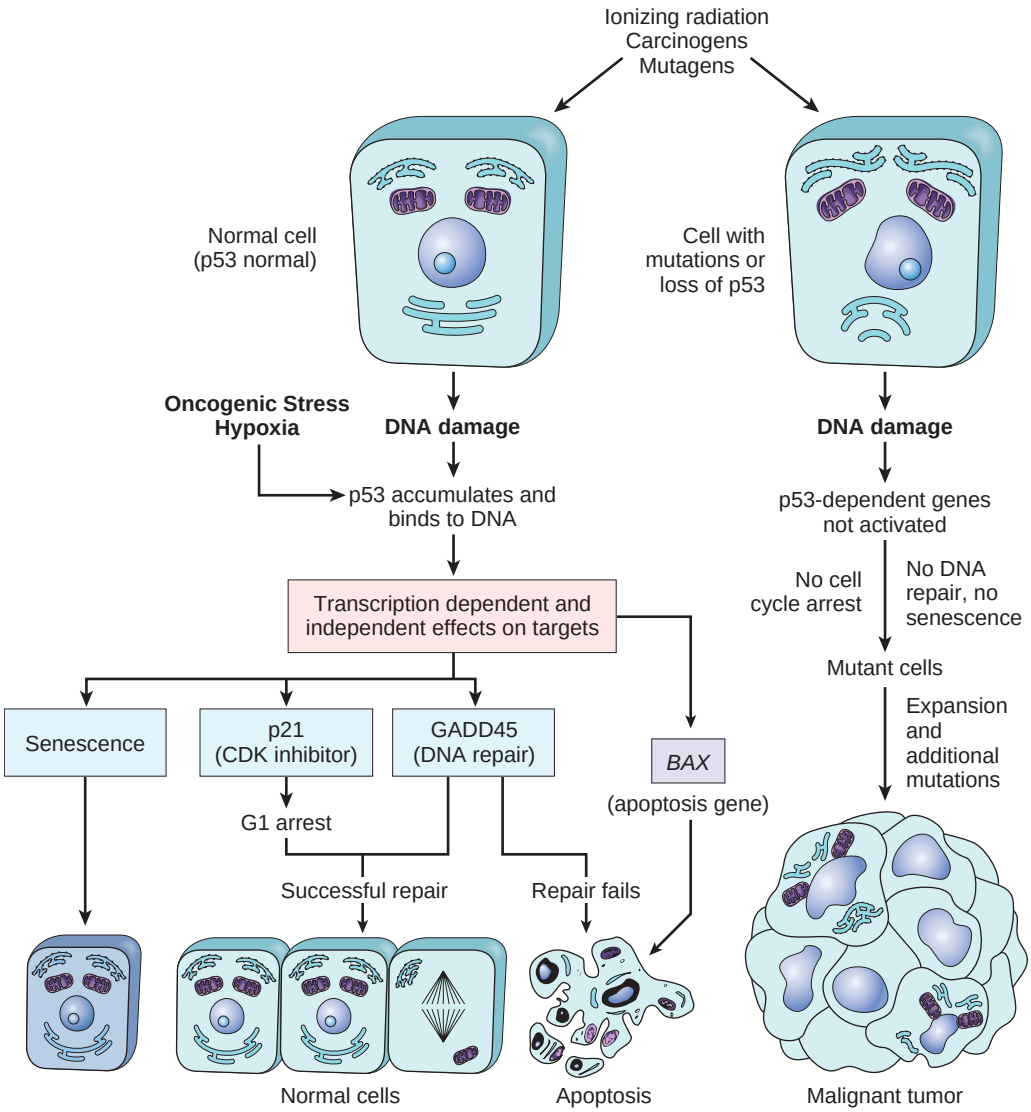

Figure 7-30 The role of p53 in maintaining the integrity of the genome. Activation of normal p53 by DNA-damaging agents or by hypoxia leads to cell cycle arrest in G_1 and induction of DNA repair by transcriptional upregulation of the cyclin-dependent kinase inhibitor *CDKN1A* (encoding the cyclin-dependent kinase inhibitor p21) and the *GADD45* genes. Successful repair of DNA allows cells to proceed with the cell cycle; if DNA repair fails, p53 triggers either apoptosis or senescence. In cells with loss or mutations of the p53 gene, DNA damage does not induce cell cycle arrest or DNA repair, and genetically damaged cells proliferate, giving rise eventually to malignant neoplasms.

- **p53-induced senescence.** Senescence is a state of permanent cell cycle arrest characterized by specific changes in morphology and gene expression that differentiate it from reversible cell cycle arrest. How cells become fixed in the senescence state is unclear. One plausible idea is that senescence is the product of epigenetic changes that result in the formation of heterochromatin at key loci, including genes that are required for progression of cells from the G_1 phase into S phase. Like other p53 responses, senescence may be stimulated in response to a variety of stresses, such as unopposed oncogene signaling, hypoxia, and shortened telomeres. The senescent cells, while not normal, are blocked from developing into tumors.
- **p53-induced apoptosis.** Apoptosis of cells with irreversible DNA damage is the ultimate protective mechanism against neoplastic transformation. p53 directs the transcription of several pro-apoptotic genes such as *BAX* and *PUMA* (described later), which are believed to tip the balance in favor of cell death via the intrinsic (mitochondrial) pathway.

What determines whether a cell repairs its DNA, becomes senescent, or undergoes apoptosis is uncertain, but both the duration and the level of p53 activation may be deciding factors. It appears that the affinity of p53 for its binding sites in the promoters and enhancers of DNA-repair genes is higher than its affinity for binding sites in pro-apoptotic genes. Thus, the DNA-repair pathway is stimulated first as p53 begins to accumulate. If p53 is sustained at this level due to ineffective DNA repair or other chronic stresses (e.g., that induced by a potentially oncogenic RAS mutation), epigenetic silencing of genes that are needed for cell cycle progression occurs, leading to