- Constitutive expression of growth factors and their cognate growth factor receptors, setting up an autocrine cell signaling loop
- Mutations in growth factor receptors, non-receptor tyrosine kinases, or downstream signaling molecules that lead to constitutive signaling, such as:
  - Activation of the EGF receptor tyrosine kinase by point mutations (lung cancer); activation of the HER2 receptor tyrosine kinase by gene amplification (breast cancer) ; activation of the JAK2 tyrosine kinase by point mutations (myeloproliferative disorders)
  - Activation of the ABL nonreceptor tyrosine kinase by chromosomal translocation and creation of a BCR-ABL fusion gene (chronic myelogenous leukemia, acute lymphoblastic leukemia)
  - Activation of RAS by point mutations (many cancers)
  - Activation of the PI3K and BRAF serine/threonine kinases by point mutations (many cancers)
- Increased expression of MYC, a master transcription factor that regulates genes needed for rapid cell growth by deregulation through chromosomal translocations (Burkitt lymphoma, other hematologic malignancies); gene amplification (neuroblastoma); increased activity of upstream signaling pathways (many cancers)
- Mutations that increase the activity of cyclin-dependent kinase 4 (CDK4)/D cyclin complexes, which promote cell cycle progression

Insensitivity to Growth Inhibition: Tumor Suppressor Genes

Whereas oncogenes drive the proliferation of cells, the products of most tumor suppressor genes apply brakes to cell proliferation, and abnormalities in these genes lead to failure of growth inhibition, another fundamental hallmark of carcinogenesis. Tumor suppressor proteins form a network of checkpoints that prevent uncontrolled growth. Many tumor suppressors, such as RB and p53, are part of a regulatory network that recognizes genotoxic stress from any source and responds by shutting down proliferation. Indeed, expression of an oncogene in normal cells with intact tumor suppressor genes leads to quiescence, or to permanent cell cycle arrest (oncogene-induced senescence, discussed later), rather than uncontrolled proliferation. Ultimately, the growth-inhibitory pathways may prod the cells into apoptosis. Another set of tumor suppressors seems to be involved in cell differentiation, causing cells to enter a postmitotic, differentiated pool without replicative potential. Similar to mitogenic signals, growth-inhibitory, pro-differentiation signals originate outside the cell and use receptors, signal transducers, and nuclear transcription regulators to accomplish their effects; tumor suppressors form a portion of these networks. Thus, the protein products of tumor suppressor genes may function as transcription factors, cell cycle inhibitors, signal transduction molecules, cell surface receptors, and regulators of cellular responses to DNA damage.

In this section, we describe tumor suppressor genes, their products, and possible mechanisms by which loss of their function contributes to unregulated cell growth (Table 7-7). Many of our current concepts of tumor suppressors evolved from studies of the retinoblastoma (*RB*) gene, the first tumor suppressor gene discovered, which remains a prototype of genes of this type. Like many discoveries in medicine, *RB* was identified by studying a rare disease, familial retinoblastoma. Approximately 40% of retinoblastomas are familial, with the predisposition to develop the tumor being transmitted as an autosomal dominant trait. Carriers of the retinoblastoma trait have a 10,000-fold increased risk of developing retinoblastoma (often in both eyes) as compared to the general population, and are also at greatly increased risk of developing osteosarcoma and other soft-tissue sarcomas. About 60% of retinoblastomas occur sporadically (virtually always in only one eye), and such patients are not at increased risk for other forms of cancer. To explain these two patterns of occurrence of retinoblastoma, Knudson proposed his now canonic **"two-hit" hypothesis of oncogenesis**. In molecular terms, Knudson's hypothesis can be stated as follows (Fig. 7-28):

- Two mutations (hits), involving both alleles of *RB* at chromosome locus 13q14, are required to produce retinoblastoma.
- In familial cases, children inherit one defective copy of the *RB* gene in the germline (the first hit), and the other copy is normal (Fig. 7-28). Retinoblastoma develops when the normal *RB* allele is mutated in retinoblasts as a result of a spontaneous somatic mutation (the second hit). Because such second hits seem to be virtually inevitable in a small fraction of retinoblasts, most individuals inheriting a germline defect in one *RB* allele develop unilateral or bilateral retinoblastoma, and the disease is inherited as an autosomal dominant trait.
- In sporadic cases both normal *RB* alleles must undergo somatic mutation in the same retinoblast (two hits). The probability of this event is low (explaining why retinoblastoma is an uncommon tumor in the general population), but the end result is the same: a retinal cell that has completely lost *RB* function and becomes cancerous.

Note that a child carrying an inherited mutant *RB* allele in all somatic cells is perfectly normal (except for the increased risk of developing cancer); it follows that one defective *RB* gene does not affect cell behavior. Thus, while the genetic trait (increased cancer risk) associated with germline mutations in *RB* is inherited in an autosomal dominant fashion, at the level of the individual cell, loss-of-function mutations in the *RB* gene behave in a recessive fashion.

Subsequent to the identification of *RB*, a large number of other tumor suppressor genes have been discovered, many through study of other types of familial cancers. In general, the major themes that were first appreciated through the study of familial retinoblastoma hold for these other famiial cancers: the risk of cancer is inherited as an autosomal dominant trait; tumors acquire a second hit in the sole normal tumor suppressor gene allele; and the same tumor suppressor gene is frequently mutated in sporadic tumors of the same type.

Some of the most important tumor suppressor genes, their associated familial syndromes, and their normal

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