otherwise these malignant stem cells will spawn proliferating offspring and the fullblown leukemia will return. This outcome highlights a second important concept that we will return to; the existence of "stem-like" cells in certain cancers that may be particularly resistant to therapeutic targeting.

In other instances, nonreceptor tyrosine kinases are activated by point mutations that abrogate the function of negative regulatory domains that normally hold enzyme activity in check. An example of this type of mutation is found in the nonreceptor tyrosine kinase JAK2. JAK2 participates in the JAK/STAT signaling pathway, which transduces mitogenic signals from growth factor and cytokine receptors that lack tyrosine kinase activity (as describe in Chapter 1). JAK/STAT activation alters the expression of target genes that bind STAT transcription factors. Several myeloproliferative disorders, particularly polycythemia vera, essential thrombocytosis, and primary myelofibrosis, are highly associated with activating point mutations in JAK2 that relieve the normal dependence of hematopoietic progenitors on growth factors such as erythropoietin (Chapter 13). Recognition of this molecular lesion has led to the clinical development of JAK2 inhibitors for treatment myeloproliferative disorders, and has stimulated searches for activating mutations in other nonreceptor tyrosine kinases in a wide variety of human cancers.

Transcription Factors. Just as all roads lead to Rome, all signal transduction pathways converge on the nucleus, where the expression of target genes that orchestrate the cell's orderly advance through the mitotic cycle is activated. Indeed, the ultimate consequence of deregulated mitogenic signaling pathways is inappropriate and continuous stimulation of nuclear transcription factors that drive growth-promoting genes. Thus, not surprisingly, growth autonomy may also occur as a consequence of mutations affecting the transcription factors that regulate the expression of pro-growth genes and cyclins. Transcription factors of this class include the products of the *MYC*, *MYB*, *JUN*, *FOS*, and *REL* proto-oncogenes. Of these, *MYC* is most commonly involved in human tumors, and hence a brief overview of its regulation and function follows.

MYC Oncogene. The *MYC* proto-oncogene is expressed in virtually all eukaryotic cells and belongs to the immediate early response genes, which are rapidly and transiently induced by RAS/MAPK signaling following growth factor stimulation of quiescent cells. Under normal circumstances, MYC protein concentrations are tightly controlled at the level of transcription, translation, and protein stability, and virtually all pathways that regulate growth impinge on MYC through one or more of these mechanisms. Several single nucleotide polymorphisms (SNPs) that are strongly linked to an elevated risk of cancers, such as prostate and ovarian carcinoma, fall within a large region devoid of recognizable genes that lies next to *MYC* on chromosome 8. Experimental data suggest that these genetic variants alter the function of enhancer elements that regulate *MYC* expression, and that increased cancer risk is associated with variants that bring about higher levels of *MYC* RNA expression in response to certain growth promoting signals.

How MYC promotes normal and neoplastic cell growth is incompletely understood, but a multitude of studies have shown that MYC has remarkably broad activities, several of which contribute not only to deregulated cell growth but also to several other hallmarks of cancer.

- **MYC activates the expression of many genes that are involved in cell growth**.
  - Some MYC target genes, like D cyclins, are directly involved in cell cycle progression.
  - MYC also upregulates the expression of rRNA genes and rRNA processing, thereby enhancing the assembly of ribosomes needed for protein synthesis.
  - MYC upregulates a program of gene expression that leads to metabolic reprogramming and the Warburg effect, another cancer hallmark (discussed later). Among the genes involved in metabolism that are upregulated by MYC are multiple glycolytic enzymes and factors involved in glutamine metabolism, both of which contribute to the generation of metabolic intermediates that are needed for synthesis of macromolecules such as DNA, proteins, and lipids.
  - Based on these protean effects, MYC can be considered a master transcriptional regulator of cell growth. Indeed, the fastest growing human tumors, such as Burkitt lymphoma, which virtually always bears a chromosomal translocation involving *MYC* (Fig. 7-26), are those with the highest levels of MYC.
- **In some contexts, MYC upregulates expression of telomerase**. As discussed later, telomerase is one of several factors that contribute to the endless replicative capacity (the immortalization) of cancer cells.
- **MYC is one of a handful of transcription factors that can act together to reprogram somatic cells into pluripotent stem cells** (Chapter 1). This capacity has led to suspicions that MYC may also contribute to cancer cell "stemness," another important aspect of the immortality of cancers.

Given the importance of MYC in regulation of cell growth, it should come as no surprise that it is deregulated in cancer through a variety of mechanisms. Sometimes deregulation involves genetic alterations of *MYC* itself. In addition to the *MYC* translocations in Burkitt lymphoma and a subset of other B and T cell tumors, *MYC* is amplified in some breast, colon, lung, and many other carcinomas. The functionally identical *NMYC* and *LMYC* genes are also amplified in neuroblastomas (Fig. 7-27) and small cell cancers of the lung, respectively. In many other instances, oncogenic mutations involving components of upstream signaling pathways elevate MYC protein levels by increasing *MYC* transcription, enhancing *MYC* mRNA translation, and/or stabilizing MYC protein. Thus, constitutive RAS/MAPK signaling (many cancers), Notch signaling (several hematologic cancers), Wnt signaling (colon carcinoma), and Hedgehog signaling (medulloblastoma) all transform cells in part through upregulation of *MYC*.

Cyclins and Cyclin-Dependent Kinases. As mentioned in Chapter 1, growth factors transduce signals that stimulate the orderly progression of cells through the various phases of the cell cycle, the process by which cells replicate their DNA in preparation for cell division. Progression of cells through the cell cycle is orchestrated by *cyclin-dependent kinases* (CDKs), which are activated by binding