Personalized Genomics of Cancer

02-223 Personalized Medicine: Understanding Your Own Genome
Fall 2014

Acknowledgement: Dr. Russell Schwarts for slides
“Old” View of Cancers
Old View of Treatment

• Target genetic features of cancer cells
  – Rapid proliferation
  – High susceptibility to DNA damage

• Not generally very selective
  – Most cells need to divide some of the time; some important ones need to divide rapidly
  – All cells susceptible to DNA damage to some degree
Why is Cancer Hard to Treat?

Courtesy KEGG PATHWAY database:
Changing Views of Cancer

• Genomic technologies have dramatically changed what questions we can ask
  – Availability of a whole reference genome
  – Ability to rapidly measure DNA/RNA content
  – Growing feasibility of rapidly resequencing whole genome

• The capabilities let us systematically ask what is changed in tumors relative to healthy cells
Tumor Subtypes

Gene Signatures of Subtypes

Subtypes and Prognosis

Genomic Diagnostics

Genomic Signatures are Now Part of Cancer Diagnosis and Treatment

• Many expression signatures now available for different tumor types
• Often available as standard assays for cancer patients (e.g., Oncotype DX signature for breast cancers)
• Can help guide prognosis and treatment of cancers
Why Do Cancers Sort Into Subtypes?

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Interaction Networks Revisited

Expression Subtype Reflects the Genetic Basis of the Tumor

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Tumor Progression Pathways

Carcinoma in situ
- E cadherin mutation

Invasive cancer
- Loss of DAP kinase

- Lobular breast cancer
- Low grade infiltrating ductal cancer
- Intermediate grade infiltrating ductal breast cancer
- High grade infiltrating ductal cancer

- 16q-
- p53 dysfunction
- Aneuploidy
- Her-2/neu amplification
- ras protein overexpression
- Rb loss?
Understanding Cancer Genetics Help Us Develop New Therapies

Examples of Targeted Therapeutics for Cancer

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Brand Name</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>traztuzumab</td>
<td>Herceptin</td>
<td>Her-2 positive breast cancer</td>
</tr>
<tr>
<td>imatinib mesylate</td>
<td>Gleevec</td>
<td>chronic myelinoid leukemia, gastrointestinal stromal tumors</td>
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<tr>
<td>bevacizumab</td>
<td>Avastin</td>
<td>metastatic colorectal cancer, non-small cell lung cancer, Her-2 negative breast cancer</td>
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<tr>
<td>cetuximab</td>
<td>Erbitux</td>
<td>colorectal cancer</td>
</tr>
<tr>
<td>gefitinib</td>
<td>Iressa</td>
<td>non-small-cell lung cancer</td>
</tr>
<tr>
<td>erlotinib</td>
<td>Tarceva</td>
<td>non-small-cell lung cancer, pancreatic cancer</td>
</tr>
</tbody>
</table>
From Targeted Therapy to Personalized Therapy

• Many patients do not fit neatly into a subtype and there are many variations within each one
• Drugs that help for a subtype in general do not help every patient in that subtype
• Many subtypes probably not yet recognized or too rare to be selectively targeted
• Every tumor is, to some degree, unique at the genetic level
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Dr. Wartman responded to a targeted therapeutic for FLT3-based kidney cancer and his cancer went into remission.

Wartman’s Experience is Not a Model for Most Patients (Yet)

- Sequencing still too slow and expensive for routine use
- Vast amounts of computing power required to process the data fast enough to put it in a usable form
- A team of experts needed to analyze and discuss the data to draw useful inferences from it
- But ... sequencing is getting cheaper, computers are getting faster, and computational biology is getting better at automating these inferences
Personalized Therapy in Routine Cancer Treatment: Hereditary Basis of Cancers
Bringing Personalized Therapy to Normal Treatment Practice

CHALLENGE: MANY MUTATIONS FOR COMMON SYMPTOMS
Example: TCGA Profiles of Breast Cancers

Refining Tumor Subtypes

Diversities of Mutations Can Contribute to Common Functional Outcomes

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CHALLENGE: TUMOR HETEROGENEITY
The Problem of Tumor Complexity

• The tumor genome varies from cell to cell: different cells have different combinations of mutations

• The tumor genome varies from day to day: tumors continue to evolve over time

• This has important implications for treatment: especially drug resistance
Challenges

• Sequence alignment and assembly can be significantly more challenging because of highly rearranged chromosomes and high variation across cancer genomes

• Somatic mutation calling is more challenging
  – the impurity of the sample
    • Normal genomes have allele copies of 0, 1, or 2
    • Cancer genomes can have allele copies of fractions of 0, 1, or 2
  – Most somatic mutations are rare

• Different cancer types have different rates of mutations. Mutator phenotype may or may not present.
Why Does It Matter?: Heterogeneity and Evolution

Characterizing Intra-tumor Genomic Heterogeneity at the Single-Cell Level

Tumor Phylogenetics

The State of the Art of Genomic Medicine for Cancer Therapy

The Good News

• Diagnostics and therapeutics based on tumor sub-types are now part of routine cancer treatment
• Many inherited mutations for tumor risk are known, some routinely used in treatment
• We have the knowledge to do much better for cancer treatment

The Bad News

• Truly personalized cancer treatment remains out of reach for most people; too costly and labor-intensive
• Tumor evolution is an unsolved problem; it is often only a matter of time before a tumor evolves to resist treatment
The Future of Cancer Therapy?

- Sequencing will soon be cheap enough to be routine, informatics advancing
  ➔ Could the Wartman story become the norm?

- Single-cell sequencing, better models of evolution may allow us stay one step ahead of resistance
  ➔ Cancer as a chronic but manageable illness?

- Still big challenges to solve; some of the hardest are computational