senescence. Alternatively, if enough p53 accumulates to stimulate the transcription of the pro-apoptotic genes, the cell dies. While this scheme seems to be generally correct, cell-type-specific variations in response to p53 activation have been observed that are not easily explained, with some cell types succumbing rapidly to apoptosis, and others opting mainly for senescence. Thus, there is still much to be learned about the nuances of p53 function.

With loss of p53 function, DNA damage goes unrepaired, driver mutations accumulate in oncogenes and other cancer genes, and the cell marches blindly along a dangerous path leading to malignant transformation. Moreover, once a cancer is established, its p53 status has several important therapeutic implications. Irradiation and conventional chemotherapy, the two common modalities of cancer treatment, mediate their effects by inducing DNA damage and subsequent apoptosis. Tumors with wild type *TP53* alleles are more likely to be killed by such therapy than tumors with mutated *TP53* alleles. Such is the case with testicular teratocarcinomas and childhood acute lymphoblastic leukemias, which usually have wild type *TP53* alleles. In contrast, tumors such as lung cancers and colorectal cancers, which frequently carry *TP53* mutations, are relatively resistant to chemotherapy and irradiation. A second less obvious but even more nefarious result is that cells with defective p53 acquire a mutator phenotype, a tendency to acquire additional mutations at a high rate. Particularly in patients with advanced stage tumors with mutator phenotypes, it is very likely (and perhaps inevitable) that genetically distinct subclones will arise by chance that are resistant to any single therapy, whether this be radiation, conventional chemotherapy, or molecularly targeted cancer drugs. This theme is discussed later when the enabling properties of genomic instability are discussed more broadly.

The discovery of p53 family members p63 and p73 has revealed that p53 has collaborators. Indeed, p53, p63, and p73 are players in a complex interconnected network with significant crosstalk that is still being unraveled. p53 is ubiquitously expressed, while p63 and p73 show more tissue specificity. For example, p63 is essential for the differentiation of stratified squamous epithelia, while p73 has strong pro-apoptotic effects after DNA damage induced by chemotherapeutic agents.

KEY CONCEPTS

p53, Guardian of the Genome

- The p53 protein is the central monitor of stress in the cell and can be activated by anoxia, inappropriate signaling by mutated oncoproteins, or DNA damage. p53 controls the expression and activity of proteins involved in cell cycle arrest, DNA repair, cellular senescence, and apoptosis.
- DNA damage is sensed by complexes containing kinases of the ATM/ATR family; these kinases phosphorylate p53, liberating it from inhibitors such as MDM2. Active p53 then upregulates the expression of proteins such as the cyclin-dependent kinase inhibitor p21, thereby causing cell-cycle arrest at the G1-S checkpoint. This pause allows cells to repair DNA damage.
- If DNA damage cannot be repaired, p53 induces additional events that lead to cellular senescence or apoptosis.
- The majority of human cancers demonstrate biallelic loss-of-function mutations in *TP53*. Rare patients with Li-Fraumeni syndrome inherit one defective copy of *TP53* and have a very high incidence of a wide variety of cancers.
- Like RB, p53 is inactivated by viral oncoproteins, such as the E6 protein of HPV

Other Tumor Suppressor Genes. There is little doubt that more tumor suppressor genes remain to be discovered. Often, their location is suspected by the detection of recurrent sites of chromosomal deletions, which are now being rapidly identified and characterized by high throughput sequencing of cancer genomes. The known tumor suppressor genes all appear to impact one of more of the hallmarks of cancer. Some that are associated with well-defined clinical syndromes (Table 7-7) or that serve to highlight various mechanisms by which tumor suppressors function are described:

APC: Gatekeeper of Colonic Neoplasia. **Adenomatous polyposis coli (APC) is a member of the class of tumor suppressors that function by downregulating growth-promoting signaling pathways.** Germline loss-of-function mutations involving the *APC* (5q21) locus are associated with familial adenomatous polyposis, an autosomal dominant disorder in which individuals born with one mutant allele develop thousands of adenomatous polyps in the colon during their teens or 20s (Chapter 17). Almost invariably, one or more of these polyps undergoes malignant transformation, giving rise to colon cancer. As with other tumor suppressor genes, both copies of the *APC* gene must be lost for an adenoma to arise. As discussed later, several additional mutations must then occur for adenomas to progress to cancers. In addition to these hereditary forms of colon cancer, 70% to 80% of nonfamilial colorectal carcinomas and sporadic adenomas also show acquired defects involving both *APC* genes, firmly implicating *APC* loss of function in the pathogenesis of colonic tumors.

APC is a component of the WNT signaling pathway, which has a major role in controlling cell fate, adhesion, and cell polarity during embryonic development (Fig. 7-31). WNT signals through a family of cell surface receptors called frizzled (FRZ), and stimulates several pathways, the central one involving β-catenin and APC. A major function of the APC protein is to hold β-catenin activity in check. In the absence of WNT signaling, APC causes degradation of β-catenin, preventing its accumulation in the cytoplasm. APC does so by forming a macromolecular "destruction" complex that leads to the proteasomal degradation of β-catenin. Signaling by WNT blocks the formation of the destruction complex, stabilizing β-catenin and allowing it to translocate from the cytoplasm to the nucleus. Once in the nucleus β-catenin forms a transcription activation complex with the DNA-binding factor TCF. The β-catenin/TCF complex promotes the growth of colonic epithelial cells by increasing the transcription of *MYC*, *cyclin D1*, and other genes. Because inactivation of the *APC* gene disrupts the destruction complex, β-catenin survives and translocates to the nucleus, where it activates the transcription of pro-growth target genes in cooperation with TCF. Thus, cells that lose APC behave as if they are