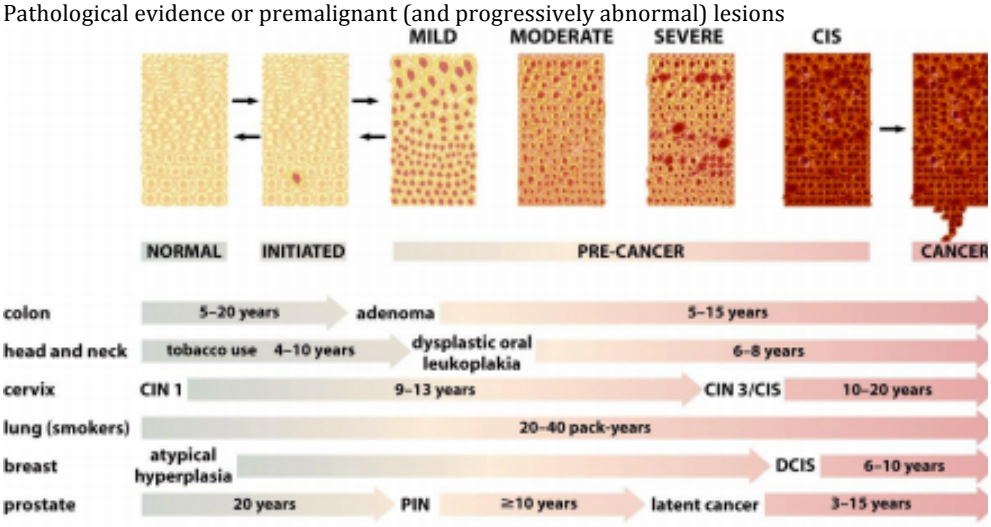
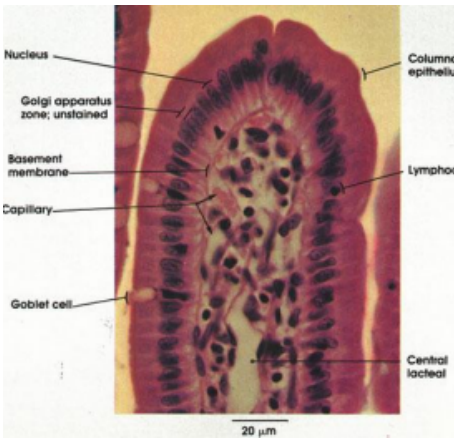
LECTURE 14
CANCER: LECTURE 2

Molecular carcinogens
Development of Cancer

- Cancer is a multi-step process that results from the accumulation of genetic and epigenetic alterations
- Evidence of a multi-step development of cancers
  - Pathological evidence of premalignant (and progressively abnormal) lesions
  - Characterization of the genetic and epigenetic alterations leading to formation of specific cancers
- Foulds, L. The natural history of cancer. J. Chronic Dis. 8, 2–37 (1958):
  - Cancer is a "dynamic process advancing through stages that are qualitatively different", progressing from precancerous stages to increasingly invasive and metastatic stages.

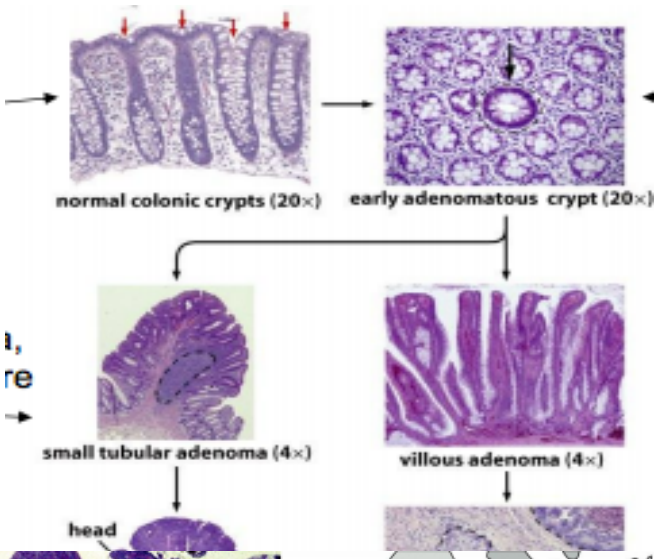
Pathological evidence or premalignant (and progressively abnormal) lesions





Colorectal Cancer

- Intestinal epithelium organised into villi
- Each villus composed of an outer layer of epithelial cells separated from a core of mesenchymal cells by a basement membrane
- Epithelial cells: constantly replaced
- Basement membrane: secreted by epithelial and stromal cells
- Mesenchymal cells: fibroblasts, endothelial cells, immune cells
- Smooth muscle layer: underlies stromal cells

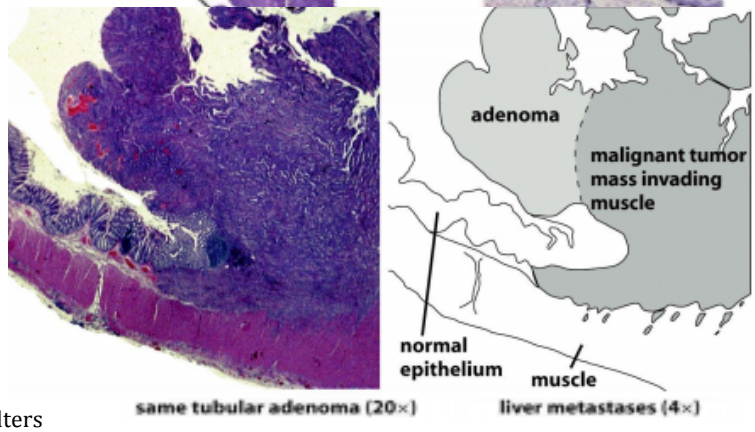


Histopathological Evidence of Multistep Carcinogenesis

1. Normal colon; longitudinal section]
2. Normal crypts in cross section, small adenomatous crypt
3. Small tubular adenoma, disrupts normal architecture of crypt Violous adenoma
4. Larger tubular adenoma, pedunculated (attached to colon via stalk)
5. Locally invasive carcinoma surrounded by stroma
6. Liver metastasis

Histopathological Evidence

- Evidence is fragmented
- Occasionally see evidence of a carcinoma growing out of an adenoma
- Clinical evidence: (population) incidence of colorectal cancer is decreased if colon polyps are removed



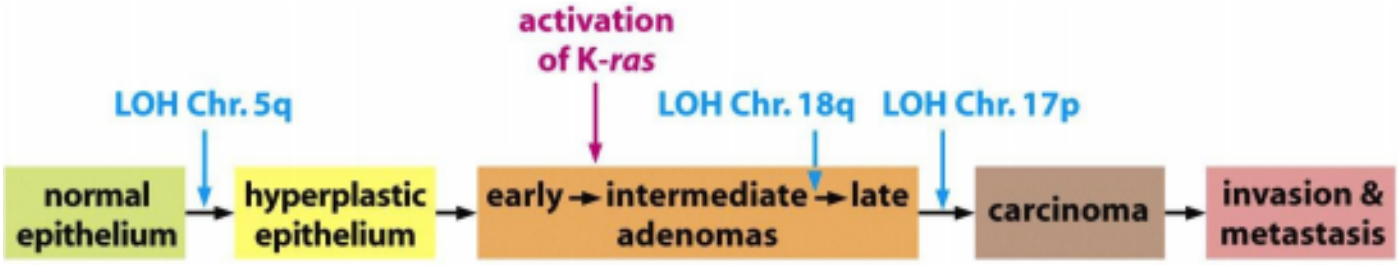
Characterization of the genetic and epigenetic alterations leading to formation of specific cancers

- Genetic alteration: involves changes in the DNA sequence
- Epigenetic alteration: changes in the behavior of a cell or the activity state of its chromatin that do not depend on alterations of DNA sequence (eg. methylation of DNA alters gene expression)

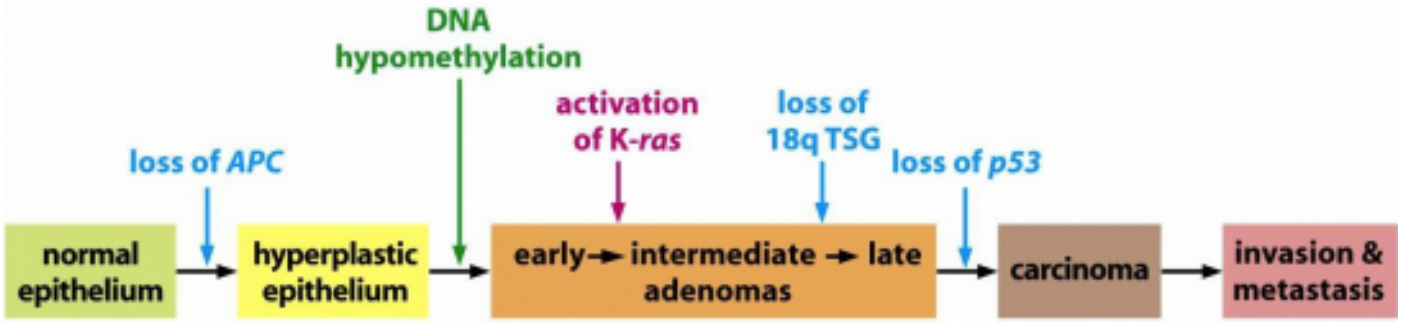
Characterization of genetic alterations leading to the formation of colorectal cancer

- Early studies of chromosomal abnormalities in cancers had identified losses of chromosomal regions (eg. short (p) or long (q) chromosome arms) that were characteristic of specific cancer types
- Mutated oncogenes (eg. K-RAS) also identified

- Occurrence of these genetic changes could be matched to pathological lesions



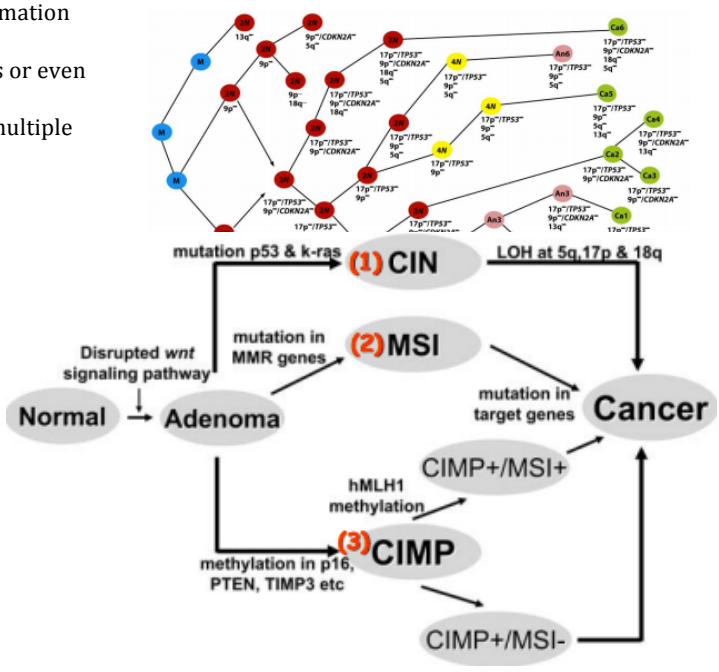
- Subsequent genetic studies have identified additional genes and the important genes disrupted due to chromosomal loss (eg. APC on Chr 5q, p53 on Chr 17p)
- Not all genes / chromosomal regions are disrupted in each colorectal cancer



- There are alternative genetic pathways to colorectal cancer formation

Cancer Genetics has not been solved;

- Haven't identified all of the mutated genes in colorectal cancers or even other cancer types
- Not all colorectal cancers form by this mechanism – there are multiple mechanism



Multiple Pathways to Colorectal Cancer

1. Carcinoma in situ (CIN), characterized by losses of tumour suppressor genes (eg. p53) and mutations of oncogenes (eg.K-RAS)
    a. Tumour suppressor gene: a gene whose partial or complete inactivation, either in the germ line or in the genome of a somatic cell, leads to an increased likelihood of cancer
    b. Oncogene: a gene whose activation (by mutation or inappropriate expression), leads to an increased likelihood of cancer
2. Microsatellite instability: polymorphic (variable) repeats of DNA (1-6 nucleotides)

- AAAAAAAAAAAAAAAAAA Mononucleotide repeat
- ATATATATATATATATAT Dinucleotide repeat
- CAGCAGCAGCAGCAGCAG Trinucleotide repeat
- Located in coding and non-coding regions (eg. Regulatory regions) of genes
- Integrity (faithfulness) of microsatellite sequences maintained by mismatch repair enzymes
- Inactivation of mismatch repair enzymes by mutation or loss of expression leads to variable alterations in the length of microsatellites = "microsatellite instability"
- Consequences of microsatellite instability – Altered function of affected genes
    - microsatellite located in coding region: amino acid sequence and therefore structure of protein is altered
    - microsatellite located in the regulatory region of gene: altered expression of gene
- Detection:
    - Highly polymorphic microsatellites: require sample of normal tissue and tumour tissue from every patient
    - Conserved microsatellites (eg. BAT 26): only require tumour tissue

3. CpG island methylator phenotype (CIMP)

CpG islands

- regions of the genome with a high frequency of CG nucleotides
- often located in gene promoters
- methylation of cytosine residues within the CpG islands of gene promoters inhibits transcription of the genes
- abnormal hypermethylation of genes associated with a proportion of colorectal cancers
- Methylation of CpG islands
    - DNA unmethylated: transcription can proceed normally
    - DNA methylated: transcription cannot proceed

- Genes silenced by hypermethylation in colorectal cancer

Function	Gene
Cell cycle control	*Rb, p16 (INK4a), p15, p73, RAR2*
DNA repair***	*hMLH1, O^6 MGMT, GSTP1, BRCA1*
Apoptosis	*DAP-kinase, $p14^{AR}$*, APAF1, caspase-8, TMS1, PTEN
Cell adhesion and invasion	*E-cadherin, VHL, APC, TIMP3, thrombospondin1, HPP1*
Growth factors	*oestrogen receptor, androgen receptor, RASSF1A, endothelin-B-receptor*

Premalingnant lesion – area of tissues, cells ir abnormal – architectire etc or tey may be too many cells dividing, there may be too many blood vessels – something tht is abnormal but is not a cancer yet
Different lesions that are pathologically abnormal

Progressively abnormal lesions progressiviely to cancer
Children who are diagnosed with leukemia
Cancer associtaetd with adults may have had a long period of development

Colon cancer
Epethilial cells aroung
Basement membrane will have collagen in it – the whiteish lines around it
If you have a cancer that arises from ep cells – glandular starture
Tumour arose from icentral lacteal – sarcoma
All of the rubbish that we eat – contatn turn over of the ep cells
Smooth muscle layer – very imp for the movement of food throught the intestinal tract
Cell types – when you do get a cancer and it gets invasive it invades all of the above

You can havevery formation of a bnign condition

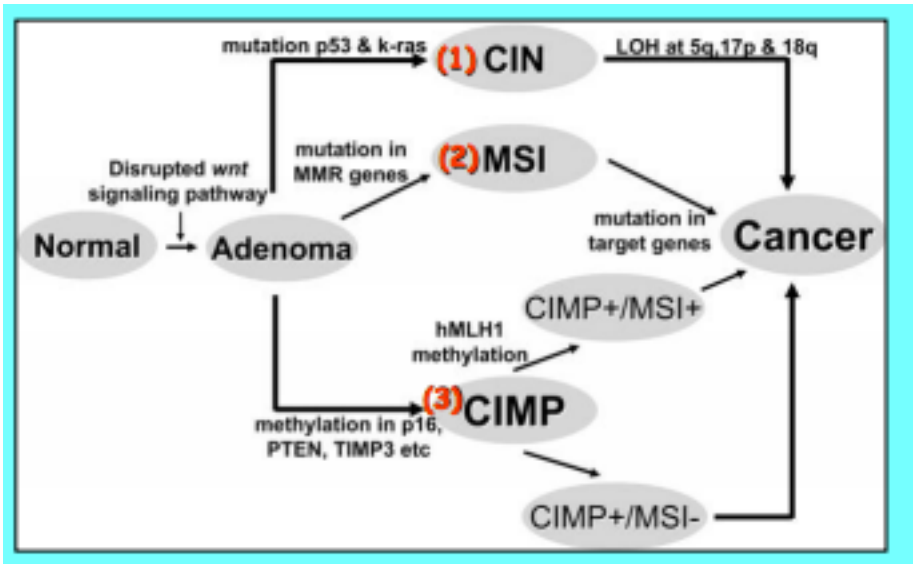
Large adenoma – attachment to the colon (the stalk and the head)
You can develop an invasive component
Spread to the colon itself
Vilus adenoma can also become invasice
Progressively abnormal lesions – pathological evidence for a multi step

Malignant tumours – the cancerous part, arose from the beningn part of the tumour – additional epigenetic changes that made it change from bening to malignant
Removing colon polps will reduce the incidence of cancers

Human genome has been puldished and these are changes to that sequence
Epigenetic – can produce quite big changes, specially in the chromatin
Doesn't depend on allteration itself
Methalation of dna – makes it accessible or inaccessible to the transcriptional machinery – it is not an actual change in the dna sequence

Q- is the long
P is the short arm
Chromosome 5 was lost very early on
K-ras usually occurred very early

APC – gene is imp for development of colon cancer, occurs randomly – cells of their tumour
Sometimes inherited mutation
Dna hypotholmenation
P53 – commonly mutated
A lot of the tumours do have these types of alterations – not every cancer is alike , there are many different pathways to cancer
Some will/wont have a mutuation



There are some commonalities in the development of colon cancer
Of we look at pathways that are linked
From a adenoma or from normal colon to development of cancer – three major type of pathways that ead to the development
Simple gene mutaitons are not the answer to everything

1. when you look at the malignant lesion you can see that the cells in it are cancer cells – abnormal nucleaus, cytoplasm etc. hasn't invaded through that basement membrane
    a. loss of activity of tumour surpression genes
    tumour cell= somatic cell
    genes that perhaps stop cells from growing so quicly
    genes that encode rpoteins – that recognize dna dmamage – stop the cell from growing
    only whn they are inacted does it increase risk of cancer
    inapproprtiate expression – higher level
2. microstatlleties – repeatied sequences od DNA

polymorphic 0 are variable
could be within the gene or in the circulatory gene
if its too high.low – causes disease
instability – every time a cell dives, should be the same number
mismatch repair enzymes – if something happens to them – mutatued or expression lost – leads to variable alterations in the microsatlettiles -> which the instabikity
coding region – huge and immediate impact
regluatoory region - you cange the regualroty gene

can affect multiple genes and protiesn

how do you detect it –
certain pattern in normal cell vs. cancerous
bat 25 – common, quite conserved
most microsateelites – varioation between person to person
a lot.little instability

3. CpG – often occur in the motots of genes, a group of them together

If you have a lot of methylation in a cpG 0 you can switch on/off the gene
Is a normal process
Abnormal hyperventailition of the gene

P –the phosphate backbone
Nnedd to have a CPG islaond in a regulatory gene
There are a lot of genes affected by the ___?
Dna mistmatch – another set of genes that can be affected by hyperventilation, sxpression is down regulated due to hyperventil – can cause micro –instabiligy
Lots of genes can be affected by hyperventilation

Cnacer can develop from an adenoma

When you identify the pathway – easier to identify the drugs etc