminal repeat) retrotransposons and (b) non-LTR retrotransposons. Non-LTR retrotransposons are further divided into SINEs (short interspersed nuclear elements) and LINEs (long interspersed nuclear elements). LINEs bear similarities to retroviruses, in that they encode the enzyme reverse-transcriptase which transcribes LINEs RNA into many DNA copies for integration into new genomic loci, thus providing a mechanism for genomic expansion. However, LINEs do not have the LTRs found in retroviruses (i.e., they are not functional retroviruses). LINEs account for approximately 20% of the human genome. SINEs are typically less than 500 bases in length, and do not encode reverse-transcriptase. They constitute about 14% of the human genome. The most common SINEs in the human genome are Alu sequences.

Eukaryotic Gene Structure and Function

A gene is the hereditary unit of a living organism. The classical concept of genes is centered around the notion that one gene encodes for one protein/enzyme. A classical eukaryotic gene is composed of exons, introns, and regulatory sequences. Exons are stretches of DNA sequences that are represented in the mature form of RNA, including mRNA and tRNA; while, introns are the intervening DNA sequences between exons that will be spliced from the maturing RNA molecule. An RNA transcript usually consists of multiple exons spliced together. A single gene may produce several different transcripts by alternative splicing. The regulatory sequences of a gene include promoters, enhancers, silencers, insulators, and locus control regions (LCRs). A promoter is a region of DNA that facilitates transcription by binding to transcription factors (TFs) and RNA polymerase II. A gene can have several promoters, usually located upstream of the transcription start site. The location of the promoter is designated by counting back from the transcription start site (i.e., –34 refers to 34 base pairs upstream). An enhancer is another type of gene regulatory element that is located either upstream or downstream of the gene, and which regulates gene expression from a greater distance.

Large-scale genomic studies have begun to challenge the classical concept of genes [6]. Data from the International Encyclopedia of DNA Elements (ENCODE) project revealed that genes are surprisingly flexible in the sense that “genes know no borders” (i.e., when a gene is transcribed, the transcript often contains not only the gene itself, but also a portion of the next gene). Such fusion transcripts are estimated to constitute 4–5% of the traditionally recognized gene sequences. In addition, a large number of novel transcription start sites, many of which are located hundreds of thousands of bases away from known start sites, as well as new promoters, have been identified. Surprisingly, nearly a quarter of the newly discovered promoters are located at the end of genes, rather than all at their beginning, as originally thought.

Only 1–2% of human DNA sequences code for proteins. However, genomic studies have shown that much of this noncoding “junk DNA” is transcribed [6]. Among thousands of RNA molecules that are transcribed from the noncoding DNA, the family of functional noncoding RNA (ncRNA) continues to expand. This family now includes tRNA, rRNA, miRNA, siRNA, small nuclear RNA (snRNA), piwi-interacting RNA (piRNA), and long ncRNA.

Telomere

A chromosome is a thread-like structure composed of a long strand of DNA and associated proteins. The chromosomal ends in eukaryotes are sealed and stabilized by special regions called telomeres. DNA at the telomeric regions is characterized by tandem repeat sequences. For example, human telomeres consist of 2–50 kilobases of TTAGGG tandem repeat sequences.

During DNA replication, the ends of chromosomes cannot be completely replicated, resulting in a shortened copy of DNA. Therefore, telomeric sequences can provide protection against the loss of vital DNA during this process. However, telomeres themselves are subject to shortening during DNA replication, unless they can be replenished by the action of telomerase, a modified RNA polymerase only active in the germ cells of most eukaryotes [7].

Somatic human cells lack telomerase, and therefore telomeres are shortened during each round of replication in these cells. In addition, oxidative stress can also result in telomere shortening. As telomeres are continuously reduced in length during replication, somatic cells will eventually reach the limit of their replicative capacity and enter senescence. Cellular senescence is thought to play an important role in the suppression of cancer development [8]. The link between telomere and cancer is well established. Cancer cells have found ways to circumvent the replicative limit imposed by shortened telomeres. In fact, most cancer cells possess telomerase activity that can replenish and maintain their telomeres [9]. In addition, some cancer cells may employ an alternative lengthening of telomeres (ALT) pathway [10], which involves the transfer of telomere tandem repeats between sister chromatids. Telomeres are not only important in cancer research, but also for aging studies [11]. Several premature aging syndromes, such as Werner syndrome, Bloom syndrome, and ataxia-telangiectasia, are characterized by an accelerated rate of telomere attrition [12]. Telomere shortening contributes to stem cell dysfunction and loss of tissue regeneration [13]. However, the use of telomere length or its attrition rate as aging biomarkers *in vivo* remains to be established.

Mitochondrial DNA

A mitochondrion contains 2–10 copies of mitochondrial DNA (mtDNA). There are 100–10,000 copies of mtDNA in a human somatic cell. The human mitochondrial genome is a circular DNA molecule with 15,000–17,000 bases, encoding 13 proteins, 22 tRNAs, and one each of the small and large subunits of rRNA. The 13 protein-coding genes of the mitochondrial genome are primarily involved in energy metabolism: subunits 1, 2, and 3 of the cytochrome c oxidase complex; cytochrome b; subunits 6 and 8 of the ATP synthase complex; and six subunits of NADH dehydrogenase. Because human sperms contain far fewer copies of mtDNA than ova, mtDNA typically follows a maternal line of inheritance.

Even though a mitochondrion contains its own DNA, it is nuclear DNA that encodes the majority of its approximate 1,500 proteins, which are transported into the mitochondrion following assembly in the cytoplasm. Therefore, genetic disorders affecting mitochondria can show Mendelian inheritance patterns. Pure mitochondrial genetic disorders show only a maternal pattern of inheritance. Because mitochondria are the “power plants” of the cell, mitochondrial diseases tend to affect organs with high energy requirements, such as muscle, heart, brain, and nerve. Some of the notable mitochondrial diseases include Leber hereditary optic neuropathy (LHON), mitochondrial encephalomyopathy, lactic-acidosis with stroke-like symptoms (MELAS), and myoclonic epilepsy and ragged red fibers (MERRF). Mitochondrial diseases are characterized by considerable heterogeneity,

due to variable distribution of defective mtDNA from organ to organ. Of note, frequent mutations in the mitochondrial genome have been reported in both melanoma and non-melanoma skin cancers [14, 15]. Mutant mtDNA in tumor cells might alter mitochondrial-mediated apoptotic pathways to prevent cell death and/or confer a selective growth advantage [14, 15].

MicroRNA

MicroRNAs (miRNAs) are a family of 19- to 22-nucleotide, noncoding small RNAs that primarily function as gene regulators. It is estimated that there may be 1,000 unique miRNAs in the human genome. Pri-miRNAs are transcribed from miRNA genes by RNA polymerase II or III. Transcription from these miRNA genes is most likely regulated by TFs that respond to multiple signals and/or are epigenetically controlled. The pri-miRNAs are processed by RNAase III enzyme Drosha complexed with DGCR8 (DiGeorge syndrome critical region gene-8) to form pre-miRNAs, which are ~70-nucleotide RNAs with an imperfect RNA duplex structure. A small number of pre-miRNAs are derived from introns via RNA splicing, and not processed by the Drosha-DGCR8 complex. These alternatively processed miRNAs are called “mirtrons” [16]. The pre-miRNAs are transported from the nucleus to the cytoplasm, and further processed by Dicer to generate an imperfect double-stranded RNA duplex called miRNA/miRNA*. The mature miRNAs contained in RISC (RNA interference silencing complex) bind to specific sites in the 3'-untranslated region of the target mRNA. If base-pairing between the miRNA and its target is perfect, the mRNA will be cleaved. Imperfect pairing between the miRNA and its target can elicit translational repression or mRNA destabilization by deadenylation (Fig. 2.2).

miRNAs can potentially regulate thousands of human genes, many of which are involved in transcriptional regulation or other basic cellular functions, such as cell differentiation, proliferation, and apoptosis. Deregulation of miRNA gene transcription may result from alterations in miRNA gene copy number, epigenetic mechanisms, or activity of the TFs that control transcription. A number of studies have shown that miRNAs may be useful biomarkers for cancer classification and prognostication, and represent potential therapeutic targets [17].

Replication, Transcription, and Translation

Replication

Replication of DNA is required to ensure that an exact copy of DNA will be passed down from the maternal cell to its progeny (Fig. 2.3). Watson and Crick first solved the double-helix structure of DNA, and suggested a copying mechanism for DNA replication. Each strand of DNA can serve as a template for the production of a new strand (semiconservative replication). DNA replication in eukaryotes is a parallel process, whereby many chromosomal sites are replicated simultaneously. A new strand of DNA is synthesized in the 5'→3' direction, because nucleotides can only be added to the 3' end of the growing nucleotide chain. Replication begins with helicase-mediated unwinding of the double-helix, producing the replication fork and allowing the two existing DNA strands to serve as templates for new strand formation. Only one of the two new strands can be synthesized continuously in the 5'→3' direction as the replication fork opens. This is called the leading strand. The other strand, which is called the lagging strand, is formed by the joining of many discontinuous

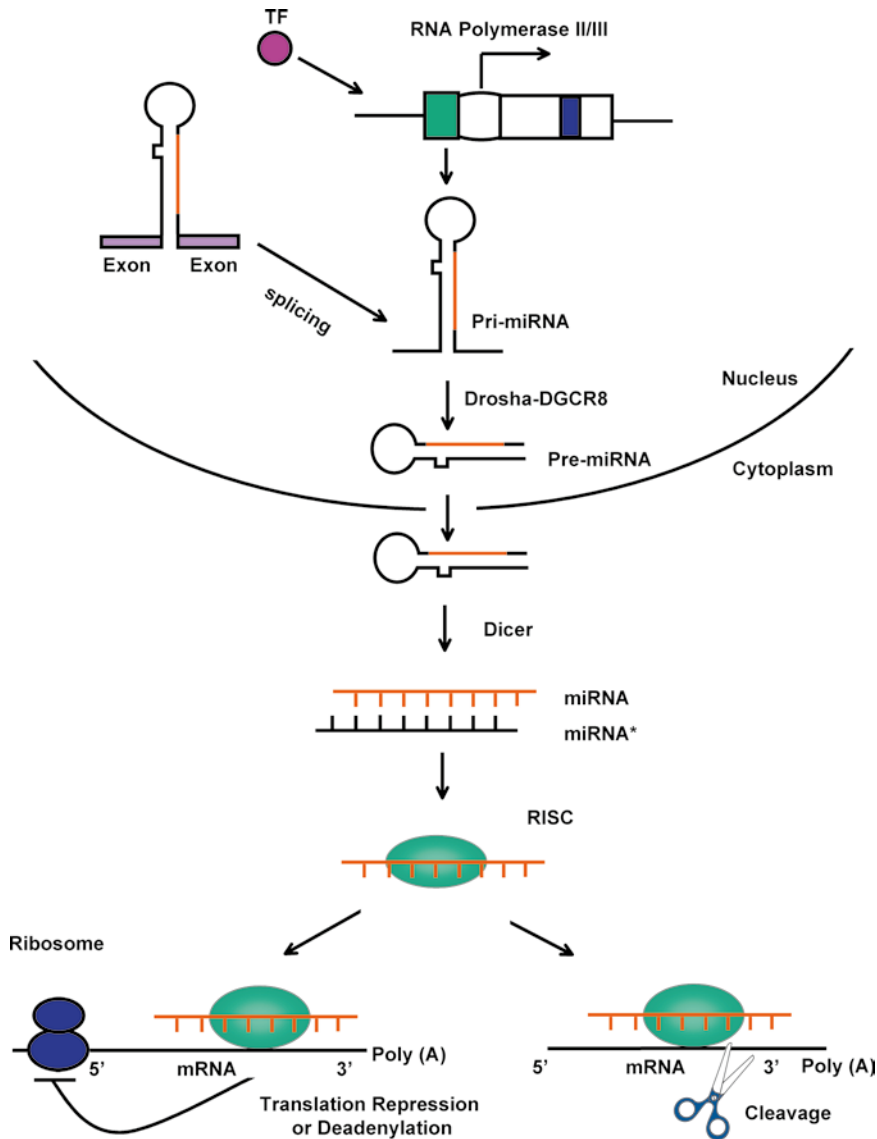


Fig. 2.2 Biogenesis of miRNA. Pri-miRNAs are transcribed from miRNA genes by RNA polymerase II or III, under the influence of transcription factors (TF). The pri-miRNAs are processed by Drosha-DGCR8 to pre-miRNAs. In an alternative pathway, miRNAs encoded in the intronic regions (“mirtrons”) form pre-miRNAs directly via RNA splicing. The pre-miRNAs are transported from the nucleus to the cytoplasm, and further processed by Dicer to generate an imperfect double-stranded RNA duplex called miRNA/miRNA*. The mature miRNAs contained in RISC (RNA interference silencing complex) bind to specific sites in the 3'-untranslated region of the target mRNA. If base-pairing between the miRNA and its target is perfect, the mRNA will be cleaved. Imperfect pairing between the miRNA and its target can elicit translational repression or mRNA destabilization by deadenylation

small segments (Okazaki fragments) that are synthesized along the lagging strand template. The DNA polymerases involved in lagging and leading strand synthesis also have proof-reading 3'→5' exonuclease activity.

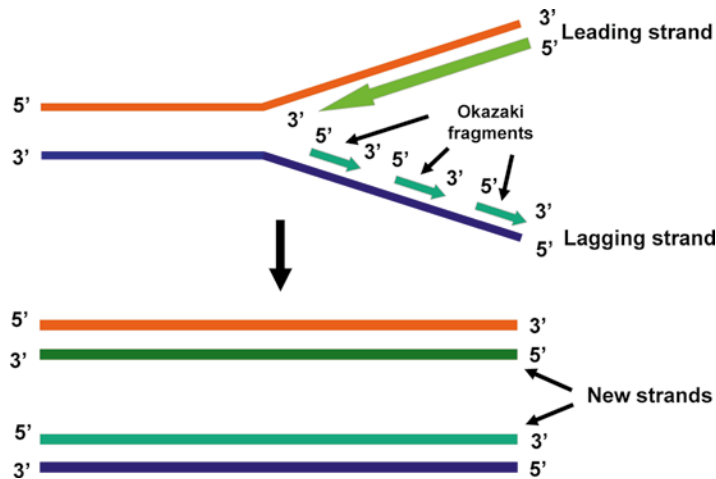


Fig. 2.3 DNA replication. DNA is unwound by helicase to form the replication fork. The leading strand is synthesized continuously in the 5' to 3' direction. The opposite strand (lagging strand) is formed by joining many discontinuous Okazaki fragments. DNA replication is semiconservative, in that each of the two newly formed DNA copies contains one old strand and one new strand

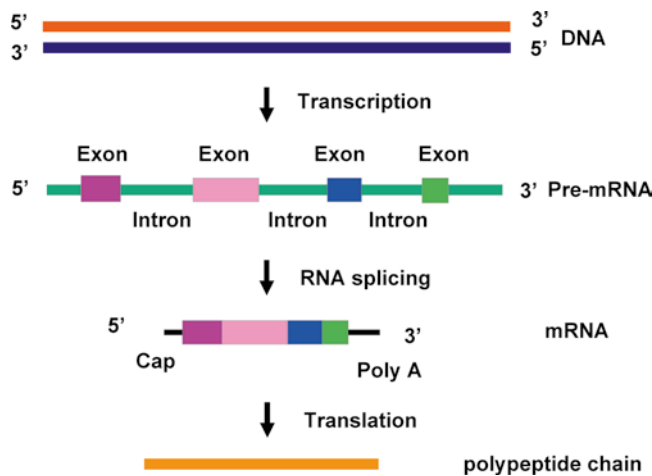


Fig. 2.4 Transcription and translation. These are two processes that decode genetic information carried by DNA. In transcription, an RNA molecule is synthesized based on its DNA template. The so-called pre-mRNA is processed by addition of a 5' “cap,” addition of a 3' polyA tail, and RNA splicing which removes intronic sequences. The mature messenger RNA, which is called mRNA, is then transported to the cytoplasm. In the cytoplasm, the mRNA sequence dictates the synthesis of a polypeptide chain on ribosomes

Transcription

The information encoded in DNA dictates RNA synthesis and subsequent protein production. The directional information flow from DNA to RNA, and finally to protein has been called the “central dogma of molecular biology” (Fig. 2.4). The transcription of DNA into RNA is a highly regulated process, involving interactions between TFs, promoters and other regulatory elements. Transcription begins at the transcriptional “start site”, which lies just upstream of the first coding sequence. From the

DNA template, the primary RNA transcript is synthesized in a 5'→3' direction, catalyzed by RNA polymerase II. The primary RNA transcript contains both intron and exon sequences, and is processed in the nucleus by “capping” at the 5' end and addition of a polyA tail to the 3' end. The RNA transcript is then further processed by removal of its intronic sequences (RNA splicing). The fully processed RNA, now called mRNA, is transported into the cytoplasm where translation takes place.

Translation

Translation is the process by which a polypeptide chain is synthesized on the basis of the mRNA nucleotide sequence. Translation occurs on ribosomes in the cytoplasm. Eukaryotic ribosomes are composed of large (60S) and small (40S) subunits. The 60S subunit contains 5S, 5.8S, and 28S RNA, and associated proteins. The 40S subunit contains 18S RNA and associated proteins. Translation is mediated by tRNAs, adaptor molecules that have the dual functions of (a) carrying specific amino acids and (b) deciphering the correct codon sequences on mRNA through their anticodon regions. The first translated codon AUG corresponds to the amino acid methionine. The synthesis of a protein involves the successive addition of correct amino acids to the growing polypeptide chain, using mRNA as a template and based on the pairing of the anticodon region of tRNA to a specific codon of mRNA. Translation stops when a stop codon (UAG, UGA, UAA) is reached. A codon is a three-base combination that holds the instructions for translation, either indicating that a particular amino acid should be added or signaling translation initiation or termination. Since there are four different bases (A, T, C, G), the number of possible codons is 4³, or 64. However, there are only 20 amino acids. Therefore, more than one codon may encode for one specific amino acid. In such cases, the codon is described as degenerate. Different degenerate codons have identical first two bases, varying only in the third base position.

Common Types of Mutations

Mutations are changes in DNA sequences (Table 2.1). At the nucleotide level, common mutations include point mutations, which can be further defined as silent mutations, nonsense mutations, missense mutations, deletions, and insertions. At the genomic level, mutations include amplifications (gene duplication), interstitial deletions, and chromosomal translocations, or inversions.

Copy Number Variation

The development and use of new genomic technologies, such as comparative genomic hybridization and microarrays, have resulted in increased recognition of copy number variation (CNV) as a common type of human genetic mutation. Studies of humans from different ethnic backgrounds have shown 1,447 CNV regions, covering ~12% of the human genome [18]. CNVs can involve a single gene or a contiguous set of genes. Variation in the copy number of dosage-sensitive genes may contribute to human phenotypic variability and disease susceptibility.

Table 2.1 Common types of mutations

Type of mutations	Characteristics
Nucleotide level	
Silent	No change in amino acid
Missense	Change in amino acid
Nonsense	Introduction of a stop codon causing premature termination of translation
Insertion, deletion	Insertion or deletion of nucleotides may result in frameshift
Genomic level	
Amplification	Multiple copies of a chromosomal region; cause increased gene dosage
Interstitial deletion	Intrachromosomal deletion; may cause gene fusion or loss of heterozygosity
Translocation	Interchange of genetic material from nonhomologous chromosomes
Inversion	Reversing the orientation of a chromosomal segment
Copy number variation (CNV)	Changes in the copy number of a chromosomal segment; can be caused by deletion or duplication

Single Nucleotide Polymorphism

Single nucleotide polymorphism (SNP) refers to a variation in the nucleotide sequence among different individuals of a species. SNP is the most common type of genetic variation, occurring every 100–300 bases in the human genome. The distinction between an SNP and a mutation is rather artificial. In general, if the allele frequency is at least 1%, it is called an SNP; otherwise, it is referred to as a mutation. However, the National Center for Biotechnology Information (NCBI) SNP database (dbSNP) contains SNPs that have allele frequency less than 1%. SNPs can occur in both coding and noncoding regions of the genome. If an SNP is located in the coding region, and it does not change the sequence of the polypeptide chain, it is called synonymous; otherwise, it is termed nonsynonymous.

The study of SNPs will lead to a better understanding of the genotype-phenotype relationship, and help determine an individual's predisposition to common diseases, and their response to the medications used to treat them. For example, studies in methotrexate-treated psoriasis patients suggest that functional SNPs in genes relevant to methotrexate metabolism may influence both the efficacy and toxicity of this drug (see Chaps. 21 and 22). In addition, geneticists can use detailed SNP maps and genome-wide association studies (GWAS) to identify disease-causing genes (genetic regions) [19].

DNA Methylation

DNA methylation is one form of epigenetic regulation, an inheritable influence on gene expression without changes in the DNA sequence. During this process, a methyl group is added to the C5 position of a cytosine pyrimidine ring. In human cells, DNA methylation typically occurs on a cytosine that is followed by a guanine (i.e., CpG dinucleotide). It is estimated that 70% of all CpG sites are methylated in mammals. The unmethylated CpG sites are concentrated in the 5' upstream region of genes, including the promoter region, forming so-called “CpG islands.” Methylation of CpG islands at the promoter region can negatively impact gene expression by blocking the access of TFs (Fig. 2.5). Promoter methylation may play an important role in carcinogenesis. More than half of all known human tumor suppressor genes, including retinoblastoma (*RB*) and *CDKN2A/p16*, are

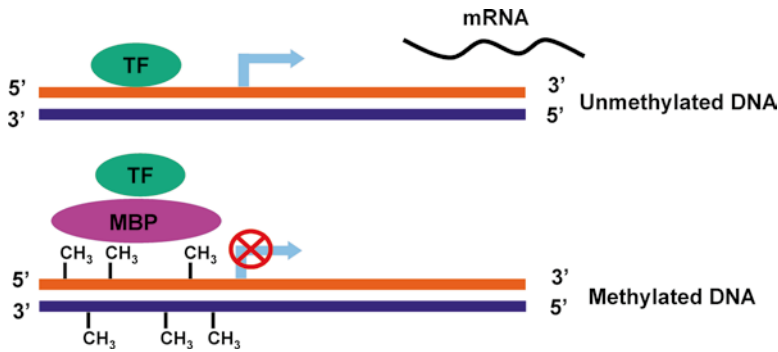


Fig. 2.5 Model of gene expression silencing by promoter methylation. In the unmethylated state, transcription factor (TF) can bind to the promoter region and activate transcription. If the promoter region is methylated, the methylated CpG site recruits methyl-binding proteins (MBPs), which further recruit other transcription repressors. TF access to the promoter is blocked and transcription is prevented

subject to promoter methylation in cancer [20]. Promoter methylation status of a select group of genes may serve as biomarkers for disease diagnosis, prognostication, and treatment response prediction. For example, methylation of the *MGMT* promoter is associated with a favorable response to temozolomide chemotherapy [21]. There is evidence to suggest that epigenetic dysregulation may be associated with not only skin cancers, but also other dermatologic disorders, such as psoriasis, atopic dermatitis, and cutaneous involvement by systemic lupus erythematosus [22].

Oncogenes and Tumor Suppressor Genes

An oncogene encodes a protein that is capable of transforming cells in culture or inducing cancer in animals. Oncogenes are derived from proto-oncogenes, normal cellular genes that provide pro-growth signals to cells. However, “gain-of-function” mutations or altered regulation of a proto-oncogene can transform it into an oncogene, resulting in excessive cellular growth. Oncogenes are classified according to their cellular functions. Common oncogenes that are associated with dermatologic neoplasms are listed in Table 2.2.

Tumor suppressor genes encode proteins that control cell cycle progression, repair damaged DNA, and regulate apoptosis. They function as “brakes,” preventing uncontrolled cell growth and ensuring genomic integrity. Inactivation of tumor suppressor genes by mutations can tip the balance toward uncontrolled cell growth or unrepaired DNA damage, which may lead to cancer. An important difference between oncogenes and tumor suppressor genes is that typically both alleles of a tumor suppressor gene need to be inactivated in order to show a pro-cancer phenotype, whereas for oncogenes, an activating mutation residing on one of the two alleles is often sufficient to drive carcinogenesis. Another distinction is that oncogene mutations are often acquired, while mutations of tumor suppressor genes can be both acquired and inherited. A classic example of biallelic mutation in a tumor suppressor gene is provided by Knudson’s study of the *RB* gene [23]. He proposed the “two-hit hypothesis” to explain that in familial retinoblastoma only one additional somatic mutation (“hit”) is sufficient to cause disease, because one “hit” has been already inherited [23]. However, in the case of non-familial retinoblastoma, two separate somatic mutations are required to cause disease [23]. Examples of tumor suppressor genes associated with dermatologic neoplasms are provided in Table 2.3.

Table 2.2 Common oncogenes associated with dermatologic neoplasms

Functional groups	Mode of activation	Human skin tumors
Transcription factor		
<i>MITF</i>	Amplification	Melanoma [24]
<i>STAT3</i>	Activation	Mycosis fungoides [25]
Growth factor		
<i>FGF2</i>	Overexpression	Melanoma [26]
Growth factor receptors – tyrosine kinase		
<i>KIT</i>	Overexpression/point mutation	Melanoma [27]
<i>c-MET</i>	Overexpression/point mutation	Melanoma [28]
Cytoplasmic serine/threonine kinase		
<i>mTOR</i>	Activation	Melanoma [29]
G-protein		
<i>K-RAS</i>	Point mutation	AK [30], BCC [31], SCC [31]
<i>N-RAS</i>	Point mutation	Melanoma [32], congenital nevus [33]
<i>H-RAS</i>	Point mutation	Spitz nevus [34], SCC [35], BCC [31]
<i>BRAF</i>	V600E point mutation	Melanoma [36], benign nevus [36]
Cell cycle regulator		
<i>CDK4</i>	Amplification/point mutation	Melanoma [37], SCC [38]
<i>CND1</i>	Amplification	Melanoma [39]
Apoptosis regulator		
<i>BCL2</i>	Translocation, amplification	Melanoma [40]
<i>AKT3</i>	Activation, amplification	Melanoma [41]
Wnt pathway		
<i>β-catenin</i>	Point mutation/activation	Melanoma [42], BCC [43]
Shh pathway		
<i>SMO</i>	Point mutation	BCC [44]

AK actinic keratosis, SCC squamous cell carcinoma, BCC basal cell carcinoma

Table 2.3 Common tumor suppressor genes associated with dermatologic neoplasms

Genes	Inherited tumor/syndrome	Non-inherited skin tumors
<i>RB</i>	Retinoblastoma	Many, including melanoma [45]
<i>TP53</i>	Li Fraumeni Syndrome	Many, including SCC, AK [46], BCC [44]
<i>CDKN2A</i> (p16 ^{INK4a} and p14 ^{ARF})	Familial melanoma	Many, including melanoma [37], MF [47], SCC [48]
<i>XPA through XPG</i>	Xeroderma pigmentosum	BCC, SCC [49]
<i>NF1, NF2</i>	Neurofibromatosis 1 and 2	Melanoma [50, 51]
<i>PRKARIA</i>	Carney complex	Pigmented epithelioid melanocytoma [52]
<i>PTEN</i>	Cowden syndrome	Melanoma [37], MF [53]
<i>PTCH1</i>	Basal cell nevus syndrome	BCC [54]

SCC squamous cell carcinoma, AK actinic keratosis, BCC basal cell carcinoma, MF mycosis fungoides

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Molecular Diagnostics in Dermatology and
Dermatopathology

Murphy, M.J. (Ed.)

2011, XIII, 478 p., Hardcover

ISBN: 978-1-60761-170-7

A product of Humana Press