APC (adenomatous polyposis coli)

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Identity
HGNC (Hugo): APC
Location: 5q21

DNA/RNA
Description
15 exons (with a particularly large 15th exon).

Transcription
9.0 kb mRNA; 8538 bp open reading frame.

Protein
Description
2843 amino acids; 310 kDa.

Function
APC is a classical tumour suppressor protein.

The APC gene product indirectly regulates transcription of a number of critical cell proliferation genes, through its interaction with the transcription factor beta catenin. APC binding to beta catenin leads to ubiquitin-mediated beta catenin destruction; loss of APC function increases transcription of beta catenin targets. These targets include cyclin D, C-myc, ephrins and caspasases. APC also interacts with numerous actin and microtubule associated proteins. APC itself stabilizes microtubules. Homozygous APC truncation has been shown to affect chromosome attachment in cultured cells. Roles for APC in cell migration have been demonstrated in vitro and in mouse models.

Homology
A second family member, APC2, is located on 19p13.3 (see non-annotated genes).

Mutations
Germinal
Germline mutations of APC cause a spectrum of diseases under the broad category of familial adenomatous polyposis (FAP).

Mutations typically cluster in or just distal to the armadillo repeat region and truncate the protein near its middle. It is not known which is pathophysiologic - absence of the full-length protein or presence of the truncated version; evidence exists for both. The second hit creates another truncation or gene deletion. There is some evidence that the position of the first hit in the gene determines the pattern of the second hit. Rare hypormorphic mutations cause attenuated polyposis.
Both copies of the APC gene are mutated in 80% of sporadic colorectal tumours.

Familial Adenomatous Polyposis (FAP)

Autosomal dominant disease in which patients develop thousands of colonic polyps during childhood and adolescence. Many of these will progress to cancers if not removed. FAP encompasses other disease syndromes with extra-colonic manifestations. In Gardner Syndrome, patients may develop the following extra-intestinal manifestations:
- Gastric and duodenal malignancies.
- Cancer of the pancreas, biliary tree and gallbladder.
- Hepatoblastoma.
- Congenital hypertrophy of the retinal pigment epithelium (CHRPE), a benign hyperpigmentation beneath the retina that is typically asymptomatic.
- Desmoid tumors, a tumor of the connective tissue that can cause morbidity and mortality by impinging on adjacent structures.
- Osteomas and dental abnormalities.
- Epidermoid cysts and other skin abnormalities.

Stage I lesions are usually cured by surgery. There is controversy about the use of chemotherapy in Stage II disease. In Stage III disease, chemotherapy improves the five year survival from ~50% to ~60%.

Oncogenesis

Loss of normal APC function is known to be an early event in both familial and sporadic colon cancer pathogenesis, occurring at the pre-adenoma stage. Current discussion is focused on whether loss of APC function precedes, follows, or is entwined with chromosomal instability. Later events include abnormalities of K-ras and p53.

Generally colon cancers show either chromosomal instability (CIN), which correlates with loss of APC function, or microsatellite instability (MIN), which correlates with loss of mismatch repair function, but not both.

Sporadic colorectal cancer

Somatic mutation of the APC gene is found in the majority of colorectal adenocarcinomas. Sporadic colorectal cancer is the third most frequent cancer in the world.

Prognosis

Without treatment, the life expectancy is in the early 40s due to colon cancer. Treatment consists of regular screening, with polypectomy of large lesions. Due to the large number of polyps, eventual complete colectomy with or without proctosigmoidectomy is needed.

Regular use of the cyclooxygenase inhibitor Sulindac and possibly other member of this class of drugs reduces the number of polyps. About ten percent of patients also experience significant morbidity from desmoid tumors.

References


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