1 Biology of cancer development in the GI tract

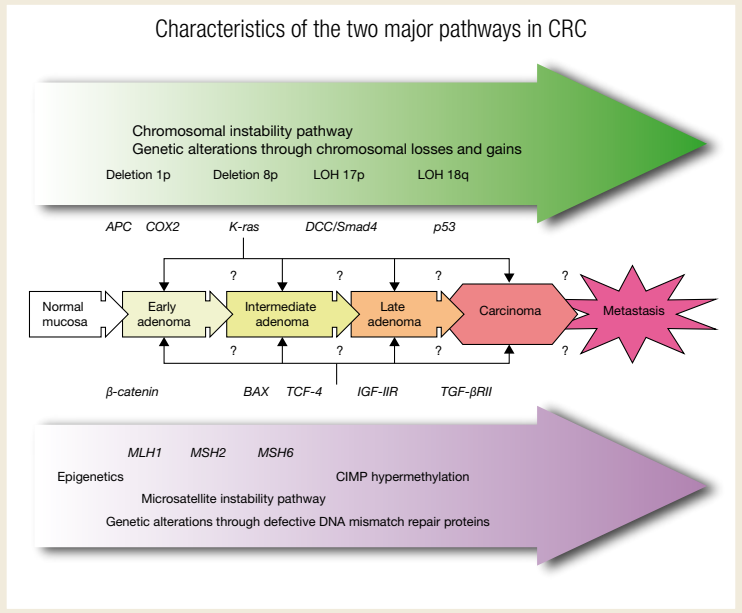
Genesis and progression of GI cancer – a genetic disease

Colorectal cancer

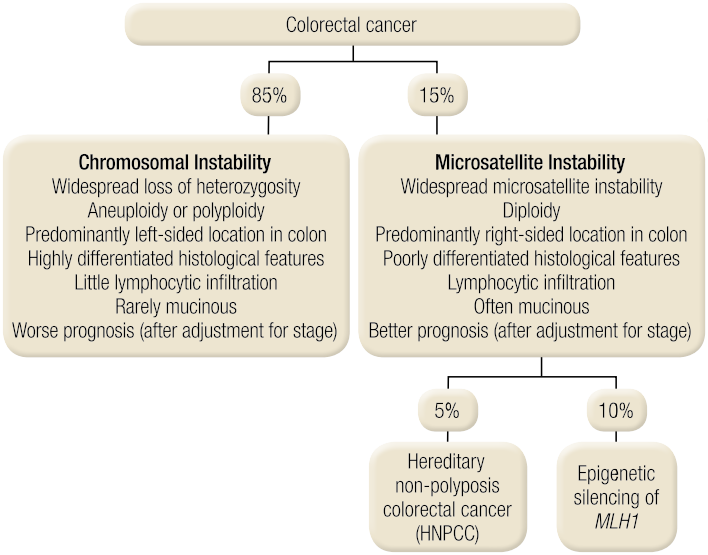
Fearon and Vogelstein proposed a genetic model to explain the stepwise formation of colorectal cancer (CRC) from normal colonic tissues.

The model states: (1) CRC results from mutations in genes with important functions in regulating cell proliferation or DNA repair, (2) mutations in >1 gene are required, and (3) the sequence of mutations is important in determining the formation of CRC.

These altered genes can be divided into two classes: tumour suppressors that either inhibit cell proliferation or promote apoptosis, and oncogenes that promote cell proliferation and tumour progression.



CRC, Colorectal cancer.



Phylogenetically, CRCs can be divided into two molecular subtypes: those with chromosomal instability (CIN) and those with microsatellite instability (MSI).

Carcinomas with MSI present cancer-initiating mutations that inactivate the function of mismatch repair (MMR) genes (e.g. *MSH2, MSH6, MLH1* and *PMS2*) leading to hypermutated genomes. This is known as the "mutator phenotype". MSI tumours frequently present a CpG island methylator phenotype (CIMP) leading to the repression of tumour suppressor genes including *MLH1*.

REVISION QUESTIONS

1. Is MSI always related to hereditary colon cancer?
2. Can you comment on potential therapies for hypermutated colon cancer?
3. Can you mention three genes involved in the chromosomal instability pathway?

Genesis and progression of GI cancer – a genetic disease (continued)

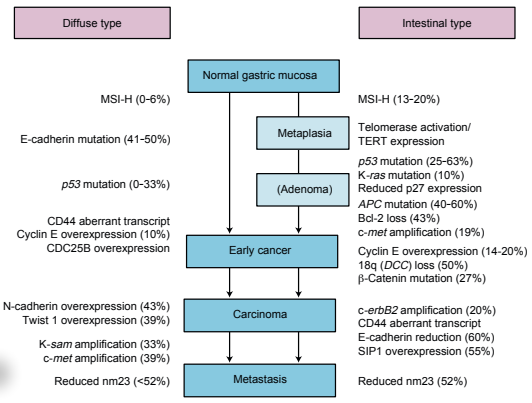
Gastric cancer

The vast majority of gastric cancers are adenocarcinomas, which can be further subdivided into intestinal and diffuse types according to the Lauren classification.

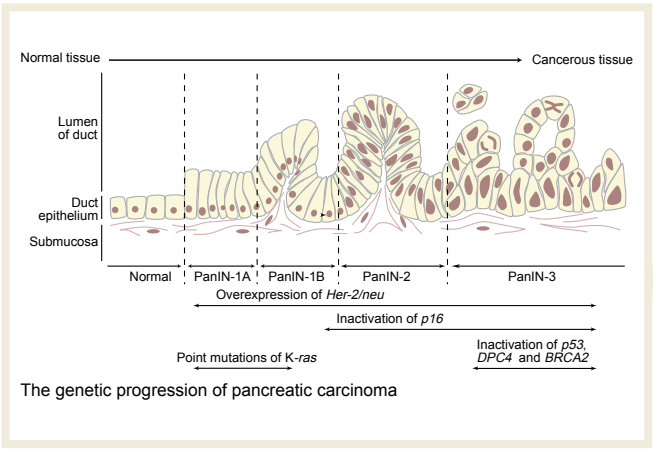
Most gastric cancers are associated with infectious agents, including the bacterium *Helicobacter pylori* and Epstein–Barr virus (EBV). A minority are associated with germline mutation in E-cadherin (*CDH1*) or MMR genes, whereas sporadic MMR-deficient gastric cancers have epigenetic silencing of *MLH1* in the context of CIMP.

Gene expression or DNA sequencing have been used in molecular profiling of gastric cancer, but have not led to a clear biological classification scheme. More recent studies by The Cancer Genome Atlas (TCGA) have permitted more precise molecular classification of gastric cancer by identifying dysregulated pathways and candidate drivers of distinct classes.

Genetic alterations in gastric cancer



Pancreatic cancer

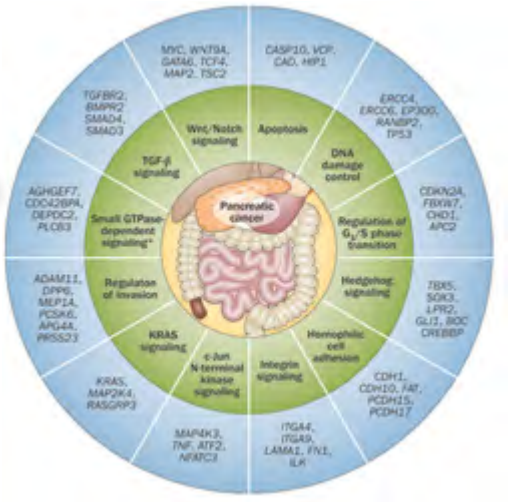


The genetic progression of pancreatic carcinoma

Pancreatic adenocarcinoma presents a progression from distinct types of precursor lesions, a propensity for both local invasion and distant metastasis, an extensive stromal reaction (desmoplasia) resulting in a hypovascular and hypoxic microenvironment, reprogramming of cellular metabolism, and evasion of tumour immunity.

There is a stepwise progression of pancreatic intraepithelial neoplasia (PanIN) from low grade to high grade in types 1, 2 and 3.

These types are associated with accumulating genetic alterations.



More than 90% of cases of PanIN of all grades have *KRAS* mutations. Mutational inactivation of the *CDKN2A*, *p53* and *SMAD4* tumour suppressors occurs later in type 2 and type 3 lesions of PanIN.

In addition, 40%–80% have activating mutations in GNAS and more than 50% have inactivation of RNF43 (an antagonist of Wnt signalling).

The pancreatic adenocarcinoma genome is also characterised by diverse, large-scale chromosomal changes with frequent amplifications, deletions and rearrangements.

REVISION QUESTIONS

1. Are there any gastric cancers with MSI?
2. How are diffuse type gastric carcinomas molecularly defined?
3. What is the most common molecular alteration in pancreatic carcinomas?

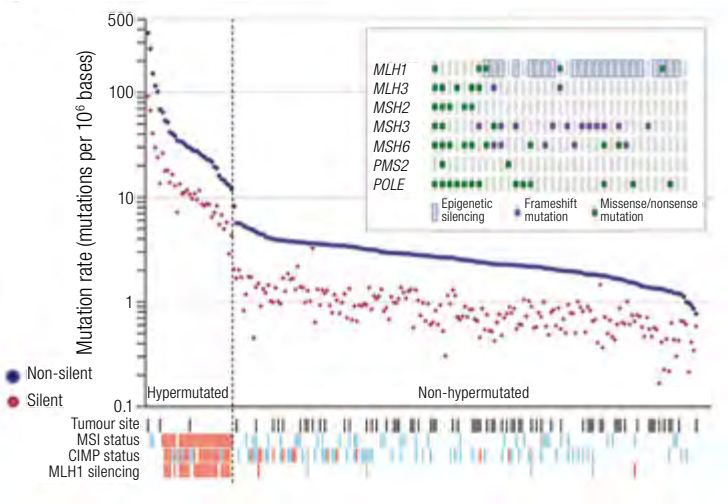
New molecular characterisation of GI tumours

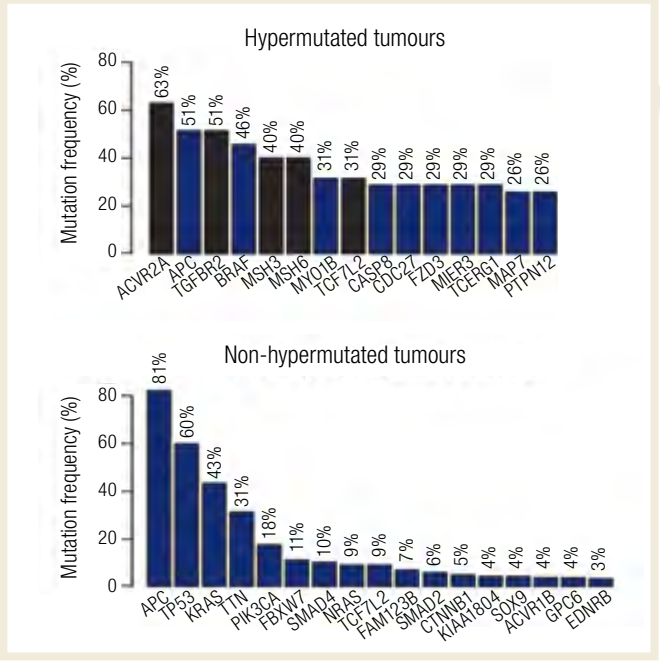
Colorectal cancer

Recent studies by TCGA show that non-hypermutated CRC tumours, irrespective of anatomical origin, present equivalent types of copy number, expression profile, DNA methylation and microRNA (miRNA) changes.

Over 94% had a mutation in one or more members of the Wnt signalling pathway, dominantly in APC. However, there were some differences between tumours from the right colon and all other sites.

Hypermethylation was more common in the right colon, and three-quarters of hypermutated samples came from the same site, although not all had MSI.





93% of non-hypermutated and 97% of hypermutated cases had a deregulated Wnt signalling pathway. New findings included recurrent mutations in *FAM123B*, *ARID1A* and *SOX9* and very high levels of overexpression of the Wnt ligand receptor gene *FZD10*.

Activation of Wnt signalling and inactivation of the TGF-β signalling pathway result in activation of *MYC*. Mutational and integrative analyses emphasise the critical role of *MYC* in CRC. Integrated analysis revealed a diverse set of changes in *TCF/LEF*-encoding genes, suggesting additional roles for TCF/LEF factors.

Mutations in the ubiquitin ligases *RNF43* and *ZNRF3* or fusions of *RSPO2/3* genes are alterations that activate Wnt/beta-catenin oncogenic signalling and represent a promising level for drug intervention.

REVISION QUESTIONS

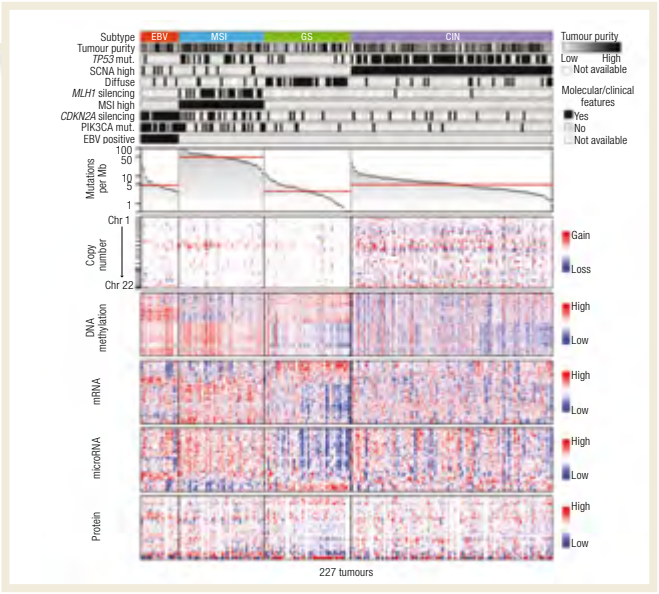
1. Which oncogenic pathway is the most frequently altered by mutations in CRC?
2. Is the TGF-β pathway activated or inactivated by mutations in CRC?
3. Which genes present fusions that activate oncogenic Wnt signalling?

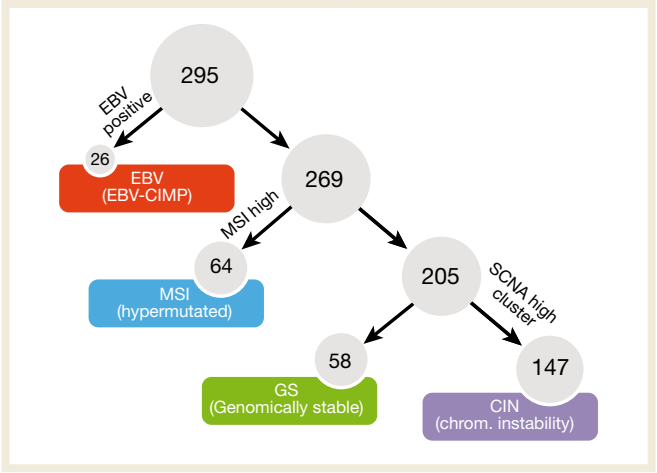
New molecular characterisation of GI tumours (continued)

Gastric cancer

Recent studies by TCGA propose a molecular classification dividing gastric cancer into four subtypes:

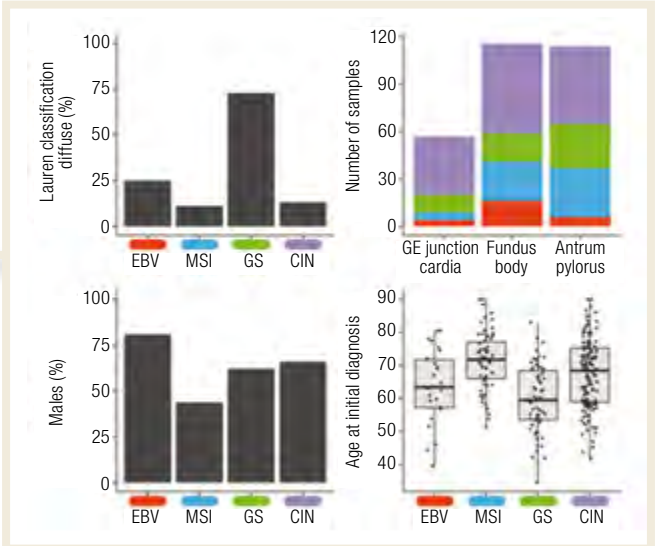
1. Tumours positive for EBV, which display recurrent *PIK3CA* mutations, extreme DNA hypermethylation, and amplification of *JAK2*, *CD274* (also known as *PD-L1*) and *DCD1LG2* (also known as *PD-L2*).





2. Microsatellite unstable tumours, which show elevated mutation rates, including mutations of genes encoding targetable oncogenic signalling proteins.
3. Genomically stable tumours, which are enriched for the diffuse histological variant and mutations of *RHOA* or fusions involving RHO-family GTPase-activating proteins.
4. Tumours with CIN, which show marked aneuploidy and focal amplification of receptor tyrosine kinases.

Identification of these subtypes provides a roadmap for patient stratification and trials of targeted therapies.



REVISION QUESTIONS

1. Do chromosome instability and mutations in tyrosine kinase receptors frequently co-occur in gastric cancer?
2. Are mutations in the *PIK3CA* gene frequent in microsatellite unstable gastric tumours?
3. With which molecular subtype of gastric cancer is a diffuse histology related?

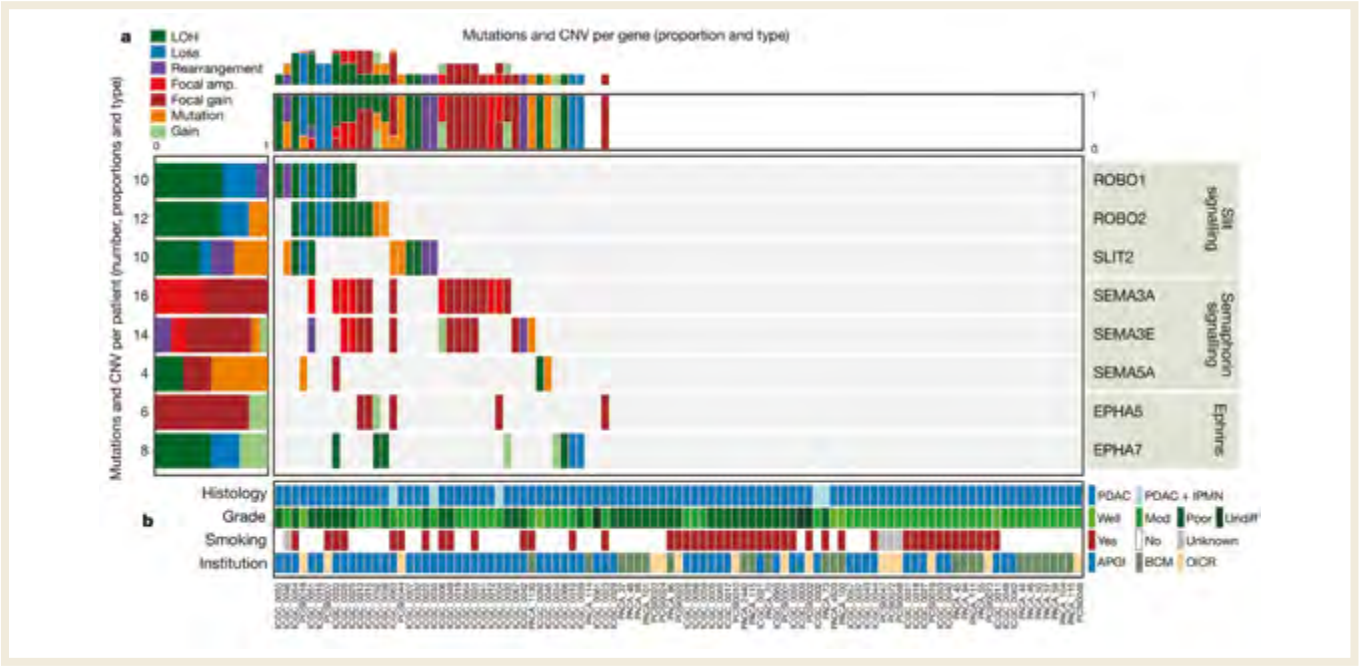
New molecular characterisation of GI tumours (continued)

Pancreatic cancer

Somatic mutations in ataxia telangiectasia mutated (ATM) are present in significant proportions of patients (8%), highlighting the importance of *BRCA*-mediated DNA damage repair mechanisms in sporadic pancreatic ductal adenocarcinoma (PDAC) as well as familial disease. Mutations in genes involved in chromatin remodelling such as *ARID1A*, *EPC1* and *ARID2* are frequently observed, indicating chromatin remodelling may have an important role in PDAC.

Novel mutations in genes traditionally described for their roles in axon guidance have been observed by a combination of genomic data and supportive experimental evidence from independent murine Sleeping Beauty (SB) mutagenesis screens. Axon guidance is integral to organogenesis, regeneration, wound healing and other basic cellular processes.

The widespread genomic aberrations observed in axon guidance genes suggest they may have a role in PDAC. This observation joins mounting evidence in other cancer, including a recent report demonstrating *ROBO2* mutations in liver fluke-associated cholangiocarcinoma.



CNV, Copy number variation; IPMN, intraductal papillary mucinous neoplasm; LOH, loss of heterozygosity; PDAC, pancreatic ductal adenocarcinoma.

REVISION QUESTIONS

1. Which genes involved in chromatin remodelling are significantly mutated in pancreatic cancer?
2. Is *BRCA*-dependent DNA repair a cellular function altered by mutations in pancreatic cancer?
3. Are genes involved in axon guidance altered in pancreatic cancer?

Summary: Biology of cancer development in the GI tract

- CRC progression is the consequence of a stepwise accumulation of mutations in tumour suppressor genes and oncogenes, the most frequent alteration observed being activation of the Wnt/beta-catenin pathway
- Both CRC and gastric cancer present a major group of non-hypermutated tumours and a minor population of hypermutated/MSI tumours
- Pancreatic cancer progressively accumulates mutations in *KRAS*, *CDKN2A*, *p53* and *SMAD4*, but also presents alterations in genes involved in chromatin remodelling and axon guidance

Further Reading

Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature 2012; 491:399–405.

Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012; 487:330–337.

Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014; 513:202–209.

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Giannakis M, Hodis E, Jasmine Mu X, et al. RNF43 is frequently mutated in colorectal and endometrial cancers. Nat Genet 2014; 46:1264–1266.

Seshagiri S, Stawiski EW, Durinck S, et al. Recurrent R-spondin fusions in colon cancer. Nature 2012; 488:660–664.