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HST.161 Molecular Biology and Genetics in Modern Medicine  
Fall 2007

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## Lecture 19

## Colon Cancer

[This lecture begins with slide 28.]

Retinoblastoma is a good case to start with, since there is only one RB1 gene (on chromosome 13).

- Mapping RB1 – esterase D polymorphism was close to RB1, so they mapped together
- RB1 spans 27 exons, with more than 100 known mutations
- Encodes Rb protein (pRb), which is involved in cell cycle regulation; interacts with E2F family which interacts with cyclins and cdk's, ultimately controlling the cell cycle
- Common genetic lesion in sporadic retinoblastomas
- Loss of RB1 activity is not the only genetic change in retinoblastoma – numerous other chromosomal abnormalities are present
- Some mutations in the gene cause retinoblastoma with low penetrance

### Wilms Tumor

- childhood kidney cancer arising from embryonic cells
- affects 1/10,000
- heritable (~5-7%) and nonheritable (>90%) forms
- multiple genes involved
- true familial tumors rarely observed (~1%)
- 5% also have bilateral aniridia
  - o when aniridia and Wilms tumor occur together, they're commonly accompanied by mental retardation and genitourinary abnormalities
  - o WAGR deletion syndrome: Wilms, Aniridia, Genitourinary defects, Retardation; deletion in chromosome 11p13
  - o WT1 gene on 11p13; tumor suppressor gene; point mutations and deletions result in Wilms tumor or genitourinary defects. Mutations observed in <10% of Wilms cases.

### Denys-Drash syndrome

- all new mutations; rare syndrome
- glomerular neuropathy
- severe urogenital malformations
- multiple Wilms tumors and gonadoblastoma
- dominant negative mutations in WT1

### Li-Fraumeni Syndrome

- current definition is complex
- typically describes someone with sarcoma, breast, brain or adrenocorticoid tumors before age 36, with at least one first or second degree relative with a similar tumor spectrum with early onset
- typically mutations in p53

Hepatitis B: people with chronic HepB are at increased risk for hepatocellular carcinoma

Melanoma: Risk Factors:

- Caucasian
- Exposure to UV radiation
- Presence of multiple or dysplastic nevi\*
- Family history of “ “
- Freckling and/or history of nonmelanoma skin cancer
- Rare hereditary syndromes: albinism, Li-Fraumeni, xeroderma pigmentosa

\* dysplastic nevi: discolored skin patches:

- flat throughout or with a flat component
- diameter > 5 mm
- asymmetric shape
- indistinct borders
- variable pigmentation

Familial Melanoma:

- 2 or more 1st-degree relatives with invasive melanoma
- In high-sun areas (where melanoma is more common), consider only families with 3 or more cases

p16 and pRB function in the same biological pathway

- p16 inhibits the complex that phosphorylates a retinoblastoma protein, which would otherwise then pass the G1 cell cycle checkpoint
- pRB acts later in the chain, upon the oncogene complex

MEN 2A mutations occur at cysteine residues to cause medullary thyroid carcinoma (MTC), especially in hereditary MTC

### ***Colorectal Cancer***

Guest Lecture

Some lessons we've learned from hereditary colon cancer have been very important in understanding cancer and hereditary cancers in general.

Polyp to Cancer Sequence:

- aberrant crypt focus – one tiny abnormality begins developing into a more discrete form, the tubular adenoma
- need to acquire a certain number of hits in tumor suppressor and DNA repair genes in order to allow the progression to continue

Colon Cancer Genetics

- as many as 90 mutated genes per tumor
- ~11 are essential for the cancer to develop
- The *order* in which mutations occur is key

- 3 main classes of genes involved: 1) tumor suppressor genes, 2) oncogenes, 3) DNA repair genes

FAP: familial adenoma polyposis: mucosa of the colon is carpeted with benign polyps; occurs relatively early in life. Untreated, it will progress to colon cancer (100% rate, in untreated patients; at least one of those polyps will develop all the necessary mutations to develop into cancer).

- only the rate of polyp formation is accelerated in FAP, **not** the rate of transformation from polyp to cancer.

APC tumor suppressor gene

- regulates Wnt signaling pathway
- controls apoptosis
- chromosomal segregation; cells with aberrant APC genes exhibit chromosomal instability, tetraploidy and aneuploidy
- somatic mutations are identified in over 70% of all colon polyps/cancers

Wnt signaling pathway

- Wnt signal binds to FRZ receptor
- Complex formed out of Axin, Beta-cat, APC, and GSK-3Beta. APC regulates Beta-cat levels; mutant APC causes the complex to not form correctly; excess B-cat accumulates and migrates to nucleus, and activates complexes there that shouldn't always be activated

10-20% have B-cat mutations

Germline mutations cause mutations in every cell of the body, but you don't develop tumors out of every cell in the body. You need a second, somatic mutation in some cells to cause tumors to grow.

Having a mutation at the far 5' end of the APC gene causes a less severe phenotype due to the rest of the gene remaining intact and inframe, and somehow this "mostly complete" version of the gene and protein allows for a less severe, later-onset series of polyps (which do develop into cancer).

Ras Gene Family

- 3 members: H-Ras, K-Ras, N-Ras
- Each encodes a 21 kD protein, p21
- K-Ras most important
- Mutations cause GTPase to be always on, constantly activating a signaling pathway

COX genes

p53: induced by cellular stress to regulate apoptosis (present in ~50% colon cancers)

Finally: chromosome 18q allelic deletions (present in ~70% of CRC)

These mutations should happen in this order; the order matters:

1) APC/B-cat; 2) COX2; 3) K-Ras; 4) p53; 5) 18q LOH

(This is true in about 85% of cancers.)

Why does order matter?

- avoid cellular repair mechanisms
- Mouse models that try the mutations out of order don't tend to develop cancer.

This process, which takes the condition from "normal" to "carcinoma," takes 7-10 years.

MYH normal function:

- oxidized guanine pairs better with A than with C; normal MYH recognizes the oxidation and repairs it
- mutated MYH can't do this
- classically autosomal recessive inheritance pattern with respect to causing CRC
- APC gene is particularly susceptible to these kinds of oxidized-G mutations...
  - o Why APC is so easily mutated is still an open question.

MYH polyp syndrome

- 15-100 colonic adenomas
- Average age of onset/diagnosis: 50 years
- Clinically resembles AFAP w/o family history
- Cancer risk for homozygotes is 100%; risk for heterozygotes is close to general population

Hereditary Nonpolyposis colorectal cancer (HNPCC) syndrome

- autosomal dominant
- CRC: early age of onset; multiple primary tumors; right-sided predominance
- Few adenomas; rapid progression from polyps to cancer
- 5 genes associated, all are DNA mismatch repair genes