of melanoma, and sporadic mutations of this locus have been detected in bladder cancer, head and neck tumors, acute lymphoblastic leukemias, and cholangiocarcinomas. In some tumors, such as cervical cancer, p16 is frequently silenced by hypermethylation of the gene rather than mutation (see discussion of epigenetic changes). Other cyclin-dependent kinase inhibitors also function as tumor suppressors and are frequently mutated or otherwise silenced in many human malignancies.

TGF-β Pathway. In most normal epithelial, endothelial, and hematopoietic cells, TGF-β is a potent inhibitor of proliferation. It regulates cellular processes by binding to TGF-β receptors I and II. Dimerization of the receptor upon ligand binding initiates intracellular signals that involve proteins of the SMAD family. Under normal circumstances, these signals turn on antiproliferative genes (e.g., genes for cyclin-dependent kinase inhibitors) and turn off genes that drive cell growth (e.g., *MYC*, cyclins, and cyclin-dependent kinases). As can be inferred from our earlier discussion, these changes result in decreased phosphorylation of RB and cell cycle arrest.

In many forms of cancer these growth-inhibiting effects are impaired by loss-of-function mutations in the TGF-β signaling pathway. Mutations affecting the type II TGF-β receptor are common in cancers of the colon, stomach, and endometrium, while mutational inactivation of SMAD4 is common in pancreatic cancers. In many other cancers, loss of TGF-β-mediated growth inhibition occurs at the level of key target genes; examples include mutations that lead to loss of p21 function and/or persistent expression of *MYC*. In such cases other preserved elements of the TGF-β-induced program of gene expression may actually facilitate acquisition of cancer hallmarks, such as immune evasion or angiogenesis. Thus TGF-β signaling is a double-edged sword that can prevent or promote tumor growth, depending on the state of other genes in the cell.

PTEN. PTEN (*p*hosphatase and *ten*sin homologue) is a membrane-associated phosphatase encoded by a gene on chromosome 10q23 that is mutated in Cowden syndrome, an autosomal dominant disorder marked by frequent benign growths, such as skin appendage tumors, and an increased incidence of epithelial cancers, particularly of the breast (Chapter 21), endometrium, and thyroid. As already mentioned, PTEN acts as a tumor suppressor by serving as a brake on the PI3K/AKT arm of the receptor tyrosine kinase pathway. *PTEN* gene function is lost in many cancers through deletion, deleterious point mutations, or epigenetic silencing.

NF1. Individuals who inherit one mutant allele of the *NF1* gene develop numerous benign neurofibromas and optic nerve gliomas as a result of inactivation of the second copy of the gene. This condition is called *neurofibromatosis type 1* (Chapter 26). Some of the neurofibromas later develop into malignant peripheral nerve sheath tumors. As already discussed, *Neurofibromin*, the protein product of the *NF1* gene, contains a GTPase-activating domain that acts as a brake on RAS signaling. With loss of neurofibromin function, RAS tends to become trapped in an active, signal-emitting state.

NF2. Germline mutations in the *NF2* gene predispose to the development of *neurofibromatosis type 2*. As discussed in Chapter 26, individuals with mutations in *NF2* develop benign bilateral schwannomas of the acoustic nerve. In addition, somatic mutations affecting both alleles of *NF2* have also been found in sporadic meningiomas and ependymomas. The product of the *NF2* gene, called *neurofibromin 2* or *merlin*, is structurally similar to the red cell membrane cytoskeletal protein 4.1 (Chapter 13), and is related to the ERM (ezrin, radixin, and moesin) family of membrane cytoskeleton-associated proteins. Cells lacking merlin do not establish stable cell-to-cell junctions and are insensitive to normal growth arrest signals generated by cell-to-cell contact.

WT1. Loss-of-function mutations in the *WT1* gene, located on chromosome 11p13, is associated with the development of Wilms tumor, a pediatric kidney cancer. Both inherited and sporadic forms of Wilms tumor occur, and mutational inactivation of the *WT1* locus is seen in both forms. The WT1 protein is a transcriptional activator of genes involved in renal and gonadal differentiation. It regulates the mesenchymal-to-epithelial transition that occurs in kidney development. Though not precisely known, it is likely that the tumorigenic effect of WT1 deficiency is intimately connected with the role of the gene in the differentiation of genitourinary tissues.

Interestingly, although WT1 is a tumor suppressor in Wilms' tumor, a variety of adult cancers, including leukemias and breast carcinomas, overexpress WT1. Since these tissues do not normally express WT1 at all, *WT1* may function as an oncogene in these cancers. Thus, some genes that regulate development may act as a tumor suppressor in one epigenetic context (e.g., *WT1* in a renal progenitor cell) and an oncogene in a second (e.g., *WT1* in a hematopoietic stem cell), an example of "crosstalk" between genes and the epigenome that we discuss later.

PATCHED (PTCH). *PTCH1* is a tumor suppressor gene that encodes a cell membrane protein called PATCHED1. PATCHED proteins are negative regulators of the Hedgehog signaling pathway. Under normal circumstances, binding of soluble factors belonging to the Hedgehog family to PATCH receptors relieves this negative regulation and activates the pathway, which stimulates downstream transcription factors. In the absence of PATCHED proteins, there is unopposed Hedgehog signaling that increases the expression of a number of pro-growth genes, including *NMYC* and D cyclins. Germline loss-of-function mutations in *PTCH1* cause Gorlin syndrome, an inherited condition also known as nevoid basal cell carcinoma syndrome (Chapter 26) that is associated with greatly increased risks of basal cell carcinoma of the skin and of medulloblastoma, an aggressive cerebellar tumor that arises in children or adolescents. *PTCH1* mutations are also present in 20% to 50% of sporadic cases of basal cell carcinoma and 10% to 25% of sporadic cases of medulloblastoma. About one half of such mutations in basal cell carcinomas are of the type caused by UV exposure. Hedgehog pathway antagonists have been developed and are approved for treatment of advanced basal cell carcinoma, and are also being tested in medulloblastoma