Current concepts and trends in cancer genetics

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Overview

• Review of basic concepts in cancer genetics

• Description of current genome sequencing methods

• Interpretation of cancer genomes

• Applications of cancer genome sequencing in cancer therapy
Cancer is caused by mutation (somatic or germ line)

• Only ~10% of cancer cases are caused by inherited cancer predisposition syndromes (*p53*, *BRCA1/2*, *APC*, *NF1*, etc.)

• Remaining cancer incidence is due to somatically acquired mutations
Mutation happens...

DNA repair proteins

~186 DNA repair proteins

exposures to carcinogens

> 50,000 DNA damaging events per day in each cell
Somatic mutations accumulate in “normal” tissue with age.
Health consequences of elevated mutation rate

- Lifestyle choices
- Environmental exposures
- Genetic defects

DNA damage → incomplete DNA repair →

- Cancer
- Immune disorders
- Accelerated aging
- Neurological disorders
Health consequences of elevated mutation rate

- Lifestyle choices
- Environmental exposures
- Genetic defects

DNA damage → incomplete DNA repair

- Cancer
- Immune disorders
- Accelerated aging
- Neurological disorders

DNA repair → Mutation
Health consequences of elevated mutation rate

- Lifestyle choices
- Environmental exposures
- Genetic defects

DNA damage → incomplete DNA repair

- Cancer
- Immune disorders
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The evolution of cancer

- How many mutations are found in an average tumor?
- Which gene mutations cause cancer?
- Can this information be used to improve treatment?
Multi-step model of cancer

normal colonic crypts (20×)

early adenomatous crypt (20×)

OR

tubular adenoma precursor

head

stalk attaching head of polyp to wall of colon

large tubular adenoma (1×)

same tubular adenoma (20×)

villous adenoma precursor

villous adenoma (4×)

invasive carcinoma (20×)

liver metastases (4×)

Figure 11.7 The Biology of Cancer (© Garland Science 2014)
Many mutations and time are required to produce a tumor.

Figure 11.8a The Biology of Cancer (© Garland Science 2014)
What are “cancer drivers”?

**Tumor suppressor gene:**

- A gene whose partial or complete inactivation, occurring in either the germ line or the genome of a somatic cell, leads to an increased likelihood of cancer development.
- Such a gene that is responsible for constraining cell proliferation.

**Oncogene:**

- A cancer-inducing gene.
- A gene that can transform cells.

definitions taken from *The Biology of Cancer* (© Garland Science 2007)
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Next-Generation DNA sequencing
(Emulsion PCR method)

Next-Generation DNA sequencing
(solid-phase amplification method)

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The Cancer Genome Atlas (TCGA) is an integrated network of hundreds of researchers across the United States and Canada. The diagram below provides a description of TCGA components and an explanation of how TCGA works.

1. **Tissue Processing**
   - Cancer patients are asked to donate a portion of tumor tissue that has been removed as part of their cancer treatment along with a sample of normal tissue, usually blood. Tissue and fluid used for analysis are called biospecimens.
   - Biospecimen samples used for genomic research need to meet a stringent set of criteria so that the genetic material (DNA and RNA) removed from them can be used by advanced genomic analysis and sequencing technologies.
   - The TCGA Biospecimen Core Resources process samples to ensure they meet the TCGA biospecimen criteria and prepare them for analysis. Part of the process includes coding the biospecimens to remove any information that might connect a sample with a patient’s private information.

2. **Research and Discovery**
   - TCGA researchers analyze tumor and normal tissue from hundreds of patients for each cancer selected for study. This provides the statistical power needed to produce a complete genomic profile of each cancer, which is crucial to identifying those genomic changes that offer the greatest opportunities for therapeutic development.
   - TCGA Genome Characterization Centers analyze many of the genetic changes involved in cancer including how the genome is rearranged or how gene expression changes in tumors compared to normal cells.
   - High-throughput TCGA Genome Sequencing Centers identify the changes in DNA sequence associated with specific types of cancer. Newly developing sequencing technologies will be used to increase the scope of DNA sequencing efforts on TCGA samples.
   - Thousands of cancer and normal tissues will be analyzed by these characterization and sequencing platforms and the data integrated within and across different tumor types. The TCGA Genome Data Analysis Centers will provide new information-processing, analysis and visualization tools to the entire research community to facilitate broader use of TCGA data.

3. **Data Sharing**
   - The information that is generated by the TCGA Research Network is centrally managed at the TCGA Data Coordinating Center and entered into public databases as it becomes available, allowing scientists to continually access the information.
   - Scientists search, download and analyze datasets generated by the TCGA Research Network through the TCGA Data Portal. Essentially, the Data Portal contains the genetic “fingerprints” of specific cancer types.

4. **Community Research and Discovery**
   - TCGA’s comprehensive and robust data is enabling research that could not be possible without it. TCGA data will continue to have a multiplier effect on the scope and quality of research from the broader cancer community.
   - The ultimate goal of TCGA is to enable the cancer community to find new ways to better care for patients and significantly reduce the suffering and death due to cancer.

http://cancergenome.nih.gov/newsevents/multimedialibrary
TCGA RESULTS & FINDINGS

- Improved our understanding of the genomic underpinnings of cancer
- Revolutionized how cancer is classified
- Identified genomic characteristics of tumors that can be targeted with currently available therapies or used to help with drug development
- TCGA's identification of targetable genomic alterations in lung squamous cell carcinoma led to NCI's Lung-MAP Trial, which will treat patients based on the specific genomic changes in their tumor.

THE TEAM

The Genomic Data Commons (GDC) houses TCGA and other NCI-generated data sets for scientists to access from anywhere. The GDC also has many expanded capabilities that will allow researchers to answer more clinically relevant questions with increased ease.

WHAT'S NEXT?

*TCGA's analysis of stomach cancer revealed that it is not a single disease, but a disease composed of four subtypes, including a new subtype characterized by infection with Epstein-Barr virus.
The evolution of cancer

- How many mutations are found in an average tumor?
- Which gene mutations cause cancer?
- Can this information be used to improve treatment?
Drivers and passengers

- driver mutations cause cancer
- passenger mutations are only along for the ride

Are tumor genomes like this? ...or this?

manageable signal-to-noise ratio (i.e. fewer background mutations)

many more passengers than drivers (i.e. very high background)
Bad news...some tumors have thousands of mutations

What distinguishes a driver from a passenger mutation?

• mutation frequency in a tumor cohort
• gene size
• nature of gene mutations
  – are mutations clustered in a single region of the gene?
  – what is the frequency of the mutation class?
Mutation patterns vary by tissue

>200 cancer genes identified

Cancer genes mutated at a low rate in many tumor types

Cancer genes mutated at high rates in many tumor types

Cancer genes mutated at a high rate in one tumor type

Background gene mutations (i.e. not cancer genes)

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Genetic analysis has improved cancer therapy

FDA has approved ~100 drugs that target specific mutant proteins found in tumors

- Normal BRAF
- Cancerous BRAF V600E

Vemurafenib
- BRAF inhibitor
- Orally active

BRAF mutation in ~50% of melanoma cases
Genetic analysis has improved cancer therapy

FDA has approved ~100 drugs that target specific mutant proteins found in tumors.

38 y.o. male with BRAF-mutant melanoma
(A) prior to treatment
(B) after 15 weeks of vemurafenib treatment

Drug resistance in cancer therapy

38 y.o. male with BRAF-mutant melanoma
(a) prior to treatment
(b) after 15 weeks of vemurafenib treatment
(c) relapse after 23 weeks on vemurafenib

Wagle et al., J Clin Oncology. 2011.
Genetic heterogeneity in cancer

Goal:
- isolate many independent biopsies from a single patient
- perform genetic analysis on each biopsy
- determine the complexity of samples
Independent tumor biopsies show tremendous genetic heterogeneity.
A second patient shows same trend

A  Regional Distribution of Mutations

<table>
<thead>
<tr>
<th>Ubiquitous</th>
<th>Shared</th>
<th>Private</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td>...</td>
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</tbody>
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B  Phylogenetic Relationships of Tumor Regions

- **VHL**
- **PBRM1**
- **PTEN** (splice site)
- **SETD2** (frameshift)
- **SETD2** (missense)
- **PS3** (missense)
- **PTEN** (missense)

- **Ubiquitous**
- **Shared**
- **Private**
Bad news for targeted therapies

A) mTOR Staining

- Phospho-S6
- mTOR (wild type)
- mTOR (L2431P)

- Phospho-4EBP
- mTOR (wild type)
- mTOR (L2431P)
What information can be gathered from these figures?

**Patient 1**

- **Ubiquitous**
- **Shared primary**
- **Shared metastasis**
- **Private**

- **KDM5C** (missense and frameshift)
- **mTOR** (missense)

- **SETD2** (frameshift)
- **SETD2** (splice site)

**Patient 2**

- **VHL**
- **PBRM1**

- **PTEN** (splice site)
- **SETD2** (frameshift)

- **SETD2** (missense)
- **PS3** (missense)

Normal tissue
Tumor evolution

Initiating mutation
(1st driver mutation)

2nd driver mutation

3rd driver mutation

Clonal expansion
(fixes “passenger mutations”)

Clonal expansion
(fixes “passenger mutations”)

Clonal expansion
(fixes “passenger mutations”)

Tumor evolution within a patient

How can we treat this?
What do we know?

• Each patient’s tumor is unique and complex
• Cancer genomes do not share many mutations
• Complexity clouds our ability to understand key genetic events in cancer
• Experimental models of cancer are needed to test ideas
What do we need to know?

- How much of the genetic complexity is meaningful?
- Can we effectively target such a large number of mutated genes with specific drugs?
- Are there other therapeutic approaches to target cancer more broadly?
This is how the new immunotherapy for cancer works

1. Normal work of the immune system
T lymphocytes are the cells of the immune system that identify tumour cells and destroy them.

2. Camouflage of tumour cells
Some tumour cells arm themselves with a shield of molecules called PD-L1. Lymphocytes possess PD-1 receptors which, by bonding to these traps, destroy their capacity to attack.

3. Action of the new inhibitor drugs
The new drugs based on antibodies block PD-1 from the cells of the immune system and PD-L1 from tumour cells to prevent their fatal action.

4. Result of immunotherapy
Lymphocytes, once freed from their blindness by the drug, regain their defence potential. They recognise cancer and reduce it.

This treatment, although still in its experimental stage, has had preliminary results on lung, kidney and skin cancers.