The Biological Basis of Cancer

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Aim of Presentation

By the end of this presentation you will:

- Be able to explain how and why cancer arises, including the alterations in genes
- Understand the special characteristics that tumour cells have which helps them grow and spread
- Understand the nature of cellular signalling and how gene mutations or activation can affect cellular signalling pathways
- Be able to explain how targeted therapies are directed at altered signalling pathways
Global Mortality in 2002

- Cancer
- Total TB+HIV+Mal
- Malaria
- HIV/AIDS
- Tuberculosis

(WHO 2003)
## Mortality Trends - 2002 and 2011

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Rank</th>
<th>2002</th>
<th>2011</th>
<th>2011</th>
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<tr>
<td>All neoplasms</td>
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<td>12.4</td>
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<tr>
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<td>9</td>
<td>2.7</td>
<td>2.2</td>
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<tr>
<td>HIV /Aids</td>
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<td>6</td>
<td>2.9</td>
<td>3.0</td>
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<td>8</td>
<td>1.8</td>
<td>2.6</td>
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<tr>
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<td>Out of top 20</td>
<td>16</td>
<td>1.1</td>
<td>1.5</td>
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</table>

(WHO 2012)
Projected worldwide annual new cases of cancer

(WHO 2003)
Population-Based Studies

Regions of Highest Incidence

U.K.: Lung cancer

CANADA: Leukemia

BRAZIL: Cervical cancer

U.S.: Colon cancer

AUSTRALIA: Skin cancer

CHINA: Liver cancer

JAPAN: Stomach cancer

CHINA: Liver cancer

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By 2020, there are expected to be 16 million new cases of cancer every year.

70% of these cases will be in the developing world.

One third of cancers in the developing world are preventable and another third are potentially treatable if detected early.

Among the poorer developing countries, 1-2% of childhood cancers are cured compared to 80% in the developed world.

80% of cases of cervical cancer occur in the developing world; every 2 mins a woman dies of cervical cancer.
75% of cancer patients in the developing countries have advanced or incurable cancers by the time they seek medical assistance.
Why is cancer important?

- **Viral infections**
  
  Human Papillomavirus (HPV) causes cervical cancer in the West, HPV+ve Head and Neck
  
  Hepatitis B and C cause liver cancer
  
  HIV causes Kaposi’s sarcoma

- Increasingly modern lifestyles – tobacco, poor diet, lack of exercise, alcohol & industrial exposures

- **Increase in life expectancy**
Viruses

Virus inserts and changes genes for cell growth

Cancer-linked virus
Scope of the Problem

Common in Western World
• \( \frac{1}{3} \) of us will develop it
• \( \frac{1}{4} \) of us will die from it

• More than 200 separate diseases

• Shared biological features
Causation

INHERITED PREDISPOSITION

ENVIRONMENT

• Tobacco
• Diet
• Radiation
• Chemicals

BALANCE
Different Kinds of Cancer

- Some common carcinomas:
  - Lung
  - Breast (women)
  - Colon
  - Bladder
  - Prostate (men)

- Some common sarcomas:
  - Fat
  - Bone
  - Muscle

- Lymphomas:
  - Lymph

- Leukaemias:
  - Bloodstream
Heredity and Cancer

All Breast Cancer Patients

Inherited factor(s)

Other factor(s)
High-Strength Radiation

Leukemia Incidence

X-ray Dose (atomic radiation)
Lag Time

20-Year Lag Time Between Smoking and Lung Cancer

Cigarette consumption (men)

Cigarettes Smoked per Person per Year

Lung cancer (men)

Lung Cancer Deaths (per 100,000 people)
Cancer Risk and Ageing

Number of Cancer Cases (per 100,000 people)

Age of Person (in years)

Cancer Risk and Aging

Colon

Breast
Cancer Cells are characterised by:

- Uncontrolled proliferation
  - how many cancer cells in a nodule of 1cm$^3$?

- Capacity to invade normal tissue

- Potential to spread to distant organs
Progression of Cancer

Without treatment, cancer undergoes multistage processes:

- Initiation
- Promotion
- Progression
- Metastasis
Loss of Normal Growth Control

Normal cell division

Cell Suicide or Apoptosis

Cell damage
no repair

Cancer cell division

First mutation

Second mutation

Third mutation

Fourth or later mutation

Uncontrolled growth
Invasion and Metastasis

1. Cancer cells invade surrounding tissues and blood vessels.
2. Cancer cells are transported by the circulatory system to distant sites.
3. Cancer cells reinvade and grow at new location.
Tumour development (1)

- Genetically altered cell
- Hyperplasia
- Dysplasia
- Capillaries develop
Tumour development (2)

In situ cancer

Invasive cancer

Tumour cells travel into developing vessels
Genes and Cancer

Chromosomes are DNA molecules

- Heredity
- Viruses
- Chemicals
- Radiation

How do Cells Normally Function?

- The nucleus controls cell function by manufacturing proteins.
- Homeostatic mechanisms keep cell turnover under control, so organs remain the correct size with an appropriate number of cells.
- Cell turnover rate depends on the tissue (e.g., intestine – rapid, muscle – slow).
- Process controlled by signal transduction pathways that integrate the signals regulating cell growth.
- Balance between stimulatory and inhibitory pathways.
What Causes Cell Growth?

- Growth factor
- Receptor
- Cell membrane

Outside the cell

Inside the cell
Relay Proteins Transmit Messages

- **Outside the cell**
- **Cell membrane**
- **Inside the cell**

**Growth factor**

**Receptor**

**Relay proteins**
Messages are Sent to the Nucleus

Growth factor

Receptor

Relay proteins = Signal transduction pathway

Cell growth
Cell Growth is Controlled by Stop as Well as Go Signals

Growth factor

Outside the cell

Cell membrane

Inside the cell

Relay proteins

Stop signals

Nucleus

Cell growth
Signal Transduction May Involve More Than One Pathway
Signal Transduction Inhibition

- Receptor kinase inhibitor
- Monoclonal antibody to receptor
- Anti-sense oligonucleotides
- Monoclonal antibody to ligand
- Transduction pathway kinase inhibitor
- Nucleus
Genes and Cancer Development

Three gene classes play a major role in triggering cancer:

- **(Proto) Oncogenes**: Encourage cell growth
- **Tumour suppressor genes**: Stop cell growth
- **DNA repair genes**: Mutations mean that defective DNA is not repaired properly

In cancer, these genes are lost or mutated.
Oncogenes Can Increase Growth Factor Signalling

**Outside the cell**
- Growth factor
- Excessive production
- Abnormally active

**Inside the cell**
- Receptor
- Over activity
- Persistence
- Constituently active

**Incorrect signal transduction**

- Nucleus
- Over-rides the receptor message
- Increased transcription

**Cell growth**
Actions of Oncogenes: Summary

- Excessive production of growth factors
- Production of an abnormally active growth factor
- Excessive production of the receptor for the growth factor
- Over-activity of the receptors for the growth factors
- Persistence of a functional receptor even after it would normally be destroyed by the cell
- A receptor to be active even in the absence of its ligand (constitutently active)
- Incorrect signals to be sent from the receptor to the nucleus
- Increased transcription at the nucleus.
Tumour Suppressor Genes are the Cell’s Natural Brake

- In cancer, tumour suppressor genes are lost
- This loss removes the normal “brake” on cell division
- Allows unregulated growth
Cell Growth is Controlled by Stop as well as Go Signals

Inhibitory factor – should send stop signal

Relay protein is lost

No stop signal

Unregulated Cell growth
DNA Repair Genes

- DNA can be damaged by environmental factors
- The cell is capable of recognising, excising and repairing the damaged DNA
- If the genes coding for these enzymes become mutated then the enzymes no longer function to correct damaged DNA which is thus passed on during replication
- Mutated repair genes allow an accumulation of damaged DNA or mutations that combine to produce a malignancy
Why Cancer Is Potentially Dangerous

Melanoma cells travel through bloodstream

Brain

Liver

Melanoma (initial tumor)
Acquired Capabilities of Cancer Cells

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Limitless replicative potential
- Evade senescence/apoptosis – programmed cell death
- Sustained angiogenesis – new blood vessels
- Tissue invasion and metastasis
How is Senescence Regulated?

Telomere shortens as cell divide

- Two important tumour suppressor genes *p53* and *pRB* regulate senescence

Strand of DNA

When the telomere is lost the cell becomes senescent, ages and eventually dies. In cancer telomerase adds back TTAGGG
What is Apoptosis?

- Apoptosis is a regulated form of cell death
- It is a normal process important in growth and development and the immune system
- It is also a way of removing infected, damaged or mutated cells
How Does Apoptosis Occur?

- “Death” signals are sent to the cell via special agents.
- These signals are relayed via pathways to the mitochondria which release cytochrome c and starts a cascade and that causes cell death.
- Tumours evade apoptosis and so unregulated growth continues.
What is Angiogenesis?

- Angiogenesis is the process of new blood vessel growth to supply a tissue with nutrients and oxygen.
- Without new vessels a tumour would become anoxic and cease to grow.
- Tumours secrete Tumour Angiogenic Factors (TAFs) that stimulate the growth of blood vessels.
Angiogenesis and Vascularisation Support Tumour Growth and Metastasis

Stages where angiogenesis plays a role in tumour progression:

- Premalignant stage (Avascular tumour)
- Malignant tumour (Angiogenic switch)
- Tumour growth (Vascularised tumour)
- Vascular invasion (Tumour cell intravasation)
- Dormant micrometastasis (Seeding in distant organs)
- Overt metastasis (Secondary angiogenesis)
Important Processes that Facilitate Metastasis

- Detachment
- Anchorage independent growth
- Motility
- Intravasation
- Extravasation
- Adhesion
Detachment, Anchorage Dependent and Anchorage Independent Growth

- Cell to cell adhesion
- Detachment from extracellular matrix

- Invasive cell
- Extracellular matrix
- Receptors for extracellular matrix
- Cell detaches
- Dead cell
- Cell attaches to inappropriate extracellular matrix
Adhesion Facilitates Metastasis

- Free cancer cells can become attached to distant tissue and start to grow new (secondary) tumours or metastases
- The site of metastasis depends on the anatomy of the body and the nature of the cancer cell’s surface cell adhesion molecules
Metastasis Also Occurs via Lymphatic Vessels

- Detached tumour cells often enter the lymphatic system
- They then become trapped in lymph nodes
- They are more likely to be trapped in the lymph nodes nearest the tumour
- This is why the extent of lymphatic spread is an important indicator in tumour staging
- Imaging techniques are important in detecting lymphatic spread
- Surgery plays an essential role in resecting lymph nodes and providing tissue for staging
Sentinel Lymph Nodes

- The sentinel node is the first node on the direct drainage pathway from the tumour.
- If the sentinel node is clear of tumour cells, it is unlikely that other nodes have been affected.
Summary - Process of Metastasis

- Early tumour cells
- Tumour cells squeeze into developing blood vessels or lymph vessels
- Lymph vessels
- Tumour cells travel to lymph nodes
- Tumour cells adhere to blood vessel walls and squeeze through to form distant metastases
Targeted Therapies

- Antireceptor, antibodies ± toxins
- Immune system activation (vaccines, monoclonal antibodies)
- Metalloproteinase inhibitors
- Matrix degradation (collagenases, gelatinases & stromalysins)
- Antimetabolites, microtubule inhibitors
- Tyrosine kinase inhibitors
- Farnesyl transferase inhibitors
- Growth factor receptors
- Intracellular signalling molecules
- Nucleus
- Apoptosis agonists
- Hormone agonists/antagonists
- Antisense nucleotides
- Angiogenesis inhibitors (angiotatin, endostatin & anti-VEGF)
Individualising Treatment

- Primary tumour
- mRNA
- Gene expression profile
- BM, Blood, LNs, Serum
- MRD detection & Proteomics
- Analyses of 30,000 human genes
- Diagnosis
- Treatment
Technology Platforms

Histopathology

Proteomics

Genomics

Imaging

Genetics

Personalised medicine

- What patient?
- What tumour?
- What biomarker?
- What drug?
Individualised Care?
Conclusion

- We now understand better the special characteristics that tumour cells have which helps them grow and spread.

- We can identify these processes and can target therapies towards overcoming the consequences of this dysregulation.

- Cancer treatment will move forward by developing new targeted therapies and integrating them with conventional treatment modalities.
Cancer Prevention

- Cancer viruses or bacteria
- Carcinogenic radiation
- Carcinogenic chemicals
The real reason dinosaurs became extinct
Breast Cancer Screening
Colon Cancer Screening
Diagnostics

- Biopsy
- Sentinel Node Biopsy
- Bone Marrow Aspiration
- Cervical Smear
- Sputum
- Bronchial Washings
- Endoscopy
- Blood Test
- Plain Film
- CT
- MR
- Ultrasound
- Genetic Analysis
- PET-CT
Hallmark of Cancer Treatments - Surgery
Intensity modulated radiotherapy

- X-rays delivered from many ports by rotating the linac around pt
- Modification of the shape and intensity of each port
Limits of RT as therapy

- Volume of therapy limited by normal tissue tolerance
- Disease outside treated volume will not be treated
- Some tumours are not sufficiently radiosensitive to be eradicated by safe RT doses eg glioblastoma
- Normal tissue tolerance precludes radical retreatment for local recurrence
Advances in Chemotherapy - Sue

- Pharmacogenetics
- Cytotoxics
- Kinase inhibitors
- Viruses
- Vaccines
Cancer Patients: A Simplified Pathway

Supportive & Palliative Care Services for Patients, Carers & Families may be accessed at any point along the pathway.
Future

- Bright
- Complex

YOU can play a leading role in this cancer revolution