mutations in *TP53*, located on chromosome 17p13.1, are found in more than 50% of cancers. Moreover, *TP53* mutations occur with some frequency in virtually every type of cancer, including carcinomas of the lung, colon, and breast—the three leading causes of cancer death. In most cases, mutations are present in both *TP53* alleles and are acquired in somatic cells (not inherited in the germline). Less commonly, individuals inherit one mutated *TP53* allele. As in the case of the *RB* tumor suppressor and retinoblastoma, inheritance of a mutated copy of *TP53* predisposes individuals to malignant tumors because only one additional "hit" in the lone normal allele is needed to abrogate *TP53* function. Such individuals, said to have the *Li-Fraumeni syndrome*, have a 25-fold greater chance of developing a malignant tumor by age 50 than the general population. In contrast to individuals who inherit a mutant *RB* allele, the spectrum of tumors that develop in persons with the Li-Fraumeni syndrome is quite varied; the most common types of tumors are sarcomas, breast cancer, leukemias, brain tumors, and carcinomas of the adrenal cortex. People with the Li-Fraumeni syndrome often develop cancer at younger ages and are more likely to suffer from multiple primary tumors of varying types than are normal individuals.

These mutational data, while impressive, only begin to tell the tale of altered *TP53* function in cancer. *TP53* encodes the protein p53, which is tightly regulated at several levels. Analogous to RB, many tumors lacking *TP53* mutations have instead other mutations affecting proteins that regulate p53 function. For example, MDM2 and related proteins of the MDM2 family stimulate the degradation of p53; these proteins are frequently overexpressed in malignancies with normal *TP53* alleles. Indeed, the *MDM2* gene is amplified in 33% of human sarcomas, leading to a functional deficiency of p53 in these tumors. Also like RB, the transforming proteins of several DNA viruses bind p53 and promote its degradation. Best known of these viral oncoproteins is the E6 protein of high-risk human papilloma viruses, which have causative roles in cervical carcinoma and a subset of squamous cell carcinomas of the head and neck.

The frequent loss of p53 function in human tumors reflects its critical role in prevention of cancer development. p53 carries out this role by serving as the focal point of a large network of signals that sense cellular stress, primarily DNA damage, but also shortened telomeres, hypoxia, and stress caused by excessive pro-growth signaling, as may occur in cells bearing mutations in genes such as RAS and MYC. In nonstressed, healthy cells, p53 is held at bay through its aforementioned association with MDM2, an enzyme that ubiquitinylates p53, leading to its degradation by the proteasome. As a result, p53 is virtually undetectable in normal cells. In stressed cells, however, p53 is released from the inhibitory effects of MDM2 via two major mechanisms, which vary depending on the nature of the stress (Fig. 7-30).

- *DNA damage and hypoxia*. The key initiators of p53 activation following DNA damage or in cells exposed to hypoxia are two related protein kinases, ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia and Rad3 related (ATR). As the name implies, the *ATM* gene was originally identified as the germline mutation in individuals with ataxia-telangiectasia. Persons with this disease, which is characterized by an inability to repair certain kinds of DNA damage, suffer from an increased incidence of cancer. The types of damage sensed by ATM and ATR are different, but the downstream effects are similar. Once triggered, both ATM and ATR stimulate the phosphorylation of a number of proteins, including p53 and MDM2. These posttranslational modifications disrupt the binding and degradation of p53 by MDM2, allowing p53 to accumulate.
- *"Oncogenic" stress*. Activation of oncoproteins such as RAS leads to sustained, supraphysiologic signaling through pro-growth pathways such as the MAPK and PI3K/AKT pathways. Through unknown mechanisms, these aberrant signals create cellular stress and lead to increased expression of p14/ARF, which you will recall is encoded by the *CDKN2A* tumor suppressor gene. p14/ARF binds MDM2 and displaces p53, again allowing p53 levels to rise in the cell.

Once activated, p53 thwarts neoplastic transformation by inducing either transient cell cycle arrest, senescence (permanent cell cycle arrest), or programmed cell death (apoptosis). Most of these effects are believed to stem from p53's ability to function as a transcription factor. p53 binds DNA in a sequence-specific fashion and activates the transcription of hundreds of different target genes with p53-binding elements. The key target genes that execute the functions of p53 are not completely defined, but appear to fall into three major categories: (1) those that cause cell cycle arrest; (2) those that cause apoptosis; and (3) those that enhance catabolic metabolism or inhibit anabolic metabolism. The latter group of genes makes intuitive sense; there is no need for a cell that has stopped its cell cycle progression to continue to synthesize the large amounts of macromolecules (e.g., lipids and proteins) that are needed for cell growth and division. Also included in the list of p53 target genes are those encoding two kinds of regulatory RNAs, micro-RNA (mIRs) and long intervening noncoding (LINC) RNAs, which presumably help to coordinate the p53-dependent cellular response to stress.

Once p53 accumulates in a cell to levels that are sufficient to activate the transcription of target genes, several different outcomes are possible, each more serious than the last with respect to the ultimate fate of the affected cell:

- **Transient p53-induced cell cycle arrest.** Rapid onset, p53-mediated cell cycle arrest may be considered a primordial response to DNA damage. It occurs late in the G_1 phase and is caused in part by p53-dependent transcription of the *CDKN1A* gene, which encodes the CDK inhibitor p21. As discussed, p21 inhibits CDK4/D cyclin complexes, thereby maintaining RB in an active, hypophosphorylated state and blocking the progression of cells from G_1 phase to S phase. This pause in cell cycling is welcome, as it gives the cells "breathing time" to repair DNA damage. p53 also helps the process by inducing certain proteins, such as GADD45 (growth arrest and DNA damage), that enhance DNA repair. If DNA damage is repaired successfully, the signals responsible for p53 stabilization cease and p53 levels fall, releasing the cell cycle block. The cells may then revert to a normal state.