Colonic polyps and colon cancer

Andrew Macpherson
Director of Gastroentology
University of Bern
Importance of the problem of colon cancers - Epidemiology

- Lifetime risk 5%
- Incidence/10^5/annum (US Detroit black 35, Canada 26.9, Geneva 25.2, India, Bombay 3.7)
- Familial risk (≥2 first or second degree relative) 20%
- Mendelian inheritance 4%
Learning goals

1. The polyp cancer sequence in the colon
2. Discovery of oncogenes and oncosuppressor genes in polyp cancer sequence. Knudson hypothesis.
3. Role of DNA repair genes in polyp cancer sequence
4. Different pathways leading to colon cancer
Colon polyps can develop into colon cancer if left to grow for long enough.
Colonic polyps

Colonoscopy image

Histology

Normal

Adenoma
Colon cancer

Colonoscopy image

Histology
Two lines of evidence for the polyp → carcinoma sequence

- Histopathology

- Clinical observations on the long term effects of removing polyps at colonoscopy
Evidence for the polyp carcinoma sequence – Histopathology

1. Many carcinomas have adenomas at their edge

2. Presence of histological malignant change within polyps
   Presence of cancer/dysplasia within polyps especially when >1cm diameter (see earlier slide)
Evidence for the polyp carcinoma sequence – Clinical consequences of polyp removal


2. Patients with polyps >10mm not removed have increased risk of cancer (Stryker, S.J et al., 1987, Gastroenterology 93 1009).
Learning goals

1. The polyp cancer sequence in the colon
2. Discovery of oncogenes and oncosuppressor genes in polyp cancer sequence. Knudson hypothesis.
3. Role of DNA repair genes in polyp cancer sequence
4. Different pathways leading to colon cancer
Genetic players in colon cancer

- Oncogenes
- Oncosuppressor genes
  Stimulation of cell birth or inhibition of cell death or cell cycle arrest

- Stability genes
  Keep genetic alterations to a minimum
Oncosuppressor genes

Special case of familial adenomatous polyposis

This is an inherited condition, where there are 1000s of polyps in the colon. Ca colon always eventually develops unless the whole colon is removed surgically.
Intestinal epithelial cell

Epithelial cells continuously renew from stem cells. Migrate upwards and are shed after 4-5 days.
Two hit ‘Knudson’ hypothesis for oncosuppressor genes

Rare families have autosomal dominant familial adenomatous polyposis (FAP) where the colon is carpeted with polyps

Most patients just have one or two polyps in the colon

How can this be explained genetically?
Two hit ‘Knudson’ hypothesis

For a ‘sporadic’ tumour you need two successive mutations in one of the colonic stem cells - unlikely, but there are many stem cells.

- Normal allele oncosuppressor gene
- Two normal alleles
- NO TUMOUR

- Somatic mutation 1
- One normal allele
- STILL NO TUMOUR

- Somatic mutant allele oncosuppressor gene
- Somatic mutation 2
- Two mutant alleles
- ONCOSUPPRESSOR DOES NOT WORK
- TUMOUR FORMATION
For a tumour with an inherited mutation, every cell in the body carries a mutant allele and you need ONE further mutation in a colonic stem cell.

- Likely that lots of tumours will form given so many stem cells
Gene for familial adenomatous polyposis

Initially mapped to long arm of chromosome 5 through restriction fragment length polymorphism linkage

Later cloned and sequenced: also called adenomatous polyposis coli (APC)

Over 800 different mutations for FAP described with different clinical phenotypes
The FAP (APC) mutation works by initiating degradation of beta-catenin – part of the WNT pathway
Cellular signalling pathways
Other mutations accumulate in the carcinoma sequence

Vogelstein, B & Kinsler, K Trends in Genetics 9, 138
Cellular signalling pathways

- Survival Factors (e.g., IGF1)
- Chemokines, Hormones, Transmitters (e.g., interleukins, serotonin, etc.)
- Growth Factors (e.g., TGFβ, EGF)
- Extracellular Matrix
  - G-Protein
  - Integrins
  - Fyn/Shc
  - FAK
  - Src

- RTK
- PLC
- PI3K
- Akt
- PKC
- Adenylate cyclase
- Ras
- Raf
- MEK
- MAPK
- MKK
- Dishevelled
- GSK-3β
- APC

- Cytokines (e.g., EPC)
- JAKs
- STAT3,5
- Bcl-xL
- Cytochrome C
- Caspase 9
- Caspase 8
- FADD
- Bcl-2
- Bad
- Abnormality Sensor
- Bim
- Death factors

- Apoptosis
- Gene Regulation
  - Myc: Mad: Max: Max
  - ERK: Fos: Jun
  - β-catenin: TCF
  - CyclD
  - CDK4
  - p16
  - E2F
  - p15
  - CyclE
  - p27
  - CDK2
  - p21

- Cell Proliferation
  - ARF
  - Mt
  - Bax
  - p53

- Wnt
- Hedgehog
- Notch
- patched
- Smo

- hedgehog
Learning goals

1. The polyp cancer sequence in the colon
2. Discovery of oncogenes and oncosuppressor genes in polyp cancer sequence. Knudson hypothesis.
3. Role of DNA repair genes in polyp cancer sequence
4. Different pathways leading to colon cancer
Another cause of multiple polyps (which can be confused with FAP clinically) is MAP (MutYH adenomatous polyposis).

MAP requires two germline mutated alleles and is recessive.

Polyposes through MTH1 or OGG1 mutations are described but rare.

Sheila S. David, Valerie L. O'Shea & Sucharita Kundu
Nature 2007 447, 941-950
Cellular signalling pathways

MutYH failed DNA repair
Hereditary non-polyposis colon cancer = cancers which occur without a ‘carpet’ of polyps
Lynch syndrome (hereditary non-polyposis colon cancer)

• R sided colon cancer associated with endometrial, bile duct, ovarian or pancreatic cancer
• 90% MSH2, MLH1, 7% MSH6, <5% PMS2
• 90% of those with known mutation will develop colon cancer
• Accelerated progression of polyps to cancer
Henry Lynch assembled large pedigrees of tumour patients.
Modified Bethesda guidelines 2004

• Colorectal Ca <50 years
• Synchronous, metachronous colorectal or HNPCC tumours regardless of age
• MSI-H histology in colon Ca <60 years
• Colorectal Ca in one of more 1° relatives (one Ca <50 years)
• Colorectal Ca in two of more 1° or 2° relatives regardless of age

80-90% sensitivity, 20% specificity for HNPCC
Good for genetic studies: poor for individual diagnosis
DNA error repair mechanisms

MutL related proteins

MutS related proteins

Microsatellite instability a hallmark of defective repair

PCR amplification of DNA sequence repeats (microsatellites)

- >30% markers unstable = MSI-H
- <30% markers unstable = MSI-L
- 0 markers unstable = MSI negative
Immunohistochemistry

Methylguanine methyltransferase

MLH1

80% sensitivity, 85% specificity for HNPCC
Can be followed up by sequencing
Learning goals

1. The polyp cancer sequence in the colon
2. Discovery of oncogenes and oncosuppressor genes in polyp cancer sequence. Knudson hypothesis.
3. Role of DNA repair genes in polyp cancer sequence
4. Different pathways leading to colon cancer
Modifier genes in colon cancer

Examples of Genes with Coding Microsatellites
- TGFβ1RII 90%
- RIZ 37%
- TCF4 35%
- BAX 33%
- IGFIIR 27%

Mismatch-Repair Genes
- MLH1
- MSH2
- MSH6

Normal epithelium
- Early adenoma
- Intermediate adenoma
- Late adenoma
- Carcinoma
- Metastasis

APC
- K-ras
- DCC
- Smad4
- p53
- Other

MSH6
- MSH3
- MSH2

Mismatch-Repair Genes with Coding Microsatellites
Heterogeneous colon cancer pathways

- Lynch syndrome
- Serrated polyps: ‘sporadic MSI-H’
- Serrated polyps: raf mutation
- Adenomas: methyl guanine methyltransferase methylation, ras mutation
- FAP, MUTYH or sporadic Vogelstein-Kudson polyp cancer pathway
# Alternatives for screening asymptomatic patients with ‘normal’ CRC risk

<table>
<thead>
<tr>
<th>Test</th>
<th>Utility</th>
<th>‘Recommendations’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood test (e.g. Sept9)</td>
<td>Avoids stool based tests and invasive procedures</td>
<td>Limited role in current screening protocols, the place of the test remains to be defined.</td>
</tr>
<tr>
<td></td>
<td>Sensitivity for polyps and early cancers is very low (20-50%)</td>
<td></td>
</tr>
<tr>
<td>High-Sensitivity Fecal Occult Blood Test (FOBT) or Stool Test; or Fecal Immunochemical Test (FIT)</td>
<td>Need to obtain 3 successive stool specimens and take special diet and altered drug regime for 1 week beforehand Sensitivity 70-80% specificity 85-95%</td>
<td>Every year, with colonoscopy when positive (large studies show a consistent CRC mortality reduction of 15-40%).</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy</td>
<td>Effective for only lower third of colon: outside Switzerland nurses allowed to do the examination.</td>
<td>Every five years recommended ± FOB every 3 years (mortality reduction up to 50%).</td>
</tr>
<tr>
<td>Colonoscopy or CT colonography</td>
<td>(Almost) complete examination invasive potential complications. Miss rate for polyps 5-10%</td>
<td>Every 10 years (mortality reduction 20-90% depending on protocol used).</td>
</tr>
</tbody>
</table>
When genetics are unknown an alternative is to screen patients with colonoscopy.
Learning goals

1. The polyp cancer sequence in the colon
2. Discovery of oncogenes and oncosuppressor genes in polyp cancer sequence. Knudson hypothesis.
3. Role of DNA repair genes in polyp cancer sequence
4. Different pathways leading to colon cancer