Cancer Genetics and Oncogenesis

**Definitions and Rules of Thumb:**

**Anaplasia:** characteristic property of tumour cells: undifferentiation (i.e. loss of those specific qualities which would otherwise make it a smooth muscle cell, breast duct cell, etc.)

**Hyperplasia:** increase in number of cells, eg. asthmatic bronchus

**Metaplasia:** change in type of cell, eg. smoker's lung epithelium slowly turning squamous

**Dysplasia:** hyperplasia of the wrong kind of cell, eg. bowel polyp: is usually **PRE-MALIGNANT**

The suffix "-blastoma" denotes a neoplasm of embryonic cells.

**WHY CANCER?**  →  due to **cumulative genetic damage** (exam keyword)

**Its all about PROLIFERATIVE STIMULUS** (i.e pedal-to-the-metal accelerating) and **DEREGULATION OF REPLICATION** (i.e taking the brakes off)

**INCREASED PROLIFERATIVE STIMULUS:**

- **Growth factors:**
  - Cell overexpresses its own growth factor, hence kinase activated

- **Growth factor Receptors:**
  - Cell hallucinates a growth factor when there really isn't one, hence kinase activated

- **G-Proteins**
  - Mutant receptor-coupled G-protein too slow to realise that its receptor is no longer being stimulated; thus kinases activated for longer

- **Non-receptor Kinases**
  - "Sorceror's apprentice" effect: Mutant accidental protein dumbly and uncontrollably performs the function of an activated kinase

- **Nuclear Regulatory Factors**
  - Abnormal activation of growth-promoting genes by mutant gene-expressor

---

**its all about activating the kinases**

**c-sis gene (simian sarcoma)**
- codes for PDGF (platelet-derived growth factor)
- thus, over-expression → autocrine stimulation (astrocytome, osteosarcoma)
- there are other genes also coding for FGF

**erb-B** (avian erythroblastosis virus)
- normally codes an EGF receptor, which in turn switches on a tyrosine kinase and kicks off a cascade of intracellular changes. BUT: mutant receptor
  - Kinase Permanently Switched On!!

**ras** is the most famous example of a G-protein
- **ras** gets switched on, binds GTP thus activating kinases
- then: **ras** is supposed to hydrolyse the GTP and thus switch itself off; but mutant **ras** does not: THUS **KINASES REMAIN ACTIVE FOR LONGER**

**myc, myb, fos, jun**
- generally responsible for binding to DNA: either stimulate or repress gene expression; if you deregulate gene expression you will have UNCONTROLLABLE GROWTH
Tumour Suppressor Genes: !! REMEMBER THESE !!

**p53:** “guardian of the genome”
- arrests the cell in g1 phase if there has been DNA damage
- induces apoptosis if the damage is not repaired
- mutant p53 cant do any of that; hence → neoplastic change,
sometimes the cancer cells have visible staining accumulations of
useless mutant p53.

**Retinoblastoma (Rb) gene**
Unphosphorylated Rb floats around the nucleus with transcription factors bound to it.

When it gets phosphorylated, the transcription factors are released
(and thus become free to transcript whatever the hell they want )
BUT: mutant Rb cant even bind the factors, because its receptor region is misshapen
and thus there is an excess of transcription going on in the nucleus, leading to
excessive mitotic activity.)
SOME VIRUSES bind to and inactivate p53 and Rb: eg. human papillomavirus, etc

**GAP proteins:**
GTPase-activating proteins) = are part of the G-protein complex;
they help the ras protein hydrolyse the GTP (to inactivate itself)

**What kind of mutations result in carcinogenesis?**

**POINT MUTATION:**
eg. in ras G-proteins, loss of one amino acid means much slower to hydrolyse GTP
and thus much slower to deactivate the kinases .]
PLUS point mutations may disable tumour suppressor proteins.

**CHROMOSOMAL TRANLOCATION:** comes in 2 flavours:
- **Leading to overexpression:** like in Burkitt's Lymphoma, when the myc gene from
  nice quiet suburban chromosome 8 gets translocated to the hectic overactive chromosome 14,
  right next to the immunoglobulin heavy chain gene.
  THUS every time there’s an infection, the B-cells start pumping out Immunoglobulins and thus
  myc proteins (which are growth-promoting transcription factors)
- **Leading to gene alteration:** like in Chronic Myeloid Leukaemia, when the abl gene (a
tyrosine kinase) from chromosome 9 gets translocated to the bcr gene on chromosome 22.
The result is a bcr-abl chimaera kinase which is always switched on.

**GENE AMPLIFICATION**
- is the repeated duplication of one gene;
thus a chromosome ends up with fifty copies of it. The more proto-oncogene
copies there are, the more over-expressed it is.

Childhood cancers are usually due to an inherited gene instability;
adult onset cancers are from a somatic (acquired) mutation

---

**THE TUMOUR SUPPRESSOR GENES ARE PRESENT ON TWO ALLELES**! i.e  both copies of a chromosome have the same tumour suppressor gene, and even if one
mutates, the other should still be able to cope.
THUS two hits are required to knock out a tumour suppressor gene.
CHEMOTHERAPY: only what's important
Of all the days of a cancer patient, only 3% are spent in hospital.

CANCER IS AN OUTPATIENT CONDITION

Goals of chemo:
- to cure (e.g., germ-cell cancers)
- to debulk (i.e., shrink tumour and make it more manageable)
- ADJUVANT (mop-up the microscopic remains after a curative treatment)
- Radioenhancing (with radiation, cytotoxic effect is amplified)
- Prolong survival
- Palliate (e.g., shrink the massive lung met so it stops choking off the superior vena cava)

RESISTANT TO CHEMO: renal and pancreas cancer
SENSITIVE TO CHEMO: seminoma, trophoblast (rare placental malignancy), all kinds of blastomas
EVERYTHING ELSE (the majority of them) is IN BETWEEN.

BEST CHEMO EFFECT when you use multiple agents with non-overlapping toxicities
→ this increases effect and reduces tumour resistance

TUMOUR RESISTANCE: high rate of mitosis + selection pressure = greater opportunity to evolve.
Some tumour cells even evolve protein pumps to pump the chemo drugs out of themselves!

SUPPORTIVE CARE:
Pre: counselling, teeth (prevent sepsis), fertility (freeze egg or sperm)
During: (antiemetics, antibiotics, antivirals)
Post: (antiemetics, laxatives, benzodiazepines, granulocyte colony stimulating factor (G-CSF)

The AGENTS
Alkylating: synthetic, oldest, classic cytotoxins- classical side effects
Eg. nitrogen mustards

Antimetabolites synthetic competitive inhibitors of naturally occurring molecules;
Methotrexate, 5FU, cytosine arabinoside

Cytotoxic antibiotics
doxorubicin = cardiotoxic
Bleomycin = lung toxicity

Vinca alkaloids plant derived; vincristine, vinblastine, = neurotoxic

Platinum compounds = best ever!! cisplatin, transplatin,
carboplatin is the least toxic of the lot

Taxanes plant products: paclitaxel, docetaxel
→ neuropathy, arthralgia, myalgia – may need steroids

ALL CHEMO DRUGS CAUSE BALDNESS EXCEPT CARBOPLATIN, 5FU and MITOXANTRONE

ALL CHEMO DRUGS CAUSE MARROW DAMAGE EXCEPT BLEOMYCIN, VINCRISTINE, CISPLATIN, 5FU

Microarrays: genetic method of predicting if a tumour will respond to chemo; new
development- takes ages (will be perfected by our internship
Palliative Care:

Patients' goals are the most important consideration.
Take a history, AGAIN!! Find out QOL: can they sleep, etc
About 80% of cancer patients will experience cancer-related pain.
YOU MUST TELL THE DIFFERENCE BETWEEN CANCER PAIN AND PAIN FROM OTHER SOURCES
(pain from other sources can probably be managed by addressing its cause; terminal cancer pain cannot.)

Nociceptive vs. neuropathic pain: cancer patients most frequently have both.
Mild nociceptive: give NSAIDs, codeine,
Severe Nociceptive: give opiates.

### Opiate Equivalents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (minutes)</th>
<th>Peak (hours)</th>
<th>Duration (hours)</th>
<th>t-1/2 (hours)</th>
<th>Parenteral</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>10-30</td>
<td>0.5-1</td>
<td>4-6</td>
<td>1-2</td>
<td>IM 1-30-130</td>
<td>Oral 200</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1-8</td>
<td>-</td>
<td>1-2</td>
<td>1.5-6</td>
<td>IM 0.1-0.2</td>
<td>Trans 100 mcg/hr</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>-</td>
<td>-</td>
<td>4-6</td>
<td>3.3-4.5</td>
<td>-</td>
<td>Oral 5-10</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>15-30</td>
<td>0.5-1</td>
<td>4.5</td>
<td>2-3</td>
<td>IM 1.3-1.5</td>
<td>Oral 7.5</td>
</tr>
<tr>
<td>Levoxanadol</td>
<td>30-90</td>
<td>0.5-1</td>
<td>6-8</td>
<td>12-16</td>
<td>IM 2</td>
<td>Oral 4</td>
</tr>
<tr>
<td>Meperidine</td>
<td>10-45</td>
<td>0.5-1</td>
<td>2-4</td>
<td>3-4</td>
<td>IM 75</td>
<td>Oral 300</td>
</tr>
<tr>
<td>Methadone</td>
<td>30-60</td>
<td>0.5-1</td>
<td>4-6</td>
<td>15-30</td>
<td>IM 10</td>
<td>Oral 10-20</td>
</tr>
<tr>
<td>Morphine</td>
<td>15-60</td>
<td>0.5-1</td>
<td>3-7</td>
<td>1.5-2</td>
<td>IM 10</td>
<td>Oral 30-60</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15-30</td>
<td>1</td>
<td>4-6</td>
<td>-</td>
<td>IM 1</td>
<td>Oral 30</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>3-10</td>
<td>0.5-1</td>
<td>3-6</td>
<td>-</td>
<td>IM 1</td>
<td>Rectal 5-10</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>30-60</td>
<td>2-2.5</td>
<td>4-6</td>
<td>6-12</td>
<td>-</td>
<td>Oral 110</td>
</tr>
</tbody>
</table>

A few notes:

1. Note that effects of opiates may be more pronounced after IV/IM administration, but the duration is less.
2. Initial doses should be lower for some medications: codeine (30 mg), oxycodone (5 mg), meperidine (50 mg), Fentanyl transdermal (25 mcg).
3. Because methadone is long-acting, its duration and half-life increase with repeated use.
4. Meperidine should not be given to patients who have taken an MAOI within 14 days.

Most of the above data were derived from Facts and Comparisons, 1997.

Neuropathic: give antidepressants (SSRIs) and anticonvulsants (eg. sodium valproate, carbamazepine)

TERMINAL CARE: sedation, laxatives, antiemetics, antidepressants, methadone; maintain dignity and comfort until the inevitable.
DO NOT ATTEMPT TO DELAY THE REAPER as this only prolongs suffering of both the patient, their family, and yourself.
Pattern of SPREAD: most common to least common

* GI cancers all end up spreading to the LIVER one way or another.

**BREAST**
- Bones → brain → liver

**COLON**:
- Liver → lungs → bones → brain → adrenals → kidneys

**LUNG**:
- Brain → bone → liver → adrenals

**CERVIX**
- Liver → Lung → Bone