Pathogenesis

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Colorectal cancer originates from premalignant precursor lesions in the epithelial lining of the colon or rectum in a stepwise progression that results in increasing dysplasia due to an accumulation of genetic abnormalities. In spontaneous colorectal cancer, as compared with hereditary cancers, this is referred to as the adenoma–carcinoma sequence. Up to 80% of colorectal cancers occur in people with little or no genetic risk. People with inflammatory bowel disease are at an increased risk, which increases with the duration of the disease, and accounts for 2% of cancers each year. Those with a family history in two or more first-degree relatives have a two- to threefold greater risk of disease and this group accounts for about 20% of all cases. A number of genetic syndromes are also associated with higher rates of colorectal cancer. The most common is hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome), which accounts for 3% of people with colorectal cancer. Other syndromes include Gardner syndrome and FAP . The most common abnormality found in colorectal cancer is mutation in the Wnt signalling pathway , which increases cell signalling activity . The mutations can be inherited or acquired. The most commonly mutated gene is the APC gene, which results in accumulation of the β -catenin protein. β -catenin activates the transcription of various proto-oncogenes that are responsible for normal cell renewal and di ff erentiation, but when overexpressed can cause cancer. Many other mutations, other than in the Wnt signalling pathway , are also found in colorectal cancer. They include mutations in the TP53 gene, which controls normal cell division and death, and in genes responsible for programmed cell death, such as the gene encoding transforming growth factor (TGF)- and DCC (deleted in colorectal cancer) gene. Other genetic abnormalities include overexpression of oncogenes, including genes encoding the proteins KRAS (Kirsten rat sarcoma homologue), RAF (rapidly accelerated fibrosarcoma) and PI3K (phosphoinositide 3-kinase), which lead to increased cell proliferation, and inactivation of tumour suppressor genes, such as PTEN (phosphatase and tensin homologue), which normally inactivates the PI3K signalling pathway . Henry Thompson Lynch , 1928–2019, physician and geneticist, Omaha, NE, USA, first presented his findings of a family with a strong history of colorectal cancer without polyposis in 1964. Eldon John Gardner , 1909–1989, geneticist, The University of Utah, Salt Lake City , UT , USA, described this syndrome in 1950. exhibit epigenetic alterations – cellular or physiological e ff ects - resulting from external or environmental factors that switch genes on or o ff . Epigenetic alterations can a ff ect hundreds of genes and include changes in the expr ession of microRNAs, hypermethylation or hypomethylation of CpG islands of protein-encoding genes and alterations in histones and chromosomal architecture, all of which can influence gene expression (see Chapter 77).

Revision #1
Created 2025-12-31 15:28:33 UTC by Omar Ayman
Updated 2025-12-31 15:28:33 UTC by Omar Ayman