expressing adhesion molecules such as integrins that promote direct physical interactions with tumor cells. There is also substantial evidence that stromal cell–cancer cell interactions increase the resistance of cancer cells to chemotherapy, presumably by activating signaling pathways that promote cell survival in the face of stresses such as DNA damage.

- **Inducing angiogenesis**. Inflammatory cells release numerous factors, including VEGF, which can stimulate angiogenesis.
- **Activating invasion and metastasis**. Proteases released from macrophages foster tissue invasion by remodeling the ECM, while factors such as TNF and EGF may directly stimulate tumor cell motility. As mentioned, other factors released from stromal cells, such as TGF-β, may promote epithelial-mesenchymal transitions, which is considered to be a key event in the process of invasion and metastasis.
- **Evading immune destruction**. A variety of soluble factors released by macrophages and other stromal cells are believed to contribute to the immunosuppressive microenvironment of tumors, including TGF-β and a number of other factors that either favor the recruitment of immunosuppressive T regulatory cells or suppress the function of CD8+ cytotoxic T cells. Furthermore, there is abundant evidence in murine cancer models and emerging evidence in human disease that advanced cancers contain mainly alternatively activated (M2) macrophages (Chapter 3), cells induced by cytokines such as IL-4 and IL-13. These macrophages produce cytokines that promote angiogenesis, fibroblast proliferation, and collagen deposition, all of which are commonly observed in invasive cancers. In addition, they appear to suppress effective host immune responses to cancer cells through mechanisms that remain to be elucidated.

A thorough understanding of how cancers "manipulate" inflammatory cells to support their growth and survival remains elusive. However, the results from animal studies are intriguing and raise the possibility of therapies directed at tumor-induced inflammation and its downstream consequences. Of note in this regard, COX2 inhibitors have been shown to decrease the incidence of colonic adenomas and are now approved for treatment of patients with familial adenomatous polyposis.

Dysregulation of Cancer-Associated Genes

The genetic damage that activates oncogenes or inactivates tumor suppressor genes may be subtle (e.g., point mutations) or may involve segments of chromosomes large enough to be detected in a routine karyotype. Activation of oncogenes and loss of function of tumor suppressor genes by mutations were discussed earlier in this chapter. Here we first discuss chromosomal abnormalities and then end this section by discussing the epigenetic changes that contribute to carcinogenesis and the role of noncoding RNAs.

Chromosomal Changes

Certain chromosomal abnormalities are highly associated with particular neoplasms and inevitably lead to the dysregulation of genes with an integral role in the pathogenesis of that tumor type. Specific recurrent chromosomal abnormalities have been identified in most leukemias and lymphomas, many sarcomas, and an increasing number of carcinomas. In addition, whole chromosomes may be gained or lost. Although changes in chromosome number (aneuploidy) and structure are generally considered to be late phenomena in cancer progression, in some cases (e.g., in cells that have lost their telomeres, Figure 7-34), it can be an early event that initiates the transformation process.

Historically, chromosomal changes in cancer were identified through karyotyping, the morphologic identification of metaphase chromosomes prepared from clinical specimens. Today, however, cancer cell karyotypes are being reconstructed in research labs from deep sequencing of cancer cell genomes, and it is possible that conventional karyotyping will be supplanted by other methods even in clinical laboratories in the years to come. Whatever technology is used, the study of chromosomal changes in tumor cells is important. First, genes in the vicinity of recurrent chromosomal breakpoints or deletions are very likely to be either oncogenes (e.g., *MYC*, *BCL2*, *ABL*) or tumor suppressor genes (e.g., *APC*, *RB*). Second, certain karyotypic abnormalities have diagnostic value or important prognostic or therapeutic implications. For example, tests that detect and quantify *BCR-ABL* fusion genes or their mRNA products are essential for the diagnosis of CML and are used to monitor the response to BCR-ABL kinase inhibitors. Many additional chromosomal aberrations that are characteristic of specific tumor types are presented in later chapters.

Chromosomal Translocations. Any type of chromosomal rearrangement—translocations, inversions, amplifications, and even small deletions—can activate proto-oncogenes, but chromosomal translocation is the most common mechanism described to date. Notable examples of oncogenes activated by chromosomal translocations are listed in Table 7-8. Translocations can activate proto-oncogenes in two ways:

- By promoter or enhancer substitution, in which the translocation results in overexpression of a proto-oncogene by swapping its regulatory elements with those of another gene, typically one that is highly expressed.
- By formation of a fusion gene in which the coding sequences of two genes are fused in part or in whole, leading to the expression of a novel chimeric protein with oncogenic properties.

Overexpression of a proto-oncogene caused by translocation is exemplified by Burkitt lymphoma. Virtually all Burkitt lymphomas have a translocation involving chromosome 8q24, where the *MYC* gene resides, and one of the three chromosomes that carry an immunoglobulin gene. At its normal locus, *MYC* is tightly controlled, and is most highly expressed in actively dividing cells. In Burkitt lymphoma the most common translocation moves the *MYC*-containing segment of chromosome 8 to chromosome 14q32 (See Fig. 7-26), placing it close to the immunoglobulin heavy chain (*IGH*) gene. The genetic notation for the translocation is t(8:14)(q24;q32). The molecular