The origins of cancer: What’s in our genes & what isn’t?

Ashok Venkitaraman
Do genes ("nature") and environment ("nurture") affect disease susceptibility?
Genes and cancer

Our body comprises multiple organs, which work together to keep us alive & well.

Organs are made up of many different types of cells - each of us has over a trillion cells.

Cells in turn contain billions of molecules that work together to execute cellular functions.
Genes and cancer

Each of our cells has an ‘instruction book’ written in its DNA.

The book contains codes called genes, organized into our ‘genome’.

It helps make each of us what we are.
Genes and cancer

- $3 \times 10^{\Delta 9}$ DNA “letters” per genome
- Vast amounts of information being collected & stored
Gene mutations cause cancer

Faults (mutations) in DNA increase as normal cells progress towards becoming cancer cells.

This process - called ‘genome instability’ - is a universal feature of cancer cells.

It makes cancer cells behave badly ….
Gene mutations make cancer cells behave badly

Cancer cells behave in ways normal cells do not ..... They grow, spread and survive without paying attention to normal cues

Hanahan & Weinberg, 2011
But the origins of cancer are not purely genetic.
Cancer rates in migrants implicate the environment

Breast and stomach cancer rates amongst Japanese migrants to Hawaii quickly trends towards the rates in local populations (Kolonel et al., Nat Rev Cancer 2004)
Smoking and lung cancer

Doll and Hill reported in 1954 that smoking can increase the rate of lung cancer by >35-fold.

Decreased exposure is correlated with reduced risk.
How does smoking cause cancer?

Tobacco smoke contains cancer-causing chemicals, which modify our DNA to induce ‘faults’ (mutations), whose accumulation causes cancer.

Golemis et al., G&D 2018
Many infections or chemicals in our environment are capable of causing ‘faults’ in our DNA that may increase the risk of cancer

The IARC monographs list >1,000 such environmental agents, classified from Group 1 (highest risk) to Group 3 (lowest risk)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Group</th>
<th>Code</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helicobacter pylori (infection with)</td>
<td>1</td>
<td>61,100B</td>
<td>2012</td>
</tr>
<tr>
<td>Microcystis extracts</td>
<td>3</td>
<td>94</td>
<td>2010</td>
</tr>
<tr>
<td>Opisthorchis felineus (infection with)</td>
<td>3</td>
<td>61</td>
<td>1994</td>
</tr>
<tr>
<td>Opisthorchis viverrini (infection with)</td>
<td>1</td>
<td>61,100B</td>
<td>2012</td>
</tr>
<tr>
<td>Schistosoma haematobium (infection with)</td>
<td>1</td>
<td>61,100B</td>
<td>2012</td>
</tr>
<tr>
<td>Schistosoma japonicum (infection with)</td>
<td>2B</td>
<td>61</td>
<td>1994</td>
</tr>
<tr>
<td>Schistosoma mansoni (infection with)</td>
<td>3</td>
<td>61</td>
<td>1994</td>
</tr>
<tr>
<td>Acheson process, occupational exposure associated with</td>
<td>1</td>
<td>111</td>
<td>2017</td>
</tr>
<tr>
<td>Acid mists, strong inorganic</td>
<td>1</td>
<td>54,100F</td>
<td>2012</td>
</tr>
<tr>
<td>Acrylic fibres</td>
<td>3</td>
<td>19, Sup 7</td>
<td>1987</td>
</tr>
<tr>
<td>Acrylonitrile-butadiene-styrene copolymers</td>
<td>3</td>
<td>19, Sup 7</td>
<td>1987</td>
</tr>
<tr>
<td>Alcoholic beverages</td>
<td>1</td>
<td>44, 96, 100E</td>
<td>2012</td>
</tr>
</tbody>
</table>
Many environmental chemicals are capable of causing ‘faults’ in our DNA. Serena Nik-Zainal’s lab in our institute, the MRC Cancer Unit, has studied 79 different chemicals to identify the patterns of faults that they cause in our cells.

Kucab, Zou et al., Cell 2019
Twin studies help to separate genetic vs environmental origins of cancer

The Nordic Twin Study followed 80K identical and 120K non-identical twins for about 35 years.

The overall heritability of cancer was estimated to be ~33%.

Different cancers carried different genetic risks.

Mucci et al., JAMA 2016
Inherited BRCA mutations & early-onset cancer risk

- Mutations (‘faults’) in the breast cancer genes BRCA1 or BRCA2 cause a high risk of breast and other cancers
- Women who inherit these mutations have an ~70% risk of developing breast cancer, by age 80 yrs.
- Their cancers tend to occur earlier in life than usual.
Inherited ‘faults’ in several genes occur in many types of cancer

- Inherited ‘faults’ in genes linked to cancer occur in 8% of 10,389 cancers of 33 different types
- Such inherited faults occur more frequently in certain cancer types (e.g., ovarian cancers ~20%; pancreatic cancers ~15%)
- Faults affecting a few genes (BRCA2, PALB2, BRCA1) are common in several cancer types

Huang et al Cell (2018)
How do BRCA2 mutations increase the risk of cancer?

Carriers inherit a single copy of faulty BRCA2

The second BRCA2 copy is lost in certain cells...

..... causing cancer

What triggers the events that lead to cancer?  
Do they ‘just happen’?  
Or is there a trigger?
Does the environment affect cancer development in people who inherit faulty BRCA2?

Aldehydes are chemical found in our environment and made in small amounts in our bodies.

*Environmental sources* include traffic pollution, industrial processes & cosmetics.

*Our body’s cells* also normally make small quantities of aldehydes.
We don’t know yet, but there are interesting clues …..

- We find that aldehydes can eliminate BRCA2 in cells
- This disturbs normal cells to make them more ‘cancer-like’
- Cells which have one ‘faulty’ copy of BRCA2 are more sensitive to this effect

Tan et al., *Cell* (2017)
We don’t know yet, but there are interesting clues ..... Tan et al., Cell (2017)
From genes to environment ..... to bad ‘luck’ during cell division?

Tomasetti et al Science (2015)

Tomasetti et al Science (2017)
From genes to environment ….. to bad ‘luck’ during cell division?

- High number of TP53 pseudogenes
  - Hypersensitivity to stress
  - Apoptosis instead of senescence

Very large animals

- Novel tumour suppressor mechanisms

Cancer resistance

From Seluanov et al., Nat Rev Cancer 2018
Genes ("nature") and environment ("nurture") **together** affect disease susceptibility.
The Medical Research Council Cancer Unit

The mission of the MRC Cancer Unit is to **discover** the fundamental mechanisms underlying early steps in carcinogenesis, and to **exploit** this knowledge for early intervention in the clinic, using innovative enabling technologies.