How do viruses cause cancer?

Principles of oncogenesis and viral-cellular pathways

Never Stand Still  Medicine  Caroline Ford  caroline.ford@unsw.edu.au
Introduction

- Metastasis Research Group
- Cell and molecular biologists
- Ovarian & endometrial cancer
- Signalling pathways
- Epithelial to mesenchymal transition
Talk outline

- Global impact of cancer
- Hallmarks of cancer
- The importance of signalling pathways
- Mechanisms by which viruses cause cancer
- Oncogenic virus example 1 - HPV
- Oncogenic virus example 2 – Merkel cell polyomavirus
Global cancer burden

Cancer worldwide

14.1 million cases

Lung 13%
Breast 12%
Bowel 10%
Prostate 8%
Liver 8%
Other 58%

2.2 million deaths

Lung 19%
Liver 54%
Bowel 10%
Prostate 8%
Other 58%
Worldwide Cancer Incidence

An estimated 14.1 million adults in the world were diagnosed with cancer in 2012. These cases were not spread evenly across the globe and the reliability of cancer statistics available for each country varies.

Most Common Cancers Worldwide

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Total: 141 million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1,825,000</td>
</tr>
<tr>
<td>Breast</td>
<td>1,677,000</td>
</tr>
<tr>
<td>Bowel (inc. anus)</td>
<td>1,361,000</td>
</tr>
<tr>
<td>Prostate</td>
<td>1,112,000</td>
</tr>
<tr>
<td>Stomach</td>
<td>952,000</td>
</tr>
<tr>
<td>Liver</td>
<td>782,000</td>
</tr>
<tr>
<td>Cervix</td>
<td>529,000</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>456,000</td>
</tr>
<tr>
<td>Bladder</td>
<td>430,000</td>
</tr>
<tr>
<td>NHL</td>
<td>386,000</td>
</tr>
<tr>
<td>Lip, oral cavity</td>
<td>300,000</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>232,000</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>44,000</td>
</tr>
<tr>
<td>Other cancers</td>
<td>4,007,000</td>
</tr>
</tbody>
</table>

Cancer Incidence by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases per 100,000 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia/New Zealand</td>
<td>265</td>
</tr>
<tr>
<td>Northern America</td>
<td>231</td>
</tr>
<tr>
<td>Western Europe</td>
<td>205</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>231</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>205</td>
</tr>
<tr>
<td>Central &amp; Eastern Europe</td>
<td>231</td>
</tr>
<tr>
<td>South America</td>
<td>205</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>231</td>
</tr>
<tr>
<td>Caribbean</td>
<td>265</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>205</td>
</tr>
<tr>
<td>Western Asia</td>
<td>231</td>
</tr>
<tr>
<td>Melanoma</td>
<td>205</td>
</tr>
<tr>
<td>South-Eastern Asia</td>
<td>231</td>
</tr>
<tr>
<td>Eastern Africa</td>
<td>205</td>
</tr>
<tr>
<td>Central America</td>
<td>231</td>
</tr>
<tr>
<td>Northern Africa</td>
<td>205</td>
</tr>
<tr>
<td>Middle Africa</td>
<td>231</td>
</tr>
<tr>
<td>South-Central Asia</td>
<td>205</td>
</tr>
<tr>
<td>Western Africa</td>
<td>231</td>
</tr>
</tbody>
</table>

Source: GLOBOCAN 2012 V1.0, Cancer Incidence and Mortality Worldwide, IARC, NHL = Non-Hodgkin lymphoma. Region boundaries are standard United Nations groupings. Data quality classifications for incidence data: a. High quality national data or high quality regional (coverage greater than 75%) b. High quality regional (coverage between 50% and 75%) c. High quality regional (coverage lower than 50%) d. National data trusted. Regional data not trusted. Frequency data g. No data. 'High quality' refers to data included in Cancer incidence in Four Continents (EC) volume 30 or 31.

International Agency for Research on Cancer

World Health Organization

CANCER RESEARCH UK
Global differences

Most Common Cancers Worldwide

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Cases per year (thousands)</th>
<th>Total: 14.1 million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1,825</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>1,677</td>
<td></td>
</tr>
<tr>
<td>Bowel (inc. anus)</td>
<td>1,361</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>1,112</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>952</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>782</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>528</td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td>456</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>430</td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>386</td>
<td></td>
</tr>
<tr>
<td>Lip, oral cavity</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Other cancers</td>
<td>4,007 (28%)</td>
<td></td>
</tr>
</tbody>
</table>

Australia & NZ

1. Prostate
2. Bowel
3. Breast
4. Melanoma

East Asia

1. Lung
2. Stomach
3. Liver
4. Bowel

★ Associated with viral infection
★★ Associated with bacterial infection
Worldwide Cancer Mortality

There were an estimated 8.2 million deaths from cancer in the world in 2012. These deaths were not spread evenly across the globe and the reliability of cancer statistics available for each country varies.

Most Common Causes of Cancer Death

- Lung: 746,000 deaths per year, 1,490,000 total
- Liver: 373,000 deaths per year, 723,000 total
- Stomach: 353,000 deaths per year, 694,000 total
- Bowel (inc. anus): 232,000 deaths per year, 484,000 total
- Breast: 182,000 deaths per year, 364,000 total
- Oesophagus: 175,000 deaths per year, 350,000 total
- Pancreas: 136,000 deaths per year, 272,000 total
- Prostate: 110,000 deaths per year, 220,000 total
- Cervix: 97,000 deaths per year, 194,000 total
- Leukaemia: 62,000 deaths per year, 125,000 total
- Lip, oral cavity: 15,000 deaths per year, 30,000 total
- Kaposi sarcoma: 7,000 deaths per year, 14,000 total
- Other cancers: 2,186,000 deaths per year, 4,372,000 total

Cancer Mortality by Region

- Eastern Asia: 1,135 deaths per 100,000
- Western Europe: 1,000 deaths per 100,000
- Central & Eastern Europe: 975 deaths per 100,000
- South-Eastern Asia: 950 deaths per 100,000
- Western Africa: 925 deaths per 100,000
- South-Central Asia: 890 deaths per 100,000
- Central America: 875 deaths per 100,000
- Eastern Europe: 850 deaths per 100,000
- Northern America: 825 deaths per 100,000
- Western Europe: 800 deaths per 100,000
- Northern Africa: 775 deaths per 100,000
- South Africa: 750 deaths per 100,000
- South America: 725 deaths per 100,000
- Australia/New Zealand: 700 deaths per 100,000
- Southern Africa: 675 deaths per 100,000
- Eastern Africa: 650 deaths per 100,000
- Northern Africa: 625 deaths per 100,000
- Middle Africa: 600 deaths per 100,000
- Western Europe: 575 deaths per 100,000
- Caribbean: 550 deaths per 100,000
- South America: 525 deaths per 100,000
- Australia/New Zealand: 500 deaths per 100,000
- Southern Europe: 475 deaths per 100,000
- Central Europe: 450 deaths per 100,000
- Western Europe: 425 deaths per 100,000
- Western Europe: 400 deaths per 100,000
- Western Europe: 375 deaths per 100,000
- Western Europe: 350 deaths per 100,000
- Western Europe: 325 deaths per 100,000
- Western Europe: 300 deaths per 100,000
- Western Europe: 275 deaths per 100,000
- Western Europe: 250 deaths per 100,000
- Western Europe: 225 deaths per 100,000
- Western Europe: 200 deaths per 100,000
- Western Europe: 175 deaths per 100,000
- Western Europe: 150 deaths per 100,000
- Western Europe: 125 deaths per 100,000
- Western Europe: 100 deaths per 100,000
- Western Europe: 75 deaths per 100,000
- Western Europe: 50 deaths per 100,000
- Western Europe: 25 deaths per 100,000
- Western Europe: 10 deaths per 100,000
- Western Europe: 0 deaths per 100,000

Cancer

- Uncontrolled division of abnormal cells leading to a malignant and invasive growth or tumour
Hallmarks of Cancer

- Sustaining proliferative signaling
- Evading growth suppressors
- Deregulating cellular energetics
- Avoiding immune destruction
- Resisting cell death
- Enabling replicative immortality
- Genome instability & mutation
- Tumor-promoting inflammation
- Inducing angiogenesis
- Activating invasion & metastasis

Hanahan and Weinberg, Cell, 2011
The importance of signalling pathways

- Govern response to external factors
- Communicate messages
- Single genes may play key roles, but it is the network of genes, or signalling cascade that alters cell behaviour
Signalling pathway example
What do viruses have to do with it?
4 IN 10 CANCERS CAN BE PREVENTED

These are proven ways to reduce the risk of cancer. Larger circles indicate greater impact on cancer risk.

LIFESTYLE

- Keep a healthy weight
- Eat fruit & veg 5-a-day or more
- Drink less alcohol
- Be sunsmart (use sunscreen and shade)
- Eat less processed & red meat
- Eat a high fibre diet
- Be active
- Eat less salt

OTHER

- Minimise risk at work (such as asbestos)
- Minimise radiation
- Minimise certain infections (HIV, HBV, Hepatitis, Helicobacter pylori)
- Breastfeed if possible
- Minimise time spent on T.V.
Viruses cause 15-20% of all human cancers

But how?
How do viruses cause cancer?

1. Expression of viral oncogenes
2. Integrations that alter oncogenes/tumour suppressors or components of signal transduction pathways
3. Chronic activation of inflammatory response

= GENETIC INSTABILITY
How do viruses cause cancer?

1. **Expression of viral oncogenes**
2. **Integrations that alter oncogenes/tumour suppressors or components of signal transduction pathways**
3. **Chronic activation of inflammatory response**
1. Expression of viral oncogenes

- Transforming retroviruses
  - Carry oncogenes
  - Usually mutated
  - Expressed constitutively
  - Malignant transformation
  - Key member: RSV
- Discovered in 1911 by Peyton Rous at Rockefeller University, NYC
- Led to the concept of oncogenes
- Causes sarcoma in chickens
- Cell free extracts from chicken tumours caused tumours when injected into healthy chickens
- Reverse transcribes RNA genome into cDNA before integration into host DNA
- SRC gene is oncogenic – triggers uncontrolled growth in host cells
- Nobel Prize, 1966
How do viruses cause cancer?

1. Expression of viral oncogenes
2. Integrations that alter oncogenes/tumour suppressors or components of signal transduction pathways
3. Chronic activation of inflammatory response
2. Integrations

- Provirus
- gene X
- gene Y
- gene Z
- gene K
- gene L
- gene M
- gene A
- gene B
- gene C
- c-myc
- gene R
- gene S

no proliferative advantage

TRANSCRIPTION

myc mRNAs

TRANSLATION

UNCONTROLLED PROLIFERATION
Integrations - retroviruses

Proviruses integrate into cellular genome as a normal part of virus life cycle. This can bring about cell growth transformation if:

A. Integrated provirus activates adjacent cellular oncogene

B. Provirus carries a 'captured' cellular oncogene

C. Provirus-coded protein activates cellular genes
Integrations – DNA viruses

Viral DNA integration into cellular genome occurs only rarely and is not a normal part of the virus life cycle.

A. Integrated viral DNA permanently expresses 'early' viral genes.

B. Viral DNA integration destabilizes cellular genome and/or activates adjacent cellular genes.
How do viruses cause cancer?

1. Expression of viral oncogenes
2. Integrations that alter oncogenes/tumour suppressors or components of signal transduction pathways
3. Chronic activation of inflammatory response
3. Inflammation

- Primary immune response to viral infection
- Recruits inflammatory cells
- Drives inflammatory signalling and cytokines
- Induces cell proliferation
- Leads to oxidative DNA damage
- Inhibits DNA repair
- Inhibition of apoptosis
Oncogenic virus example 1: HPV

- Human papillomavirus
- dsDNA virus discovered in 1950s
- Associated with cervical cancer (& others)
- E6 and E7 oncogenic proteins
- Inhibits multiple pathways
- Alter DNA damage response pathways

White et al, Clin Micr Rev, 2014
HPV & cervical cancer

A. Transmission (via sexual contact) and infection of cervical epithelium.

B. Virus replication in cervical epithelium – papilloma.

C. Viral DNA integration and constitutive E6/E7 expression in rare papilloma cells

D. Accumulated genetic changes in such a cell leads to cancer
Oncogenic virus example 1: MCV

- Merkel Cell Polyomavirus
- dsDNA virus discovered in 2008
- Associated with >80% of Merkel cell carcinomas (rare, yet highly lethal)
- Mutated and truncated large T antigen
- Inhibits tumour suppressors, Rb and p53
- Alter DNA damage response pathways

White et al, Clin Micr Rev, 2014
The power of genomics

- Most knowledge around oncogenic viruses gathered in the pre-genomic era
- Advances in technology allow deeper and broader analysis

---

Tang et al, Nature Communications, 2013
Detailed genomic analysis

Tang et al, Nature Communications, 2013
Hallmarks of Cancer

Sustaining proliferative signaling

Evading growth suppressors

Avoiding immune destruction

Enabling replicative immortality

Tumor-promoting inflammation

Resisting cell death

Deregulating cellular energetics

Genome instability & mutation

Inducing angiogenesis

Activating invasion & metastasis

Hanahan and Weinberg, Cell, 2011
Summary

- Viral infection can alter almost all the “hallmarks of cancer”
- 3 major mechanisms
  - Possession of a viral oncogene
  - Integration & disruption of host genome
    - Direct, indirect, DNA, RNA, epigenome level
  - Chronic inflammation
- Genomics will change the landscape of oncogenic virus studies in the future