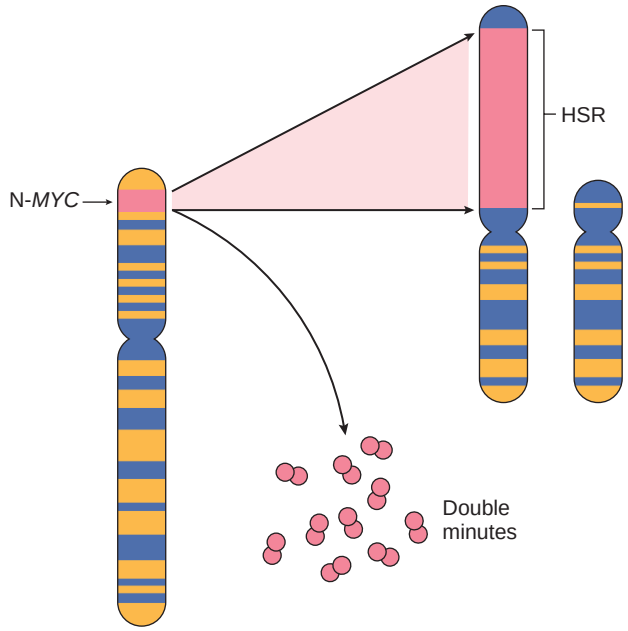

Figure 7-27 Amplification of the *NMYC* gene in human neuroblastomas. The *NMYC* gene, normally present on chromosome 2p, becomes amplified and is seen either as extra chromosomal double minutes or as a chromosomally integrated, homogeneous staining region (HSR). The integration involves other autosomes, such as 4, 9, or 13. (Modified from Brodeur GM: Molecular correlates of cytogenetic abnormalities in human cancer cells: implications for oncogene activation. In Brown EB (ed): Progress in Hematology, Vol 14. Orlando, FL, Grune & Stratton, 1986, p 229-256.)

Table 7-6 Cell Cycle Components and Inhibitors That Are Frequently Mutated in Cancer

Cell Cycle Component	Main Function
Cyclins and Cyclin-Dependent Kinases	
CDK4; D cyclins	Form a complex that phosphorylates RB, allowing the cell to progress through the G_1 restriction point
Cell Cycle Inhibitors	
CIP/KIP family: p21, p27 (CDKN1A-D)	Block the cell cycle by binding to cyclin-CDK complexes p21 is induced by the tumor suppressor p53 p27 responds to growth suppressors such as TGF-β
INK4/ARF family (CDKN2A-C)	p16/INK4a binds to cyclin D-CDK4 and promotes the inhibitory effects of RB p14/ARF increases p53 levels by inhibiting MDM2 activity
Cell Cycle Checkpoint Components	
RB	Tumor suppressive "pocket" protein that binds E2F transcription factors in its hypophosphorylated state, preventing G_1/S transition; also interacts with several transcription factors that regulate differentiation
p53	Tumor suppressor altered in the majority of cancers; causes cell cycle arrest and apoptosis. Acts mainly through p21 to cause cell cycle arrest. Causes apoptosis by inducing the transcription of pro-apoptotic genes such as *BAX*. Levels of p53 are negatively regulated by MDM2 through a feedback loop. p53 is required for the G_1/S checkpoint and is a main component of the G_2/M checkpoint.

to *cyclins*, so called because of the cyclic nature of their production and degradation. The CDK-cyclin complexes phosphorylate crucial target proteins that drive cells forward through the cell cycle. While cyclins arouse the CDKs, *CDK inhibitors* (CDKIs), of which there are many, silence the CDKs and exert negative control over the cell cycle (Table 7-6). Expression of these inhibitors is down-regulated by mitogenic signaling pathways, thus promoting the progression of the cell cycle.

There are two main cell cycle checkpoints one at the G_1/S transition and the other at the G_2/M transition, each of which is tightly regulated by a balance of growth promoting and growth suppressing factors, as well as by sensors of DNA damage (Chapter 1)**.** If activated, these DNA-damage sensors transmit signals that arrest cell cycle progression and, if cell damage cannot be repaired, initiate apoptosis. Understandably, defects in the G_1/S checkpoint are more important in cancer, in that these lead to dysregulated growth as well as a mutator phenotype, which (as mentioned) enables cancer development and progression. The major cancer-associated mutations that affect the G_1/S checkpoint can be broadly grouped into two classes:

- **Gain-of-function mutations in D cyclin genes and CDK4, oncogenes that promote G_1/S progression**. There are three D cyclin genes, D1, D2, and D3, which are functionally interchangeable and often dysregulated by acquired mutations in cancer, including chromosomal translocations in lymphoid tumors and gene amplification in a variety of solid tumors. Amplification of the *CDK4* gene also occurs in melanomas, sarcomas, and glioblastomas. Mutations affecting cyclin B and cyclin E and other CDKs also occur, but they are much less frequent, presumably because of the preeminent importance of the G_1/S transition in regulating tumor growth rates.
- **Loss-of-function mutations in tumor suppressor genes that inhibit G_1/S progression**. CDKIs that inhibit cyclin D/CDK complexes are frequently mutated or otherwise silenced in many human malignancies. For example, germline mutations of *p16* (*CDKN2A*) are present in 25% of melanoma-prone kindreds, and somatically acquired deletion or inactivation of *p16* is seen in 75% of pancreatic carcinomas, 40% to 70% of glioblastomas, 50% of esophageal cancers, 20% to 70% of acute lymphoblastic leukemias, and 20% of non–small-cell lung carcinomas, soft tissue sarcomas, and bladder cancers. Furthermore, the two most important tumor suppressor genes, *RB* and *TP53*, both encode proteins that inhibit G_1/S progression.

KEY CONCEPTS

Oncogenes, Oncoproteins, and Unregulated Cell Proliferation

Proto-oncogenes: normal cellular genes whose products promote cell proliferation

Oncogenes: mutated or overexpressed versions of proto-oncogenes that function autonomously, having lost dependence on normal growth promoting signals

Oncoprotein: a protein encoded by an oncogene that drives increased cell proliferation through one of several mechanisms