Cancer

Questions about cancer

- What is cancer?
- What causes unregulated cell growth?
  - What regulates cell growth?
- What causes DNA damage?
- What are the steps in the development of cancer?
- How do cancer therapies work?

What is cancer?

- No single disease

Characterised by

- Unregulated cell growth (compared to benign tumours)
- Invasive properties
- Metastasis (migration to new tissues)

Mutations in oncogenes give new properties

- Hyperactive growth and division, protection against programmed cell death (apoptosis), loss of respect for normal tissue boundaries, ability to become established in diverse tissue environments

Mutations in tumour-suppressor genes lose normal functions

- Accurate DNA replication, control over the cell cycle, orientation and adhesion within tissues, interaction with immune system

Some terminology

- Tumour
  - Cell masses – usually neoplastic – can be malign or malignant

Many types of cancer

- Carcinoma: From epithelial cells
- Melanoma: From melanocytes
- Lymphoma: From lymphocytes (B, T and NK cells)
- Leukaemia: From WBC in bone marrow
- Blastoma: From precursor cells (e.g. in retina)
- Neuroma: From nervous system
- Sarcoma: From connective/supporting tissue
- ...
Incidence in UK
- 1 in 3 develop cancer during their lives
- 1 in 4 people die from cancer
- 3 out of 4 cases of cancer occur in people aged > 60
- Age-corrected incidence of cancer has increased by 21% in males and 41% in females over last 30 years
- Survival rates vary hugely between cancers
  - From <5% for lung cancer to >80% for breast cancer

Cervical cancer
- Carcinoma (cancer of epithelial cells)
- Human papillomavirus responsible for almost all cases
  - STD
- Produces proteins which inhibit key tumour suppressor genes
- P53
  - Activates DNA repair
  - Holds cell cycle at G1/S check point till repair carried out
  - Initiates apoptosis
- Rb (Retinoblastoma)
  - Holds cell cycle at G1/S check point till DNA repair carried out

The cell cycle
- G2/M checkpoint
- G1/S checkpoint
- What causes DNA damage?
  - Spontaneous damage
  - Hydrolysis
  - C > U mutation (1000 per cell per day)
  - Free radical attack from reactive oxygen species (O and H$_2$O$_2$)
  - Alkylation of G
  - Loss of G base
What causes DNA damage?

- **DNA replication errors**
  - Mis-pairing (AC, GT) from rare tautomeric shifts
  - Errors in proof-reading
  - Polymerase slippage
  - Template strand dislocation

Exonuclease site – preferentially binds AC and GT mis-matches
Polymerase site – preferentially binds AT and GC matches

Actively identifies mismatches
Autoreverse on stalling
Associated proof-reading
Later MMR
$10^5/10^6$ to $10^9/10^{11}$ accuracy

What causes DNA damage?

- **Environmental mutagens**
  - UV produces cyclobutane pyrimidine dimer
  - Ionising radiation produces clustering of oxidative-stress like damage (from ROS)
  - Chemicals (e.g. Benzopyrene – responsible for ‘sooty warts’ in 18th C. chimney sweeps, major mutagen in tobacco smoke)

‘Intercalates’ in DNA preventing correct DH formation leading to G > T mutations in p53 transversion hotspots

How is damaged DNA detected?

- **Double-strand breaks**
  - Homologous recombination repair

- **Single-stranded DNA**
  - Stalled replication forks
  - Nucleotide excision repair
  - Homologous recombination repair

- **Chemically modified bases**

Recognition of damage leads to
- Cell cycle checkpoint activation
- DNA repair
- Gene transcription
- Apoptotic cell death

DNA damage repair and classic tumour suppressor genes

- ATM
- ATR

Exact activation pathway unknown

Li-Fraumeni syndrome
Breast, Ovarian, Prostate cancer
**Rous sarcoma virus**

- RSV is retrovirus with standard *gag*, *pol*, and *env* genes
- Also has *v-src* gene – tyrosine kinase. Like host gene (chicken), but lacks inhibitory site so is constantly ‘on’ leading to cell proliferation
- Mutation of normal *src* gene can have same phenotype
  - Led to notion of oncogene
- Oncogene = Mutant form of normal gene (proto-oncogene) that over-rides regulatory controls and/or gains new functions

**Oncogene activation**

- Translocation
  - 8/14 translocation of B cells in Burkitt’s lymphoma
  - 9/22 Philadelphia chromosome in CML

- Amplification
  - Extra-chromosomal segments to form ‘double minutes’
  - Integration to form HSRs
- Regions associated with palindromic sequence
  - Hairpin structures

- Point mutation
  - Single base changes in
    - Growth factors (TGF-α)
    - Cell surface receptors (EGFR)
    - Cellular messengers (RAS oncogene mutated in 30% all human tumours)
    - Transcription factors (MYC)
A quick calculation

- There are maybe $10^{12}$ - $10^{13}$ cells in the human body
- DNA polymerase has an error rate of one in $10^9$-$10^{11}$
- RBCs last about 120 days – other cells are maybe longer lasting (say a year on average)
- Every year you would expect 10 – 10,000 mutations in your body at any given nucleotide position
- The average gene is about 1500 nucleotides long – so each gene experiences $10^4$-$10^7$ point mutations per year
- Why aren’t we dead?

6 or 7 steps to cancer

- In the early 1950s epidemiological studies showed that cancer incidence increases with the 6th power of age
  - Though risk from mutagen exposure is linear (but also delayed)
- Armitage and Doll (1954) showed that this can be explained if transformed cell lineages require 6-7 events in a particular order

What are the steps?

- Immortalisation (avoidance of apoptosis)
- Loss of DNA repair
- Activation of cell growth
- Changes in cell shape/motility/adhesion
- Changes in cell metabolism
- Recruitment of vascularisation
- Suppression of immune system

Therapies

- Surgery
  - Other therapies often used in combination
- Radiotherapy
  - Problems with hypoxia in solid tumours
- Non-specific chemotherapy
  - Targets cell division, so greater effect on fast-growing cells (includes hair, epithelial lining)
  - Usually not specific to cancer cells
- Specific chemotherapy
  - E.g. Imatinib targets TK domains of 3 oncogenes (e.g. specific to CML)
- Monoclonal antibodies
  - Rituximab is a modified monoclonal targeting B cell leukaemias
**Chemotherapies from natural products**

- Paclitaxel (tradename Taxol)
  - From Pacific Yew Tree
  - Used to treat ovarian and breast cancer
  - Promotes microtubule assembly

- Camptothecin
  - From Chinese ornamental tree
  - Used to treat colon, lung and ovarian cancer
  - Inhibits topoisomerases

**The future**

- Use antibodies to target specific chemicals
  - Immune activators (cytokines such as Interleukins)
  - Lethal chemicals

- Use antibodies to target radiotherapy

**Genetic predisposition**

- Many cancers have strong heritable component

- Sometimes this is due to highly penetrant mutations
  - BRCA1, BRCA2

- Genome-wide association studies are identifying other loci with much weaker effects
  - Though still explains no more than 5% of genetic risk

- Familial aggregation of different cancers points to common genetic risk factors
  - Breast and prostate cancer
  - Melanoma and squamous cell carcinoma

**UK survival rates (1999 – 2003)**