Cell Signaling in Colorectal Cancer

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Topics

- Concepts of carcinogenesis
- Signaling pathways
- Growth factors
- Summary

Colorectal Cancer

- Second leading cause of cancer death
- 147,000 cases per year
- 50,000 deaths per year
- Medical treatment not curative

Concepts of Carcinogenesis

Bert Vogelstein

“Cancer is, in essence, a genetic disease”
Carcinogenesis

- No single gene mutation
- Series of mutated genes
- Solid tumors- 3 to 8 genes
- Tumor suppressor, oncogene, caretaker

Adenoma-Carcinoma Sequence

Normal

Normal Aberrant crypt foci

Normal Aberrant crypt foci Small adenoma

Normal Aberrant crypt foci Small adenoma Large adenoma
Chromosomal Instability (CIN)

Tumor Suppressor Genes
- Gene activity decreased by mutation
- Biallelic mutations necessary
- Defective brakes in auto
- APC, TP53

Oncogenes
- Gene activated by mutation
- Monoallelic mutation-growth advantage
- Stuck gas pedal in auto
- K-RAS gene

Caretaker Genes
- Repairs mistakes- mutation more mistakes
- Inept auto mechanic
- Mismatch repair genes

Analysis of Cancers
- Analyzed 20,000 genes in tumors
- Somatic mutation, amplification, deletion
- Validates findings in second set
Gene Mutations in Tumors

- Gene mountains
  - few frequently mutated genes - 20
  - driver gene mutations - causative

- Gene hills
  - many infrequently mutated genes - 60
  - passenger gene mutations - go for ride
Many Gene Alterations

CIN

MSI

CIMP

Carcinogenesis

Several Signaling Pathways

Cancer

Cancer
CANCER

Wnt Signaling
KRAS Signaling
TGF-β Signaling
G1/S phase Signaling
Hedgehog Signaling
Apoptosis

APC Gene and Wnt Signaling

APC Gene

• 1986- Herrera- pt with retardation & polyposis- deletion chromosome 5
• Linkage in FAP families at 5q21
• 1991 isolation of APC (Adenomatous Polyposis Coli) gene
APC Gene Functions

- Tumor suppressor
- Gatekeeper gene
- Cell adhesion
- Signal transduction
- Transcriptional activation
- Apoptosis

Clinical Correlations of APC Gene Mutations

- Somatic mutations- sporadic CRC
- Germline mutations
  - Familial adenomatous polyposis (FAP)
  - Attenuated FAP

APC, B-Catenin, Wnt Signaling

- B-Catenin usually in cytoplasm, degraded by phosphorylation
- APC, axin complex facilitates degradation
- Not degraded, goes to nucleus stimulates transcription including oncogenes (c-myc, cyclin d)

APC, B-Catenin, Wnt Signaling

- Activation of WNT pathway though protein disheveled interrupts APC, Axin, B-Catenin pathway
- Mutations in APC or B-catenin prevent phosphorylation and B-catenin activation
Wnt Signaling Activation
TGF-B Signaling Pathway

- Important in stem cell development
- Nearly all colon cancers have mutations inactivating components of pathway
- Tumor caused by loss of inhibitor effect
- Implicated in tumor invasion
TP53

- Tumor suppressor gene
- Transition for late adenoma to cancer
- Most common allelic loss in CRC
- Anticancer effects-G1 cell cycle arrest, apoptosis
Growth Factors

Epidermal Growth Factor Receptor

- HER family of receptors
- Cell surface receptor
- Activated by ligand binding
- Receptor stimulates tyrosine kinase
  - Cell proliferation, angiogenesis, antiapoptotic
- Expressed in 60 – 80% of CRC
**VEGF and Colorectal Cancer**
- VEGF associated with initiation and maintenance of angiogenesis
- Expressed from premalignant adenoma to metastatic cancer
- VEGF associated with poor outcomes, mets and patient survival

**Angiogenic Switch**
- Off

**Angiogenic Switch**
- Off
  - VEGF
  - IL-8
  - Angiostatin
  - Interferon

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Summary
Normal

\[ \text{Adenoma} \rightarrow \text{Cancer} \]

\[ \text{APC} \quad \text{K-RAS} \]

\[ \text{DCC, Smad} \quad \text{TP53} \]

\[ \text{Wnt-APC-B-catenin} \]

\[ \text{B-catenin} \]

\[ \text{TGFB} \]

\[ \text{Smad} \]

\[ \text{TP53} \]
Case 1
Case 1

- 49 yo health white male
- 8 months of rectal bleeding
- PCP referred for colonoscopy

Question 1

All of the following are in the differential diagnosis of this family except?

A. HNPCC
B. Familial adenomatous polyposis
C. Attenuated FAP
D. MYH associated polyposis
Question 1
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A. HNPCC
B. Familial adenomatous polyposis
C. Attenuated FAP
D. MYH Associated Polyposis

Question 2
Which genetic testing would you order?
A. MSI and IHC on rectal cancer
B. MSH2 and MLH1 gene testing
C. APC gene testing
D. MYH gene testing
E. APC and MYH gene testing
Question 3

- Based on the patient’s gene test results, what assumptions can be made about the risk status of the patient’s first degree relatives?
Case 2

- 37 yo pt for gene testing for FAP
- Hematochezia age 12
- Multiple polyps -report adenoma/hyper
- 22 yo- colectomy ileorectal anastomosis
- 35 yo- polyps in gastric antrum
  - Bxs report acute and chronic inflammation
- 36 yo- rectal polyps- acute/chronic inflam.

Question 1

What additional information do you need before proceeding with genetic testing?

Answer: Histology of polyps

Question 2

The diagnosis in this family is?

a. Hereditary nonpolyposis colorectal ca
b. Familial adenomatous polyposis
c. MYH associated polyposis
d. Juvenile polyposis
e. Peutz-Jeghers syndrome
Question 2

The diagnosis in this family is?

a. Hereditary nonpolyposis colorectal ca
b. Familial adenomatous polyposis
c. MYH associated polyposis
d. Juvenile polyposis
e. Peutz-Jeghers syndrome

Question 3

What gene test would you select?

a. MSH2 and MLH1
b. APC and MYH
c. HFE gene test
d. STK 11 gene test
e. SMAD4 and BMPR1A

Question 4

The patient is at highest risk for what cancer?

a. Colorectal
b. Gastric
c. Small bowel
d. Pancreatic

Cancers

<table>
<thead>
<tr>
<th>Cancer</th>
<th>No.</th>
<th>Frequency (974)</th>
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<tbody>
<tr>
<td>Colon</td>
<td>115</td>
<td>12%</td>
</tr>
<tr>
<td>Gastric</td>
<td>11</td>
<td>1%</td>
</tr>
<tr>
<td>SB</td>
<td>12</td>
<td>1%</td>
</tr>
<tr>
<td>Panc.</td>
<td>4</td>
<td>0.4%</td>
</tr>
</tbody>
</table>
Colon Cancer Risk -PY Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative Risk</th>
<th>CL</th>
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<tbody>
<tr>
<td>Males</td>
<td>36.3</td>
<td>13.0-77</td>
</tr>
<tr>
<td>Females</td>
<td>30.1</td>
<td>3.5-103</td>
</tr>
<tr>
<td>Combined</td>
<td>34.5</td>
<td>15.0-492</td>
</tr>
</tbody>
</table>

Absolute Risk

- Absolute risk CRC- 39.4% at 80 yrs
- Mean age of diagnosis 44 yo +10
- No other GI tumors noted in cohort
- Metachronous cancer in rectum

Case 3

Question 1

Which of the following is not in the differential diagnosis of this family?

A. HNPCC  
B. Muir Torre syndrome  
C. Attenuated FAP  
D. Familial syndrome- unknown type
Question 1
Which of the following is not in the differential diagnosis of this family?

A. HNPCC
B. Muir Torre syndrome
C. Attenuated FAP
D. Familial syndrome- unknown type

Question 2
What genetic testing would you do?

A. MSI and IHC in the sebaceous adenoma
B. MLH1 and MSH2 gene testing
C. APC gene testing
D. MYH gene testing
E. None
Question 2

What genetic testing would you do?

A. MSI and IHC in the sebaceous adenoma
B. MLH1 and MSH2 gene testing
C. APC gene testing
D. MYH gene testing
E. None
1. What is differential dx?
HNPCC
Muir-Torre

2. What genetic testing?
MSH2, MLH1

3. What screen recommend?
colon, derm, Hx, pe, labs
CASE 5

1. Differential Diagnosis?
   • HNPCC
   • AFAP
   • MYH
   • I1307K

2. Genetic Testing?
   • MSI/ IHC
   • APC
   • MYH
1. Differential Diagnosis?
   - HNPCC
   - AFAP
   - MYH
   - I1307K

2. Genetic Testing?
   - MSI/ IHC
   - APC
   - MYH

CASE 4
Family 10

1. Differential diagnosis?
   AFAP, MYH, 11307K

2. Recommended treatment?
   Colectomy

3. Recommended screening?
   APC, MYH gene testing

CASE 1a
1. What is differential dx?
Oligopolyposis

2. What genetic tests?
APC and MYH

1. What is differential dx?
Oligopolyposis

2. What genetic tests?
APC and MYH
COLORECTAL CANCER

Sporadic

Hereditary
Cetuximab

- Monoclonal antibody
- Binds to EGFR
- Blocks ligand binding
- Prevents receptor dimerization and induced phosphorylation
- Antiapoptotic or antiangiogenic

Sporadic Colorectal Cancer

- APC mutations in most sporadic CRC
- Occur early in tumorigenesis
  - crypts, small, large adenomas, cancer
- Most truncation mutations
- Inactivation of both alleles common

Mouse Model

- Min mouse model
- C57BL/6J mouse with ethylnitrosurea
- Nonsense mutation codon 850 mAPC
- 30-50 intestinal tumors at 90 days

DCC/MADH2/MADH4

- TGF-B pathway
Question 3
Who would you test first?
A. The patient
B. The patient’s father
C. The patient’s mother
D. The patient’s daughter

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Colorectal Cancer

- Point mutations  76
- Amplifications  4
- Deletions  3

total  83