Reconstructing Human Tumor Histories By Comparing Genomes From Different Parts of the Same Cancer

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Somatic Evolution in the Clinic

• Widely Accepted That Tumors Evolve
• Many Different Possible Pathways
• Serial Observations Impractical
• A Patient “Suddenly” Has Cancer
• Clinical Questions (Patient Specific):
  --- How Did This Tumor Evolve?
  --- Do Different Evolutionary Histories Matter?
An Approach To Patient Specific Tumor Histories

• Coalescent Theory
• “Molecular Clocks”
• Topography

Number of Differences (“time” or PWD)

First Transformed Cell

Left Right

Time

Present

Past

tumor genomes
A Problem: The Evolution of Any Individual Human Cancer is Unknown

Older Parts More Diverse

Uniform Diversity
Colorectal Cancer: Adenocarcinoma
(small glands or populations
or neighborhoods of adjacent cells)
How To Sample Tumor Diversity?

EDTA Washout: Single Cancer Glands

Isolate DNA → PCR clock locus → clone PCR products into bacteria → sequence individual clones → calculate PWD (pairwise distance)
How To Sample Tumor Diversity?

Common Gland Ancestor

First Transformed Cell

Common Gland Ancestor

“young” cancer

gland age
tumor age
gland age

“older” cancer

tumor age
gland age
gland age

Time Or Diversity

start
Somatic Cell Molecular Clock

Problems:
--- Somatic Cell DNA Replication Fidelity Too High!

Potential Solution: Epigenetic Molecular Clock

5’ CGATCTGCATCGACTGCCGCG 3’
GCTAGACGTAGCTGACGGCGC

Substitute the 5’ to 3’ Order of Bases With the 5’ to 3’ Order of CpG DNA Methylation
Replication Clock

Molecular Clock: Information Passed From Cell to Cell

Epigenetic Fidelity is less than Genetic Fidelity

$10^{-9}$ versus $10^{-5}$
Human Colorectal Cancer

left side

right side

six cancer glands

five cancer glands

left side

right side
Different human cancers have different ages
Cancer Glands From Left and Right Sides Are Similar For The 12 Human CRCs

Glands Within A Cancer Have Similar Ages
Older Cancers Have “older” Glands

Within-gland pairwise distances for “younger” cancer are lower than for “older” cancer, and the distances between sides are higher for “older” cancer.

Transformed cell

First tumor side first

Right tumor side right

transformed cell

0 1 2 3 4 5

Pairwise Distance

“younger” cancer

“older” cancer

within gland

between sides

within gland

between sides
Simple Models of Tumor Growth

- BGN
- Cancer 2
- Cancer 12

Intragland PWD

First transformed cell

Glands have similar ages or PWDs
Molecular Clocks: Different "Speeds"

1) DNA CpG Methyla*on (Epigenetic)
2) Chromosomal Copy Number ("CIN")
3) Loss of Heterozygosity (LOH)
4) DNA Sequence Mutations

Fast

Slow

Challenge Is to Gather the Data and Then Interpret the Data

Illumina 660 SNP Microarray
Chromosomal Changes

LOH

5'  3'

......AGCTCGCA
TCTTCAAGCCT
ACCATTAAAT....

Left  Right

5'  3'

......AGCTCGCA
TCTTCAAGCCT
ACCATTAAAT....

5'  3'

......AGCTCGCA
TCTTCAAGCCT
ACCATTAAAT....

5'  3'

......AGCTCGCA
TCTTCAAGCCT
ACCATTAAAT....
An Approach To Patient Specific Tumor Histories

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Genomes Are “Historical” Documents (almost perfect copies of copies)

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