haphazard way, creating many chromosome rearrangements and also resulting in the loss of some chromosome segments. It is hypothesized that such catastrophic events by chance simultaneously activate oncogenes and inactivate tumor suppressors, thereby expediting the process of carcinogenesis.

KEY CONCEPTS

Genetic Lesions in Cancer

- Tumor cells may acquire several types of oncogenic mutations, including point mutations and other nonrandom chromosomal abnormalities, such as translocations, deletions, and gene amplifications.
- Balanced translocations contribute to carcinogenesis by overexpression of oncogenes or generation of novel fusion proteins with altered signaling capacity. Deletions frequently cause loss of tumor suppressor gene function, and occasionally activate proto-oncogenes. Gene amplification generally increases the expression and function of oncogenes.
- Genomic sequencing has revealed numerous "cryptic" (subcytogenetic) rearrangements, mainly small deletions and insertions ("indels"), as well as chromothrypsis, in which a chromosome is "shattered" and then reassembled in a haphazard way.

Epigenetic Changes

Epigenetic changes have important roles in many aspects of the malignant phenotype, including the expression of cancer genes, the control of differentiation and self-renewal, and even drug sensitivity and drug resistance. As discussed in Chapter 1, "epigenetics" refers to factors other than the sequence of DNA that regulate gene expression (and, thereby, cellular phenotype). Recall that these factors include histones modifications catalyzed by enzymes associated with chromatin regulatory complexes; DNA methylation, a modification created by DNA methyltransferases; and other less well characterized proteins that regulate the higher order organization of DNA (e.g., looping of enhancer elements onto gene promoters).

It has been recognized for more than a hundred years that the nuclei of cancer cells display abnormal morphologies, which (as discussed earlier) may take the form of hyperchromasia, chromatin clumping, or chromatin clearing (so-called vesicular nuclear chromatin). These altered appearances stem from disturbances of chromatin organization, the basis of which has been obscure. One of the most notable findings emerging from the sequencing of cancer genomes has been the identification of numerous mutations involving genes that encode epigenetic regulatory proteins (Table 7-9). As a result, it is now suspected that the altered morphologic appearance of cancer cells reflects acquired genetic defects in factors that maintain the epigenome. Indeed, methods that allow genome-wide assessment of the cell's epigenome are now available and have begun to reveal widespread epigenetic alterations in cancers, which can be broadly divided into the following categories:

- **Silencing of tumor suppressor genes by local hypermethylation of DNA**. Some cancer cells exhibit selective hypermethylation of the promoters of tumor suppressor genes that results in their transcriptional silencing. Typically, hypermethylation occurs on only one allele and the function of the other copy of the affected tumor suppressor gene is lost through another mechanism, such as a disabling point mutation or a deletion. One of several examples of a tumor suppressor gene that is hypermethylated in several cancers is *CDKN2A*, which you will recall is a complex locus that encodes two tumor suppressors, p14/ARF and p16/INK4a, that enhance p53 and RB activity, respectively.
- **Global changes in DNA methylation**. In addition to local hypermethylation of tumor suppressor genes, many tumors exhibit abnormal patterns of DNA methylation throughout their genomes, sometimes in the form of hypermethylation and other times as hypomethylation. Tumors commonly exhibiting abnormal DNA methylation, such as acute myeloid leukemia, sometimes have mutations in genes encoding DNA methyltransferases or other factors that influence DNA methylation (Table 7-9), suggesting that the observed alterations have a genetic basis. The most obvious potential consequence of global changes in methylation is altered expression of multiple genes, which may be overexpressed or underexpressed compared to normal depending on the nature of local changes. In addition, however, mice engineered to have hypomethylated genomes also exhibit chromosomal instability; thus, altered DNA methylation may contribute to tumorigenesis in several ways.
- **Changes in histones**. Cancer cells often demonstrate changes in histones near genes that influence cellular behavior. As with changes in DNA methylation, in an increasing number of instances it appears that these alterations have a genetic basis, being attributable to mutations that affect the activities of protein complexes that "write", "read" and "erase" histone marks, or that position nucleosomes on DNA (Table 7-9). Details have yet to emerge, but it is virtually certain that these lesions somehow alter the expression of sets of genes that contribute to the malignant phenotype.

Table 7-9 Examples of Epigenomic Regulatory Genes that are Mutated in Cancer

Gene(s)	Function	Tumor (Approximate Frequency of Mutation)
DNMT3A	DNA methylation	Acute myeloid leukemia (20%)
MLL1	Histone methylation	Acute leukemia in infants (90%)
MLL2	Histone methylation	Follicular lymphoma (90%)
CREBBP/ EP300	Histone acetylation	Diffuse large B cell lymphoma (40%)
ARID1A	Nucleosome positioning/chromatin remodeling	Ovarian clear cell carcinoma (60%), endometrial carcinoma (30%-40%)
SNF5	Nucleosome positioning/chromatin remodeling	Malignant rhabdoid tumor (100%)
PBRM1	Nucleosome positioning/chromatin remodeling	Renal carcinoma (30%)