cells. Most invasive cancers develop only after multiple genes are mutated, and they seem to retain genetic flexibility or a mutator phenotype. Mutations can occur on exposure to environmental carcinogens, in the setting of dysregulated DNA repair, as a consequence of random replication errors during cell turnover and normal aging, or, occasionally, in families with hereditary germline mutations in a cancer gene. Mutations in cancer are classified into three categories depending on the functional consequence of the mutation: oncogenes, tumor suppressor genes, and stability or caretaker genes. However, there are newly discovered mutations that do not fall neatly into one of these categories. Table 53-2 shows the clinical consequences of selected mutations.

## Oncogenes

Oncogene mutations convert a normal cell into a cancerous cell; they include chromosomal translocations, gene amplifications, and intragenic mutations. Oncogenes often activate pathways that are important for cancer. For example, CML occurs when the proto-oncogene *ABL* from chromosome 9 translocates to the *BCR* gene on chromosome 22. The new protein formed by expression of the combined gene *BCR-ABL* sends unchecked growth-promoting signals to the nucleus. An activating mutation in one allele of an oncogene is usually sufficient to promote tumorigenesis (e.g., in *KRAS*).

Because oncogenes activate pathways that drive cancer growth, their discovery has led to specifically designed drugs that target the products of these genes and the pathways they control. For example, among patients with breast cancer, HER2 amplification serves as a biomarker that identifies those who will benefit from treatment with the anti-HER2 monoclonal antibody, trastuzumab. Similarly, activating mutations in EGFR serve to identify patients with non–small cell lung cancer who will improve with the use of drugs that specifically inhibit the mutated form of EGFR. Another example is BRAF mutations in melanoma. This paradigm—identify a mutated oncogene, find a specific drug that inhibits the activated mutant protein, and treat patients who have the specific mutation with a drug that affects the mutated protein—has repeatedly been proven to be a successful approach.

**TABLE 53-2** CANCERS ASSOCIATED WITH SELECTED GENETIC MUTATIONS

| GENE | ASSOCIATED HEREDITARY SYNDROME | MAJOR TUMOR TYPES |
|---|---|---|
| **ONCOGENES** | | |
| *KRAS* | – | Pancreatic, lung, bladder, and colon cancers |
| *BCR-ABL* translocation | | Chronic myelogenous leukemia |
| *BCL2* | – | Chronic lymphocytic leukemia |
| *KIT, PDGFRA* | Familial gastrointestinal stromal tumors | Gastrointestinal stromal tumors |
| **TUMOR SUPPRESSOR GENES** | | |
| *TP53 (p53)* | Li-Fraumeni syndrome | Breast, sarcoma, adrenal, brain, multiple others |
| *APC* | Familial adenomatosis polyposis | Colon, stomach, intestine |
| *VHL* | Von Hippel–Lindau syndrome | Kidney |
| *SMAD4* | Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome | Colon, gastric, and pancreatic cancer |
| *CDKN2A (p16)* | Familial atypical multiple mole melanoma syndrome | Melanoma, pancreatic adenocarcinoma, non–small cell lung cancer |
| **STABILITY GENES** | | |
| *BRCA1, BRCA2* | Hereditary breast cancer | Breast, ovary |
| *MSH2, MLH1* | Lynch syndrome | Colon, uterus, stomach |

## Tumor Suppressor Genes

Tumor suppressor genes control cellular replication and growth. Point mutations or deletions of tumor suppressor genes give cells harboring these mutations a growth advantage. Inactivation of tumor suppressor genes may lead to diminished activity of the protein product by several mechanisms: silencing or inactivating point mutations, large DNA deletions or rearrangements, or methylation and chromatin remodeling of the regions harboring the gene. In contrast to oncogene activation, inactivation of both alleles of a tumor suppressor gene is required for tumorigenesis. For instance, an inherited mutation in a single retinoblastoma gene (*RB1*, a tumor suppressor gene) may not, by itself, cause retinoblastoma in a young child. However, a "second hit" after birth (i.e., an *RB1* somatic mutation) can result in multiple tumors including bilateral retinoblastomas. The tumor suppressor gene *TP53* is the most commonly mutated gene in sporadic human cancers. Deletion of this gene can be inherited, and families with inherited mutations have higher rates of a variety of cancers, including breast and brain tumors, leukemia, and sarcoma, a pattern termed the *Li-Fraumeni syndrome*.

## Stability Genes

Mutations in stability or caretaker genes can also promote tumorigenesis. These genes are responsible for the repair of errors in normal DNA replication. They include mismatch repair genes, base-excision repair genes, and nucleotide-excision repair genes. Mutations in stability genes lead to increased errors in DNA replication. Eventually, DNA replication errors (mutations) are introduced in oncogenes and tumor suppressor genes, resulting in malignant transformation. Lynch syndrome, also called hereditary nonpolyposis colon cancer, is an inherited syndrome of defects in DNA mismatch repair genes. Colon and endometrial cancers are commonly observed in families with this syndrome, and rates of many gastrointestinal cancers are also higher in these families.

# THE ORIGINS OF CANCER

## Steps Toward Cancer

Many malignancies, including colon, breast, pancreas, and liver cancers, develop in a stepwise progression from normal to cancerous cells that is driven by a cascade of genetic events. This model was first articulated in colon cancer, where precancerous polyps were found to harbor some of the same mutations found in advanced cancers. This type of progression provides the genetic and biologic basis for the efficacy of many cancer screening and prevention programs that focus on identifying