Genome Chaos

Creating New System Information to Drive Macroevolution

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Current framework

Somatic Mutation Theory

Out of control growth → Phenotype

Key gene mutations → Genotype

Stepwise evolution → Process

Accumulated cancer gene mutations are key drivers.
Cancer: new systems emergent from various constraints via evolution

Key shared phenotype: Phase Transition

- Normal cell phase
- Non-invasive phase
- Drug sensitive phase

- Transformed phase
- Invasive phase
- Drug resistant phase
Genome theory of Cancer Evolution

Systems replacement via macroevolution

Phase transition  Phenotype

Karyotype heterogeneity  Genotype

Genome chaos - Selecting  Mechanism

Two phased evolution  Process
Karyotype heterogeneity & non clonal chromosome aberrations (NCCAs)

They are not “noise” but transitional structures for creating new genomes for information survival.
Watch evolution in action experiments

DNA clones differ from karyotype clones

Normal cells

↓

Pre-immortal cells

↓

Phase transition

↓

Post-immortal cells

(in vitro immortalization model: Li-Fraumeni fibroblast)

↑

Non clonal

↑

Clonal
Two phased evolution

Macroevolution differs Microevolution + Time

Punctuated Evolution
Discontinuous macro-evolution

Darwinian evolution
Stepwise clonal evolution

Crisis

Normal growth
Slower and heterogenous growth with cell death
Selected stable genome
Stable growth with transformed features

Heng et al., JCP 2006
Phase transition is common for cancer

- Each run of evolution is achieved by different molecular pathways
- The evolutionary pattern unifies diverse molecular mechanisms of cancer

Karyotype heterogeneity is the common driver, but why?
Karyotype Coding

Karyotype organizes gene interactive network
Order of genes along chromosome is a new coding

Architecture is a key information

Gene codes “parts inheritance”
Karyotype codes “System inheritance”
Blueprint

Heng 2009, BioEssays
Heng et al, 2011, Genomics
Heng et al, 2013, Can Metastasis Rev
Karyotype defines transcriptome

Different successful karyotypes display different transcriptomes

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Stevens et al, 2014 IJC
Most animals and plants display unique karyotypes. How genes are arranged within the genome matters.

- Genes + topo = function. Species specific.
- Spatial is key information.
- Gene’s order matters.
- Karyotype rules gene.
- Karyotype and disease.

Sponges have 18,000 genes (immune- and neuro-), but no “designed” functions.

- Chromosome has 3D address; It impacts genes’ function; position effect.
- Hox gene cluster; Histone gene cluster; Synteny: conserved blocks of gene order.
- Aneuploidy restores gene-/- phenotype; Translocation brings gene’s new function.
- Chromosome changes are overwhelming. Better clinical prediction power.
Mechanism of preserving karyotype coding

The main function of sexual reproduction is to maintain the karyotype for species identity

- Maintaining gene coding
- Replication by A-T and G-C pairing
- Clone

Fact: Asexual organisms and cell populations are not clonal!

- Maintaining karyotype coding for sexual organisms
- Meiotic pairing to check gene order
- Fertilization and development eliminate altered karyotypes

Sexual reproduction = “Filter” to maintain “core” genome
The genome defines species, the genes modify some features

"The conclusion is surprising: the initial function of chromosome pairing was to limit, not enhance, recombination". Wilkins AS, Holliday R. Genetics. 2009
Cancer evolution: no constraint of sexual reproduction

The main function of sexual reproduction is to maintain the karyotype for species identity.

**Classical model**

Species A → Gradual population replacement → Species B

**Population phase transition model**

Emergent Karyotype → Reproductive partners with same karyotype

Mechanism of cancer: rapid and massive speciation by reorganizing genomes without constraint of sex.
Genome chaos: rapid massive macroevolution

Re-organizing karyotypes to create new information

Each runs of genome chaos leads to new karyotype
Chaotic genomes are responsible for phase transition
Drug induces chaotic genomes (structural/numerical)

Pattern of chaotic genomes in phase transition: populational view

Structural chaotic

Numerical chaotic
Causes: survival strategy under crisis via passing life-info

Consequences: creating new species with new genomes

The pattern of genome chaos is often predictable

Diverse stresses:
Massive death
chaos is active

Diverse forms of chaotic karyotypes: micronuclei, translocations, giant cells, chromosome fragmentation

Population growth for Survived cells (new karyotypes).
A key mechanism for generating cellular mass of cancer

Parental genome prior to phase transition

Chaotic genomes under macroevolution

Microevolution with cancer genes and epigenetics

Ideal stage for population control
Evo-stasis pattern dominates the history of life, but cancer system information is maintained by sex and development.

Cancer as a trade-off of dynamics for cellular and individual adaptation.

Devo separating Germline/Somatic cell

Sex filter Constraint Core genome

New species

Cellular species

Germline karyotype

Gene mutations can come and go

Epigenetics Are important for adaptation

Altered somatic genomes & genes

Generation 1

Generation 2

Generation 3

Long term evo-stability within species

Short term dynamics

Somatic genome

New Germline

Speciation

Control micro-Evo; Bob Gatenby’s Adaptive Therapy

Gene chaos; Jinsong Liu’s Giant Cell Life Cycle

Paul Davies’s atavism

Lee Hood, Azra Raza earlier diagnoses

Ken Pienta’s Hyper-speciation

Genome chaos; Jim Shapiro’s Natural Genetic Engineering

Long term evo-stability within species

Sex filter Constraint Core genome

Devo separating Germline/Somatic cell
Implications in cancer research/treatment

1. Two-phased evolution is the key for research/diagnosis/treatment
2. Avoiding induced genome chaos should reduce drug resistance
3. Maximal killing initially reduces cancer cells, but could harm patients by induced genome chaos. Cancer is a game of outliers

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A new genomic coding system?

What defines a systems?
How does karyotype, impact system inheritance?

Gene centric inheritance: “Gene-protein-Phenotype”
chromosomes are carrier of gene

1. Gene defined inheritance is limited ("Missing heritability")

2. Gene codes: Parts inheritance; how to make parts (protein)
New codes: System inheritance; how to organize genes’ interaction, the blueprint

New genomic coding: organize gene interactive network
Chromosome set is the highest genomic information