

## Solid Tumour Section Review

### Colon: Colorectal adenocarcinoma

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#### Classification

**Note:** Hereditary colorectal cancers can be broadly classified into three types:

1- Familial adenomatous polyposis (FAP): characterized by the development of hundreds of polyps at a very early age, due to mutations in the APC gene.

2- Attenuated familial adenomatous polyposis (AFAP): Fewer polyps, and later onset of cancer than FAP. The difference is due to extreme 5' mutations in APC gene.

3- Hereditary nonpolyposis colon cancer (HNPCC) or Lynch syndrome: develops without the polyps, 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).

#### Clinics and pathology

##### Disease

Adenocarcinoma

##### Etiology

75% colorectal cancers occur sporadically. 25% are associated with family history. 5-6% through genetic mutations. 85% arise from chromosomal instability, 15% due to microsatellite instability. Most arise from adenomatous polyps.

History with ulcerative colitis, breast, uterine and ovarian cancers. Personal or familial history of colon cancer increases the risk (23% of all colorectal cancers).

High fat diet, obesity, smoking may also increase the risk.

##### Epidemiology

Colorectal cancer is the third most frequent cancer in the world in both sexes and the third most frequent cause of cancer related deaths.

Until age 50, men and women are susceptible at same levels, but after 50 years of age, men are more susceptible.

##### Clinics

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

##### Pathology

Dukes's staging system, modified by Astler-Coller. Detection through colonoscopy, flexible sigmoidoscopy, barium enema, chest x-ray, faecal occult blood testing (FOBT).

##### Treatment

Surgery is the most common method.

- For colon cancer, the tumour together with a small portion of the surrounding tissue is removed with the adjacent lymph nodes.

- For rectal cancer, rectum is totally removed and replaced with colostomies.

After surgery, micrometastasis can be experienced, which requires chemotherapy to destroy the metastatic cells (adjuvant chemotherapy). 5FU is the most frequently used drug. Radiotherapy may be used for rectal cancer, but it is not useful in colon cancer.

##### 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. Metastasis

resulting from penetration of the tumor through the bowel wall of the colon is very common with lymph node involvement. Patients with early colon cancer can survive with surgery (more than 80%). For patients with metastasis, 5 year survival rate is less than 10%.

Genetic alterations have been studied in relation to prognosis with contradictory results. Loss of heterozygosity (LOH) of chromosomes 18q and 17p and overexpression and mutation of the p53 gene result in poorer prognosis in primary cancer patients.

## Cytogenetics

### *Cytogenetics morphological*

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

- Aneuploid tumours showing numerous allelic losses;
- Aneuploidy, loss and rearrangements of chromosome 1p (about 70%), 5q (55%, loss of APC), 15q, 18q (65%, loss of DCC), 17p (80%, TP53), and 17q (30%); and abnormalities in 7q(25%) and 8p (55%). Reciprocal translocation t(5;10)(q22;q25), inv(5)(q22-q31.3).

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. A model for the genetic basis of colorectal tumourigenesis is proposed.

### **APC**

**Location:** 5q21-22

#### **DNA/RNA**

16 exons, 10702 bp mRNA.

#### **Protein**

Tumour suppressor protein composed of 2843 amino acids; the APC interacts with the adherens junction proteins a and beta-catenin suggesting involvement in cell adhesion. APC may also inhibit the pathway regulated by the beta-catenin /Tcf complex. Other functions include anterior-posterior pattern formation, axis specification, cell cycle, cell migration, apoptosis, chromosome segregation and spindle assembly.

#### **Germinal mutations**

Point mutations in APC gene results in the generation of stop codons, small deletions, LOH, 1-2 bp insertions. Most mutations result in a truncated protein, mostly in the first half. Results in FAP and AFAP.

#### **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. APC loss may also be due to interstitial deletion or mitotic recombination, LOH, and nonsense mutations. Most of the somatic mutations are clustered in the exon 15 in mutation cluster region (MCR). about 20% of APC mutations are observed with mutation of TP53. Methylation of the promoter may be related.

### **P53**

**Location:** 17p13

#### **DNA/RNA**

11 exons.

#### **Protein**

Tumour suppressor has essential role in cell cycle regulation, in G1 DNA damage checkpoint. 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 regulating the transcription of genes whose products inhibit cell growth and proliferation and induce apoptosis. It is also called the 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. Mutant form of p53 is found to be overexpressed in primary colon cancer. p53 mutation is observed in 40-50% of colorectal carcinomas, and is associated with aggressive carcinomas. p53 mutation or LOH of chromosome 17p is observed mostly in carcinoma rather than adenoma, in both familial and non-familial patients.

80% of mutations result from deamination of methylated cytosine in CpG region of the gene (codons 175, 248 and 273).

### **MLH1**

**Location:** 3p21.3

#### **DNA/RNA**

19 exons, 2524 bp mRNA.

#### **Protein**

Human homolog of E. coli DNA mismatch repair gene MutL. Defects observed in 30% of HNPCC.

#### **Germinal mutations**

Results in HNPCC. Deletion of codons 578 to 632 (they constitute a single exon), deletion and frameshifts, nonsense mutations, insertions, truncated protein. Both of the genes should be impaired for phenotype to occur. Mutations give rise to microsatellite instability.

**Somatic mutations**

Methylation of the promoter, mostly responsible for HNPCC.

***MSH2***

**Location:** 2p22-p21

**DNA/RNA**

16 exons.

**Protein**

Human homolog of E. coli MutS protein, functional in mismatch repair, defects observed in about 60% of HNPCC.

**Germinal mutations**

Truncated protein, nonsense mutation, results in HNPCC.

***MSH6***

**Location:** 2p16

**DNA/RNA**

10 exons.

**Protein**

Functions in mismatch binding.

**Germinal mutations**

Deletion (of CT at nucleotide 3052 in exon 4), frameshift mutations, truncated protein.

***PMS2***

**Location:** 7p22.2

**DNA/RNA**

15 exons.

**Protein**

Functional in mismatch repair.

**Germinal mutations**

In frame deletion, out of frame deletion, point mutation. The mutations give rise to microsatellite instability.

***AXIN2***

**Location:** 17q23-q24

**DNA/RNA**

10 exons, 4259 bp mRNA.

**Protein**

The protein has role in regulation of beta-catenin pathway.

**Somatic mutations**

Axin2 is mutated in MMR deficient CRC cells. The mutations result in the stabilization of beta catenin and activation of the T-cell factor signaling. Also epigenetic silencing is associated with CRC.

***STK11***

**Location:** 19p13.3

**DNA/RNA**

10 exons, 3276 bp mRNA.

**Protein**

Tumor suppressor serine-threonine kinase, functions in cell cycle arrest. Mutations result in Peutz-Jeghers syndrome.

**Germinal mutations**

Nonsense, missense, frameshift mutations.

**Somatic mutations**

Mutations give rise to Peutz-Jeghers syndrome, which results in polyps in gastrointestinal tract.

***PTEN***

**Location:** 10q23.3

**DNA/RNA**

9 exons, 3417bp mRNA.

**Protein**

Tumor suppressor protein, which negatively regulates AKT/PKB signaling. Also known as 'mutated in multiple advanced cancers' since mutations are found in many cancers. The protein is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase, removing phosphates from serine, tyrosine and threonine.

**Germinal mutations**

Results in Cowden Syndrome, a cancer prone syndrome and Bannayan-Riley-Ruvalcaba Syndrome.

**Somatic mutations**

Somatic mutations of PTEN are a result of MLH1-MSH2 deficiency in HNPCC patients. Frameshift mutations in MMR deficient cells. Nonsense, missense, and splice-site mutations.

***BMPR1A***

**Location:** 10q22.3

**DNA/RNA**

13 exons, 3616bp mRNA.

**Protein**

Transmembrane serine-threonine kinase, type1 receptor.

**Germinal mutations**

Nonsense, missense, frameshift and splice-site mutations.

***SMAD4***

**Location:** 18q21.1

**DNA/RNA**

13 exons, 3202 bp mRNA.

**Protein**

Protein is coded from 11 exons. A tumor suppressor, functioning in TGFbeta signaling, mediating signals from cell surface to nucleus.

**Germinal mutations**

Result in juvenile polyps.

**Somatic mutations**

Deletion of SMAD4 results in epithelial cancers. Minimally lost region on chromosome 18q21, containing the SMAD4 gene is found in colorectal cancers. 4-basepair deletion in exon 9 of SMAD4 is found in colon cancers, resulting in a new stop codon.

**MYH**

**Location:** 1p34.1

**DNA/RNA**

16 exons, 1839 bp mRNA.

**Protein**

DNA glycosylase. Functions in oxidative DNA damage repair (base excision repair), nicks A-G mismatches, as well as A-8oxoG and A-C mismatches.

**Germinal mutations**

Tyr82-Cys and Gly253 -Asp transitions affect glycosylase activity, resulting in APC mutations in somatic cells. Nonsense mutations, missense and truncated protein mutations. Mutations cause 93-fold increase in colorectal cancer risk.

**DCC**

**Location:** 18q21.3

**DNA/RNA**

29 exons, 4609 bp mRNA.

**Protein**

DCC is thought to be receptor for neptin-1 (axonal chemoattractant). In absence of ligand, it induces apoptosis but when neptin-1 is bound, it prevents apoptosis.

**Germinal mutations**

Chromosome 18 sequences are frequently (74%) lost in colorectal carcinoma. Loss of DCC is mostly observed in metastatic cancers.

**KRAS2 (or Ki-ras)**

**Location:** 12p12.1

**DNA/RNA**

3 exons.

**Protein**

Ki-ras belongs to the ras gene family containing also Ha-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.

Homozygous deletion of 5' end, point mutation in one of the introns (for example intron 13), probably interfering with splicing, DNA insertions.

**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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