Estrogen receptors (ERs) and androgen receptors (ARs), members of the steroid hormone family of nuclear receptors, are targets of inhibition by drugs used to treat breast and prostate cancers, respectively. Tamoxifen, a partial agonist and antagonist of ER function, can mediate tumor regression in metastatic breast cancer and can prevent disease recurrence in the adjuvant setting. Tamoxifen binds to the ER and modulates its transcriptional activity, inhibiting activity in the breast but promoting activity in bone and uterine epithelium. Selective ER modulators (SERMs) have been developed with the hope of a more beneficial modulation of ER activity, i.e., antiestrogenic activity in the breast, uterus, and ovary, but estrogenic for bone, brain, and cardiovascular tissues. Aromatase inhibitors, which block the conversion of androgens to estrogens in breast and subcutaneous fat tissues, have demonstrated improved clinical efficacy compared with tamoxifen and are often used as first-line therapy in patients with ER-positive disease. A number of approaches have been developed for blocking androgen stimulation of prostate cancer, including decreasing production (e.g., orchiectomy, luteinizing hormone–releasing hormone agonists or antagonists, estrogens, ketoconazole, and inhibitors of enzymes such as CYP17 involved in androgen production) and AR blockers **(Chap. 108)**.

ONCOGENE ADDICTION AND SYNTHETIC LETHALITY

The concepts of oncogene addiction and synthetic lethality have spurred new drug development targeting oncogene- and tumor-suppressor pathways. As discussed earlier in this chapter and outlined in Fig. 102e-3, cancer cells can become dependent on signaling pathways containing activated oncogenes; this can effect proliferation (i.e., mutated Kras, Braf, overexpressed Myc, or activated tyrosine kinases), DNA repair (loss of *BRCA1* or *BRCA2* gene function), survival (overexpression of Bcl-2 or NF-κB), cell metabolism (as occurs when mutant Kras enhances glucose uptake and aerobic glycolysis), and perhaps angiogenesis (production of VEGF in response to HIF-2α in RCC). In such cases, targeted inhibition of the pathway can lead to specific killing of the cancer cells. However, targeting defects in tumor-suppressor genes has been much more difficult, both because the target of mutation is often deleted and because it is much more difficult to restore normal function than to inhibit abnormal function of a protein. Synthetic lethality occurs when loss of function in either of two genes alone has limited effects on cell survival but loss of function in both genes leads to cell death. Identifying genes that have a synthetic lethal relationship to tumor-suppressor pathways that have been mutated in tumor cells may allow targeting of proteins required uniquely by those cells (Fig. 102e-3). Several examples of this have been identified. For instance, cells with mutations in the *BRCA1* or *BRCA2* tumor-suppressor genes (e.g., a subset of breast and ovarian cancers) are unable to repair DNA damage by homologous recombination. PARP are a family of proteins important for single-strand break (SSB) DNA repair. PARP inhibition results in selective killing of cancer cells with *BRCA1* or *BRCA2* loss. Preliminary trials have suggested some effectiveness of PARP inhibition, especially in combination with chemotherapy; clinical trials are ongoing. The concept of synthetic lethality provides a framework for genetic screens to identify other synthetic lethal combinations involving known tumor-suppressor genes and development of novel therapeutic agents to target dependent pathways.

EPIGENETIC INFLUENCES ON CANCER GENE TRANSCRIPTION

Chromatin structure regulates the hierarchical order of sequential gene transcription that governs differentiation and tissue homeostasis. Disruption of chromatin remodeling (the process of modifying chromatin structure to control exposure of specific genes to transcriptional proteins, thereby controlling the expression of those genes) leads to aberrant gene expression and can induce proliferation of undifferentiated cells. *Epigenetics* is defined as changes that alter the pattern of gene expression that persist across at least one cell division but are not caused by changes in the DNA code. Epigenetic changes include alterations of chromatin structure mediated by methylation of cytosine residues in CpG dinucleotides, modification of histones by acetylation or methylation, or changes in higher-order chromosome structure **(Fig. 102e-4)**. The transcriptional regulatory regions of active genes often contain a high frequency of CpG dinucleotides (referred to as *CpG islands*), which are normally unmethylated. Expression of these genes is controlled by transient association with repressor or activator proteins that regulate transcriptional activation. However, hypermethylation of promoter regions is a common mechanism by which tumor-suppressor loci are epigenetically silenced in cancer cells. Thus one allele may be inactivated by mutation or deletion (as occurs in loss of heterozygosity), while expression of the other allele is epigenetically silenced, usually by methylation.

Acetylation of the amino terminus of the core histones H3 and H4 induces an open chromatin conformation that promotes transcription initiation. Histone acetylases are components of coactivator complexes recruited to promoter/enhancer regions by sequence-specific transcription factors during the activation of genes (Fig. 102e-4). Histone deacetylases (HDACs; at least 17 are encoded in the human genome) are recruited to genes by transcriptional repressors and prevent the initiation of gene transcription. Methylated cytosine residues in promoter regions become associated with methyl cytosine–binding proteins that recruit protein complexes with HDAC activity. The balance between permissive and inhibitory chromatin structure is therefore largely determined by the activity of transcription factors in modulating the "histone code" and the methylation status of the genetic regulatory elements of genes.

The pattern of gene transcription is aberrant in all human cancers, and in many cases, epigenetic events are responsible. Unlike genetic events that alter DNA primary structure (e.g., deletions), epigenetic changes are potentially reversible and appear amenable to therapeutic intervention. In certain human cancers, including pancreatic cancer and multiple myeloma, the $p16^{Ink4a}$ promoter is inactivated by methylation, thus permitting the unchecked activity of CDK4/cyclin D and rendering pRb nonfunctional. In sporadic forms of renal, breast, and colon cancer, the von Hippel–Lindau (*VHL*), breast cancer 1 (*BRCA1*), and serine/threonine kinase 11 (*STK11*) genes, respectively, are epigenetically silenced. Other targeted genes include the $p15^{Ink4b}$ CDK inhibitor, glutathione-*S*-transferase (which detoxifies reactive oxygen species), and the E-cadherin molecule (important for junction formation between epithelial cells). Epigenetic silencing can occur in premalignant lesions and can affect genes involved in DNA repair, thus predisposing to further genetic damage. Examples include MLH1 (mut L homologue) in hereditary nonpolyposis colon cancer (HNPCC, also called Lynch's syndrome), which is critical for repair of mismatched bases that occur during DNA synthesis, and O^6-methylguanine-DNA methyltransferase, which removes alkylated guanine adducts from DNA and is often silenced in colon, lung, and lymphoid tumors.

Human leukemias often have chromosomal translocations that code for novel fusion proteins with enzymatic activities that alter chromatin structure. The promyelocytic leukemia–retinoic acid receptor (PML-RAR) fusion protein, generated by the t(15;17) observed in most cases of acute promyelocytic leukemia (APL), binds to promoters containing retinoic acid response elements and recruits HDAC to these promoters, effectively inhibiting gene expression. This arrests differentiation at the promyelocyte stage and promotes tumor cell proliferation and survival. Treatment with pharmacologic doses of all-*trans* retinoic acid (ATRA), the ligand for RARα, results in the release of HDAC activity and the recruitment of coactivators, which overcome the differentiation block. This induced differentiation of APL cells has improved treatment of these patients but also has led to a novel treatment toxicity when newly differentiated tumor cells infiltrate the lungs. However, ATRA represents a treatment paradigm for the reversal of epigenetic changes in cancer. For other leukemia-associated fusion proteins, such as acute myeloid leukemia (AML)-eight-twenty-one (ETO) and the MLL fusion proteins seen in AML and acute lymphocytic leukemia, no ligand is known. Therefore, efforts are ongoing to determine the structural basis for interactions between translocation fusion proteins and chromatin-remodeling proteins and to use this information to rationally design small molecules that will disrupt specific protein-protein associations, although this has proven to be technically difficult. Drugs that block the enzymatic activity of HDAC are