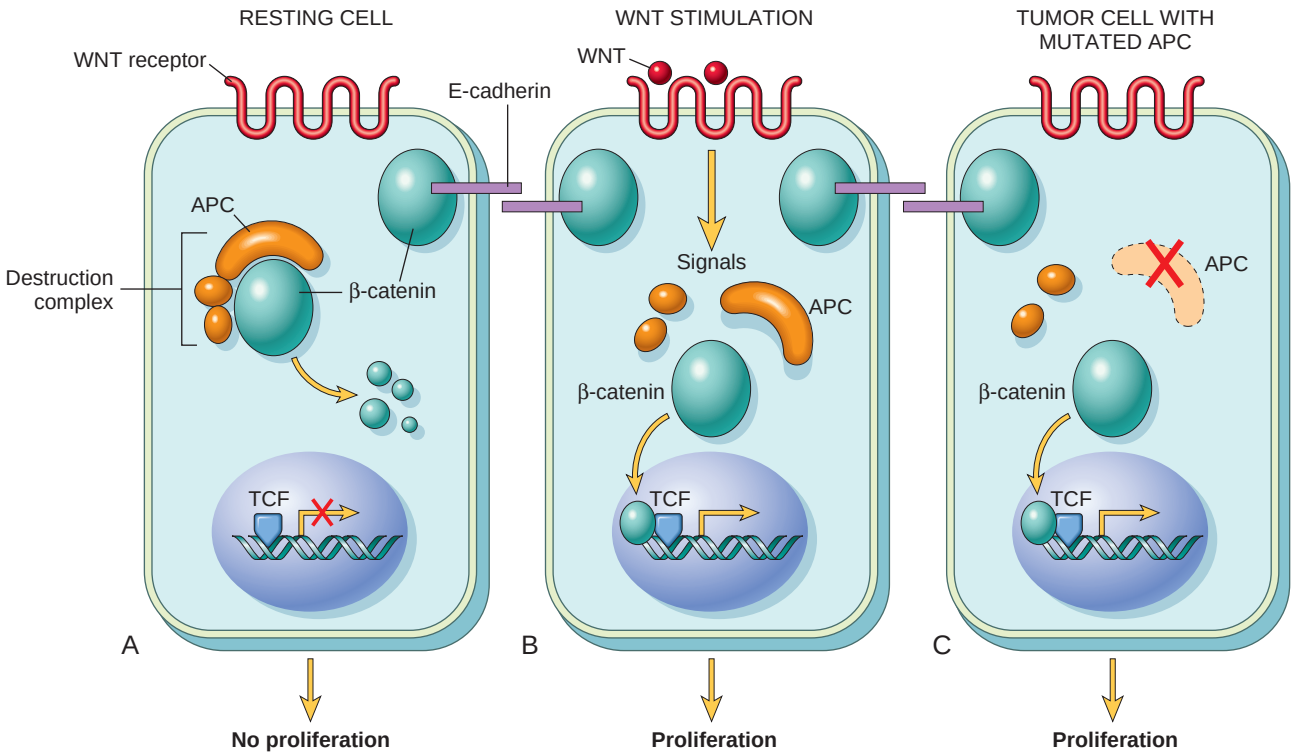

Figure 7-31 The role of APC in regulating the stability and function of β-catenin. APC and β-catenin are components of the WNT signaling pathway. **A,** In resting colonic epithelial cells (not exposed to WNT), β-catenin forms a macromolecular complex containing the APC protein. This complex leads to the destruction of β-catenin, and intracellular levels of β-catenin are low. **B,** When normal colonic epithelial cells are stimulated by WNT molecules, the *destruction complex* is deactivated, β-catenin degradation does not occur, and cytoplasmic levels increase. β-catenin translocates to the nucleus, where it binds to TCF, a transcription factor that activates genes involved in cell cycle progression. **C,** When *APC* is mutated or absent, as frequently occurs in colonic polyps and cancers, the destruction of β-catenin cannot occur. β-catenin translocates to the nucleus and coactivates genes that promote entry into the cell cycle, and cells behave as if they are under constant stimulation by the WNT pathway.

being continuously stimulated by WNT. The importance of the APC/β-catenin signaling pathway in tumorigenesis is attested to by the fact that many colon tumors with normal *APC* genes harbor mutations in β-catenin that prevent its APC-dependent destruction, allowing the mutant protein to accumulate in the nucleus and stimulate transcription. Thus, β-catenin, the target of APC, is itself a proto-oncoprotein. Dysregulation of the APC/β-catenin pathway is not restricted to colon cancers; for example, gain-of-function mutations in β-catenin are present in more than 50% of hepatoblastomas and in approximately 20% of hepatocellular carcinomas.

E-Cadherin. β-catenin binds to the cytoplasmic tail of E-cadherin, a cell surface protein that maintains intercellular adhesiveness. Loss of cell-cell contact, such as in a wound or injury to the epithelium, disrupts the interaction between E-cadherin and β-catenin, and also promotes increased translocation of β-catenin to the nucleus, where it stimulates genes that promote proliferation; this is an appropriate response to injury that can help repair the wound. Reestablishment of these E-cadherin contacts as the wound heals leads to β-catenin again being sequestered at the membrane and reduces in the proliferative signal; these cells are said to be "contact-inhibited." Loss-of-contact inhibition, by mutation of the E-cadherin/β-catenin axis, or by other changes, is a key characteristic of carcinomas. Furthermore, loss of E-cadherin can contribute to the malignant phenotype by allowing easy disaggregation of cells, which can then invade locally or metastasize. Reduced cell surface expression of E-cadherin has been noted in many carcinomas, including those that arise in the esophagus, colon, breast, ovary, and prostate. Germline loss-of-function mutations of the E-cadherin gene, known as *CDH1*, cause familial gastric carcinoma, and a variable proportion of sporadic gastric carcinomas are also associated with loss of E-cadherin expression. The molecular basis of reduced E-cadherin expression in sporadic cancers is varied. In a small proportion of cases, there are mutations in the E-cadherin gene (located on 16q); in other cancers, E-cadherin expression is reduced as a secondary effect of activating mutations in β-catenin genes. Additionally, E-cadherin may be downregulated by transcription repressors, such as SNAIL, that are implicated in epithelial-to-mesenchymal transition and metastasis (discussed later).

CDKN2A. The *CDKN2A* gene locus encodes two protein products: the p16/INK4a cyclin-dependent kinase inhibitor, which blocks CDK4/cyclin D-mediated phosphorylation of RB, thereby reinforcing the RB checkpoint; and p14/ARF, which activates the p53 pathway by inhibiting MDM2 and preventing destruction of p53. Thus, mutation or silencing of *CDKN2A* impacts both the RB and p53 tumor suppressor pathways. p16 also appears to be important in induction of cellular senescence (described later). Germline mutations in *CDKN2A* are associated with familial forms