Cancer as Complex Adaptive System

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Central Themes in Cancer Biology

• Cancer as a multi-dimensional ecosystem involving complex interactions between cancer cells and host systems

• Genotoxic insults (DNA damage), mutations and genomic instability as drivers of initiation and progression

• Progressive evolution of genomic and phenotypic diversity (tumor subtypes and clonal heterogeneity)

• Tumor-progression as a dynamic process with adaptive evolution of tumor cell clones to diverse selection pressures (fitness)

• Clonal heterogeneity and phenotypic diversification posing formidable therapeutic challenges

Exposure to carcinogens
Invasion and Metastasis: the Deadly properties of cancer

- basal cell carcinoma
- glioblastoma
- lung
- colorectal
- breast
- prostate

Invasion Without Metastasis

Invasion and Metastasis
New Biological Insights Enabled by Technology:
Quintessential Example Is Cancer Complexity

• Cancer genome complexity revealed: Formidably complex catalog of genomic changes and molecular network disruptions
  – Networks are highly interactive and redundant

• Cancer evolution exposed: Continued accumulation of genomic alterations generating numerous clones and sub-clones with different genomic alterations and phenotypes (heterogeneity)
  – In a patient
    • Within a lesion
    • Between lesions
  – Between patients
  – Treatment-driven evolution (selection and fitness)
Panorama of Extravagant Genomic Alterations in Cancer

Mutations per megabase tumor DNA (3K megabases in human genome)

Average 10 per megabase for lung cancer and melanoma

Copy number alterations in solid tumors


From: G. Iyer et al. (2013) JCO 31, 3133
The Complexity of Gene, Chromosome, and Network Interactions
Complicated Systems
Versus
Complex Systems
The Biological Complexity of Cancer

• What is the difference between complicated and complex systems?
• What features of cancer make it a complex system?
• What is meant by “emergence” in complex systems?
• What are the implications of the complex behavior of cancer for diagnosis, treatment and prevention?
Complicated Systems:
Low Degrees of Design Freedom

- Behavior of components and the assembled system is predictable
- Knowledge of tolerance limits and likely failure points is possible
- Performance of the system is fixed and not capable of autonomous evolution
Failure Does Occur In Complicated Systems: When the Source of Failure is Identified, the outcome is predictable.
Characteristics Of A Complex Adaptive System (CAS)

CAS:

• Innumerable individual parts or agents
• No leader that coordinates the actions of the individual parts
  • System is “self-organizing”
  • System is stochastic (governed by chance)
  • Behavior is non-linear
• Individual parts generate (new) emergent patterns
  • Patterns form even though parts not “directed” to make a pattern
• If the elements of the system are altered, the system adapts or reacts
  • “Adaptive” = “Reactive to Change”
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Characteristics of Complex Systems

- Across types of systems, across scales, and thus across disciplines
  - Which exhibit common behaviors
  - Giving rise to a number of hierarchical levels
  - Dynamically interacting
  - Many components
  - Complex systems involve

A 'complex' system

Emergent behavior that cannot be simply inferred from the behavior of the components

- Emergence
- Hierarchies
- Control structures
- Self-organization
- Decomposability into subsystems
Emergence: The Hallmark of Complex Systems

• **New** properties emerge from the interactions of simpler units (molecules, cells, agents, people).

• An emergent property is a property that a complex system has but individual components do not have.

• Properties (behavior) of the whole system cannot be reliably predicted from knowledge of the properties of the simpler units.

  – “The whole is more than the sum of its parts”

• New and **unexpected** patterns of interactions between components can shift the system to a new state with very different properties (emergence).
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Emergent properties are those that arise through interactions among smaller parts that alone do not exhibit such properties.
Emergence: The Hallmark of Complex Systems

Levels Hierarchies

Emergent Properties.
Life itself is an emergent property
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A complex adaptive system is a "complex macroscopic collection" of relatively "similar and partially connected micro-structures" formed in order to adapt to the changing environment and increase its survivability as a macro-structure.

Examples:
• The Global Macroeconomic Network
• The Stock Market
• Political Parties
• Terrorist Networks
• War
• The Brain
• The Immune System
• CANCER
Cancer: Emergent Properties and System State Shifts

- Escape From Controls for Normal Tissue Architecture
- Genome Instability and Emergence of Clonal Variants
- Evasion of Detection/Destruction by Host Immune System
- Use of Host Systems by the Tumor to Promote Progression
- Invasion and Metastasis
- Emergence of Drug-Resistant Clones
Complex Adaptive Systems Are Ubiquitous in Nature

The Behavior of All Biological Systems Is Defined by Darwinian Evolution
Charles Darwin and Species Evolution
Evolution and Diversification of Tumor Clones and Subclones

One beneficial mutation at a time (simple linear clonal succession)

Multiple beneficial mutations simultaneously (compete with one another or co-exist)
Localized ecological systems are known to **shift** abruptly and irreversibly from one **state** to another when they are forced across critical thresholds.

A change in ecosystem conditions can result in an abrupt shift in the state of the ecosystem, such as a change in population or community composition.

In cancer it may be hypoxia-induced or therapy-induced metabolic state shifts.
Evolution and Selection Pressures

- Systemic regulators:
  - Hormones, growth factors
  - Immune/inflammatory response cells and cytokines

- Local regulators:
  - Oxygen/metabolism/nutrients
  - Cell-cell and cell-stroma/matrix
  - Space

- Architectural constraints:
  - Physical compartments
  - Basement membranes
  - Restricted niches

Exposures/lifestyle (aetiology)

Constitutive genetics
Evolution and Diversification of Tumor Clones and Subclones

Selective pressures (vertical lines) allow some mutant clones to expand but pushes others to become extinct or dormant
- Shaded boxes = tissue ecosystems
- Smaller boxes (dotted lines) = niches within an ecosystem
- Rx = Therapy (a powerful selective pressure)
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Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones with Progression Over Time
Understanding the Disruption of Molecular Information Networks in Disease

Encoded information and expression

Patterns of information flow within signaling networks

Stable networks and information fidelity (health)

Dysregulated networks and altered information patterns (disease)
Understanding State Shifts and Triggers of Emergence in Complex Adaptive Systems

- Network Topology
  - black swans
  - dislocations
  - tipping points
  - irreversible cascades

- State Shifts
  - phase shifts
  - perturbations
  - inflection points
  - unintended consequences
  - critical thresholds
  - bifurcations
  - trigger points

Emergence (E)

$E_1, E_2, \ldots, E_n$
Phylogenetics Profiles of Intratumoral Clonal Heterogeneity in 11 Lung Cancers:

DIFFERENT CLONES

- Trunk (Blue)
- Branch (Green)
- Private (Red)
Mapping Tumor Heterogeneity
Tumor Cell Heterogeneity: The Greatest Obstacle to Curative Cancer Therapy
“Malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations (such as epigenomic changes)

Disturbing implications for therapeutic ‘cure’ and development of new Rx
Intra-tumoral Genetic Heterogeneity:
Multiple Regions of Primary Kidney Cancer and 3 Different Metastases
How many molecular subtypes? Implications of the unique tumor principle in personalized medicine

Shuji Ogino, Charles S Fuchs & Edward Giovannucci
Pages 621-628 | Published online: 09 Jan 2014

Essentially, each tumor possesses its own unique characteristics in terms of molecular make-up, tumor microenvironment and interactomes within and between neoplastic and host cells. Starting from the
Complex Systems in a Complex World

New Scientific Strategies of Prediction and Prevention Required!!
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