

# Solid Tumour Section

## Mini Review

### Colon: Colorectal adenocarcinoma

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## Clinics and pathology

### Disease

Adenocarcinoma

### Etiology

5-10% of colorectal cancers are hereditary; there are two forms of predisposition: 1- familial adenomatous polyposis (FAP) is characterized by the presence of hundreds to thousands of adenomas, and is due to germline mutations of the APC gene on 5q21; 2- the hereditary nonpolyposis colorectal cancer (HNPCC, or Lynch syndrome) is due to germline mutations in genes intervening in the repair of DNA mismatches occurring during replication (mostly hMSH2 and hMLH1 on 2p16 and 3p21 respectively).

### Epidemiology

Third most frequent cancer in the world in both sexes; estimated world total of 572 000 new cases a year in 1980; in developed countries, colorectal cancer ranks second (e.g.: 26 000 new cases each year in France).

### Clinics

The majority of colorectal cancers arise from pre-existing adenomatous polyps.

### Pathology

Dukes's staging system, modified by Astler-Coller.

### Treatment

Resection with adjuvant chemo and/or radiotherapy in higher stages.

### Prognosis

Survival, although improving is not much more than 50% after 5 years, depending mainly of the stage of tumour growth at the time of diagnosis; genetic alterations have been studied in relation to prognosis with contradictory results (loss of heterozygosity on 17p and 18q, overexpression and mutation of the p53 gene).

## Cytogenetics

### Cytogenetics, morphological

There are two types of colorectal cancers, according to the ploidy:

- Aneuploid tumours showing numerous allelic losses; loss of heterozygosity (LOH) on chromosomes 17 and 18 have been found in more than 75% of colorectal cancers; complete allelotyping showed that chromosome arms 1q, 4p, 5q, 6p, 6q, 8p, 9q, 18p and 22q exhibited LOH in about 50% of the cases;
- Diploid tumours without frequent allelic losses.

## Genes involved and Proteins

**Note:** A number of genes are known to be implicated in tumour progression in colorectal cancers; they are either oncogenes or tumour suppressor genes; Fearon and Vogelstein proposed a model for the genetic basis of colorectal tumorigenesis.

### APC

**Location:** 5q21-22

**DNA / RNA**

15 exons.

### Protein

Tumour suppressor gene; the APC interacts with the adherens junction proteins a and beta-catenin suggesting involvement in cell adhesion; APC may also inhibit the transcription pathway regulated by the beta-catenin/Tcf complex.

### Germinal mutations

In familial adenomatous polyposis.

### Somatic mutations

The APC gene is mutated in about 50% of sporadic colorectal tumours; most mutations are frameshifts of nonsense mutations resulting in premature stop codons; some mutations on beta-catenin have been described in

tumours and cell lines without mutations in the APC gene.

### **P53**

**Location:** 17p13

#### **DNA / RNA**

11 exons.

#### **Protein**

Tumour suppressor; 5 highly-conserved regions containing a transactivation domain, a DNA-binding domain, nuclear localization signals and a tetramerization domain; P53 is thus a transcriptional regulator: guardian of the genome preventing cells from dividing before DNA damage is repaired.

#### **Somatic mutations**

Mutations of P53 are mostly located in exons 4 to 8 with hotspots at codons 175, 245, 248, 273 and 282; they can be either missense mutations, or non-sense, deletions, insertions and splicing mutations resulting in a truncated p53 protein.

### **KRAS2 (or Ki-ras)**

**Location:** 12p12.1

#### **DNA / RNA**

3 exons.

#### **Protein**

Ki-ras belongs to the ras gene family containing also H-ras and N-ras; they encode for closely related 21-kDa (189 amino acids) GTP-binding proteins with a role in growth signal transduction; oncogenes.

#### **Somatic mutations**

These genes are activated by point mutations at codons 12, 13 and 61, and, in the case of colorectal cancers, Ki-ras is mutated on codons 12 or 13 in about 40% of the cases.

There is incomplete data to implicate a gene(s) on chromosome 18; it could be DCC (Deleted in Colon Cancer), DPC4 (Deleted in Pancreatic Cancer) or/and J18, a Mad-related gene thought to transduce signals from TGFbeta family members.

### **Mismatch repair genes (MMR genes): hMSH2, hMLH1, hPMS1, hPMS2, GTBP (hMSH6), and hMSH3 (DUG)**

**Location:** 2p16 (hMSH2, GTBP), 2q31-33 (hPMS1), 3p21 (hMLH1), 7p22 (GTBP), 5q (hMSH3)

#### **Protein**

The proteins encoded by these genes are human homologs of the E. Coli Mut HLS system; they are implicated in the reparation of mismatches due to errors during DNA replication; the more visible consequence of the defect in mismatch repair is the presence of additional alleles at microsatellite loci which are repeats of 1 to 5 nucleotides scattered on the genome; due to their repetitive structure, microsatellite are particularly prone to replication errors; microsatellite instability is the hallmark of the RER (Replication Error) or MSI (MicroSatellite Instability) phenotype characteristic of HNPCC tumours and of 15% of sporadic colorectal cancers.

#### **Germinal mutations**

In HNPCC (Lynch syndrome), most patients have germline mutations of either hMSH2 or hMLH1.

## **To be noted**

- The RER+ sporadic colon cancers are mostly diploid, without LOH, with few mutations of p53 and APC and right-sided; they contain mutations in repetitive coding sequences of a number of genes such as the TGFbeta type II receptor, the receptor of the Insulin-like growth factor and the BAX gene implicated in apoptosis.
- the RER- are polyploid, with LOH (5q, 17p, 18q), mutations in p53, and more often left-sided, they have a worse prognosis.

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