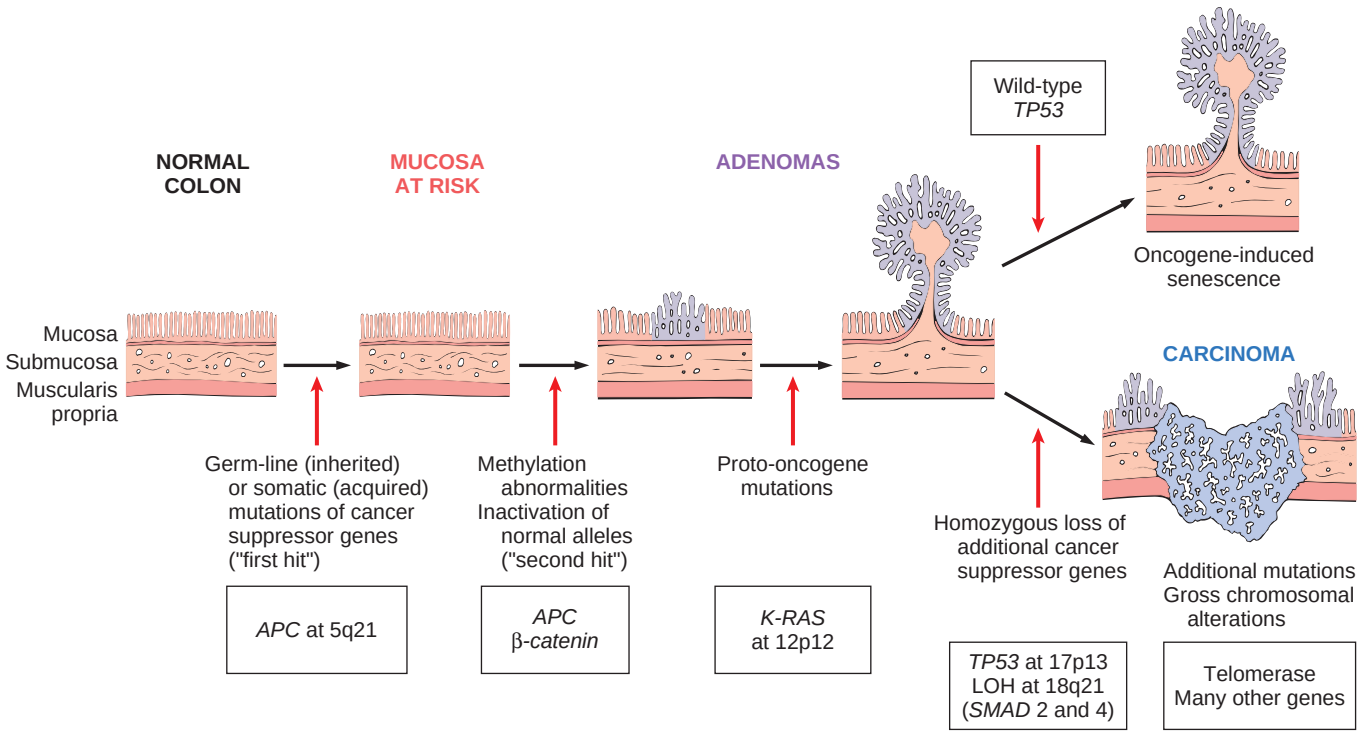

Figure 7-42 Molecular model for the evolution of colorectal cancers through the adenoma-carcinoma sequence. Although *APC* mutation is an early event and loss of *TP53* occurs late in the process of tumorigenesis, the timing for the other changes may be variable. Note also that individual tumors may not have all of the changes listed. *Top right*, cells that gain oncogene signaling without loss of *TP53* eventually enter oncogene-induced senescence. LOH, loss-of-heterozygosity.

to many thousands of mutations in tumors that arise following chronic exposure to carcinogens, such as lung cancers associated with cigarette smoking. Although the presence of multiple mutations is consistent with the idea that no single mutation will suffice to produce a cancer, as already mentioned it is often difficult to determine which mutations in a tumor drive oncogenesis and which are "passengers," mutations that provide no advantage to the tumor cell and are merely along for the ride.

A more direct answer to the question "how many mutations does it take to establish a fully malignant tumor?" comes from experimental attempts to transform normal human cells with combinations of oncogenes, some derived from transforming viruses (described later). For example, normal human epithelial cells can be transformed by the following combination of events: (1) activation of RAS; (2) inactivation of RB; (3) inactivation of p53; (4) inactivation of PP2A, a tumor suppressive phosphatase that is a negative regulator of many signaling pathways; and (5) constitutive expression of telomerase. Cells bearing all of these alterations are immortal and produce invasive, fully malignant growths when injected into immunodeficient mice.

Unlike in the laboratory, these events presumably never occur simultaneously during the natural development of a human cancer, but instead occur in a stepwise fashion. What is the evidence that this is so? A classic example of incremental acquisition of the malignant phenotype is found in colon carcinoma. Many of these cancers evolve through a series of morphologically identifiable stages: colon epithelial hyperplasia followed by formation of adenomas that progressively enlarge and ultimately undergo malignant transformation (Chapter 17). Molecular analyses of proliferations at each of these stages have indeed shown that precancerous lesions have fewer mutations than adenocarcinomas and suggest a tendency to acquire particular mutations in the sequence illustrated in Figure 7-42. According to this scheme, inactivation of the *APC* tumor suppressor gene occurs first, followed by activation of *RAS* and, ultimately, loss of a tumor suppressor gene on 18q and loss of *TP53*. While multiple mutations, including gain of oncogenes and loss of tumor suppressors, are required for carcinogenesis, the precise temporal sequence of mutations does not appear to be fixed and may be different in each organ and tumor type.

Similar evidence for stepwise progression also exists for other recognizable precursor lesions to epithelial cancers, such as dysplasias of the cervix, hyperplasias of the endometrium, and the evolution of oral cancers. These are described in subsequent chapters.

Carcinogenic Agents and Their Cellular Interactions

More than 200 years ago the London surgeon Sir Percival Pott correctly attributed scrotal skin cancer in chimney sweeps to chronic exposure to soot. Based on this observation, the Danish Chimney Sweeps Guild ruled that its members must bathe daily. No public health measure since that time has achieved so much in controlling a form of