and other tumors associated with Hedgehog pathway activation.

***VHL*. Germline loss-of-function mutations of the von Hippel-Lindau (*VHL*) gene on chromosome 3p are associated with hereditary renal cell cancers, pheochromocytomas, hemangioblastomas of the central nervous system, retinal angiomas, and renal cysts.** Mutations of the *VHL* gene have also been noted in sporadic renal cell cancers (Chapter 20). The VHL protein is a component of a ubiquitin ligase, a type of protein complex that covalently links ubiquitin chains to specific protein substrates, thereby promoting their degradation by the proteasome. A critical substrate for the VHL ubiquitin ligase is the transcription factor HIF1α (hypoxia-inducible transcription factor 1α). In the presence of oxygen, HIF1α is hydroxylated and binds to VHL, leading to its ubiquitination and degradation. In hypoxic environments the hydroxylation reaction does not occur, and HIF1α escapes recognition by VHL. As a result HIF1α accumulates in the nuclei of hypoxic cells and turns on many target genes, including genes encoding the growth/angiogenic factors vascular endothelial growth factor (VEGF) and PDGF, the glucose transporter GLUT1, and several glycolytic enzymes. Loss-of-function mutations in VHL also prevent the ubiquitination and degradation of HIF1α, even under normoxic conditions, and are accordingly associated with increased levels of angiogenic growth factors and alterations in cellular metabolism that favor growth.

***STK11*. The *STK11* gene, also known as *LKB1*, encodes a serine/threonine kinase that is an important regulator of cellular metabolism.** Loss-of-function mutations of *STK11* give rise to Peutz-Jeghers syndrome, an autosomal dominant disorder associated with benign polyps of the gastrointestinal tract and an increased risk of multiple epithelial cancers, particularly gastrointestinal and pancreatic carcinomas. The function of *STK11* is still being elucidated, but it appears to have pleiotropic effects on multiple facets of cellular metabolism, including glucose uptake, gluconeogenesis, protein synthesis, mitochondrial biogenesis, and lipid metabolism. Sporadic mutations causing *STK11* loss-of-function are found in diverse carcinomas, a finding pointing to the important role of altered cellular metabolism in the establishment and maintenance of the transformed state (discussed later).

KEY CONCEPTS

Mechanism of Action of Major Tumor Suppressor Genes

APC: encodes a factor that negatively regulates the WNT pathway in colonic epithelium by promoting the formation of a complex that degrades β-catenin

- Mutated in familial adenomatous polyposis, autosomal dominant disorder associated with development of thousands of colonic polyps and early onset colon carcinoma; tumor development associated with loss of the single normal *APC* allele
- Mutated in about 70% of sporadic colon carcinomas; tumor development associated with acquired biallelic defects in *APC*

E-cadherin: cell adhesion molecule that plays an important role in contact-mediated growth inhibition of epithelial cells; also binds and sequesters β-catenin, a signaling protein that functions in the WNT pathway

- Germline loss-of-function mutations in the E-cadherin gene (*CDH1*) associated with autosomal dominant familial gastric carcinoma
- Loss of expression seen in many sporadic carcinomas; associated with loss of contact inhibition, loss of cohesiveness, increased invasiveness, and increased WNT signaling

CDKN2A: complex locus that encodes two tumor suppressive proteins, p16/INK4a, a cyclin-dependent kinase inhibitor that augments RB function, and ARF, which stabilizes p53

- Germline loss-of-function mutations are associated with autosomal dominant familial melanoma
- Biallelic loss-of-function seen in diverse cancers, including leukemias, melanomas, and carcinomas

TGF-β *pathway*: potent inhibitor of cellular proliferation in normal tissues

- Frequent loss-of-function mutations involving TGF-β receptors (colon, stomach, endometrium) or downstream signal transducers (SMADs, pancreas) in diverse carcinomas
- Complex role in carcinogenesis; may also have a pro-oncogenic role by enhancing the immune evasiveness of tumors

PTEN: encodes a lipid phosphatase that is an important negative regulator of PI3K/AKT signaling

- Germline loss-of-function mutations associated with Cowden syndrome, autosomal dominant disorder associated with a high risk of breast and endometrial carcinoma
- Biallelic loss-of-function common in diverse cancers

NF1: encodes neurofibromin 1, a GTPase that acts as a negative regulator of RAS

- Germline loss-of-function mutations cause neurofibromatosis type 1, autosomal dominant disorder associated with a high risk of neurofibromas and malignant peripheral nerve sheath tumors

NF2: encodes neurofibromin 2 (merlin), a cytoskeletal protein involved in contact inhibition

- Germline loss-of-function mutations cause neurofibromatosis type 2, autosomal dominant disorder associated with a high risk of bilateral schwannomas

WT1: encodes a transcription factor that is required for normal development of genitourinary tissues

- Germline loss-of-function mutations associated with Wilms tumor, a pediatric kidney cancer; similar *WT1* mutations also found in sporadic Wilms tumor

PTCH1: encodes membrane receptor that is a negative regulator of the Hedgehog signaling pathway

- Germline loss-of-function mutations cause Gorlin syndrome, autosomal dominant disorder associated with a high risk of basal cell carcinoma and medulloblastoma