BIO 302:
MARCH 4 & 6, 2014

WEEK 8 LECTURE 2:
CANCER AS A COMPLEX ADAPTIVE SYSTEM

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Central Themes in Cancer Biology

- cancer as multi-dimensional ecosystem involving complex interactions between cancer cells and host systems
- genotoxic insult(s), mutations and genomic instability (drivers)
- progressive evolution of genomic and phenotypic diversity (tumor subtypes and clonal heterogeneity)
- tumor-progression is a dynamic process with adaptive evolution of tumor cell clones to diverse selection pressures (fitness)
- clonal heterogeneity and phenotypic diversification pose formidable therapeutic challenges
Central Themes in Cancer Biology

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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 Versus Complex Systems
Complicated Systems: Low Degrees of Design Freedom

- behavior of components and the assembled whole system is predictable
- proactive awareness of tolerance limits and likely failure points
- performance of the system is fixed and not capable of autonomous evolution
Failure Does Occur In Complicated Systems But Was a Predictable Outcome Once the Source of Failure Was Identified

- Faulty O-Ring
- Ageing Support Structure
- Wrong Glide Path
Emergence: The Hallmark of Complex Systems

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

- Properties (behavior) of the whole system cannot be reliably predicted from knowledge of the properties of the simpler isolated 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).
Anthropogenic Complex Adaptive Systems: Emergence, Unanticipated Consequences and Cascading Shift to New ‘State Space’

- Internet, Social Media and New Communication Networks
- Internet Hacking and Fraud
- Financial Systems and Triggered Fragility
- Economic Collapse
- Transportation and Supply Chain Logistics
- Anti-terror Defenses
- Political Instability
- Emergence of Antibiotic Resistance
The Ubiquity of Complex Adaptive Systems in Nature: High Degrees of Design Freedom

- Earth Systems
- Eco-Systems
- Food Webs and Predator: Prey Relationships
- Coordinated Community Behavior
- Host-Pathogen Interactions
- Physiological Regulatory Networks
- Genome Regulatory Networks
- Signaling Network Dysregulation in Disease
Cancer as a Complex Adaptive System With Emergent Properties

- the full spectrum of a tumor’s behavior in any individual and the accompanying clinical risk cannot be predicted from knowledge of the properties of the multiple components involved in tumor initiation and progression
  - environment and nature of the initiating genotoxic insult
  - tumor progression
  - metastasis
  - host responses
  - treatment outcomes
the full spectrum of a tumor’s behavior and the accompanying clinical risk cannot be predicted from knowledge of the properties of the multiple components involved in tumor progression

unknown but likely different patterns of environmental exposure and genotoxic insult as triggers of tumor initiation
  - different individuals
  - different tissues
Cancer as a Complex Adaptive System With Emergent Properties

- emergence of multiple tumor cell clones with different properties in the primary tumor and metastases in same patient and in different patients
- patterns of host cell responses to the primary tumor, metastases in different body organs plus differences between patients
- impact of different treatment regimens on the tumor and host components
Cancer as a Complex Adaptive System: Emergent Phenomena and Tumor Progression (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
Darwinian Evolution
• selection by variation
• adaptation
• evolvability
• “fitness” for selection pressures operating in a particular environment

“The future of humanity and microbes will likely evolve as episodes of our wits versus their genes”

Dr. Joshua Lederberg,
Nobel Laureate
Science (2000) 6, 427-30
Microbe: Host Interactions
A Complex Ecosystem and Evolutionary Co-dynamics

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Emergence and Adaptive Evolution of Tumor Clones With Different Properties During Tumor Progression

Dynamic Heterogeneity
Emergence of Tumor Cell Clones with Different Genotypes and Phenotypes During Tumor Progression

- chemical
- virus
- hormone
- nutrition

Adapted from A. Barker and K. Buetow
The Quest for Effective Cancer Treatments: Fundamental Challenges

- lengthy time for full progression to metastatic disease after tumor initiation

- general lack of presymptomatic diagnostic methods

- 1 cm³ lesion (early detection threshold) = $10^9$ tumor cells
  - typically asymptomatic at this stage

- highly heterogenous clonal composition even at initial detection
The Highly Heterogenous Clonal Composition of Cancers Even At Initial Detection

- 1 cm³ lesion (early detection threshold) = $10^9$ tumor cells
  - typically asymptomatic at this stage
- mutation frequency of $10^{-2}/10^{-3}$ per tumor cell generation = prospect of $10^7$ to $10^6$ potential variant clones present at first diagnosis
- clones present at initial detection reflect a long (years) interaction between tumor and host and a dynamic process of clonal elimination and emergence of new clones
- ‘fitness’ of surviving clones reflects their evasion of destruction by host immune system and escape from tissue-specific growth controls
Clonal Expansion and Phenotypic Diversification (Heterogeneity) with Tumor Progression

- Initiating mutation
- Second mutation
  - ~10^6 cells
  - Increased mutation rate
  - Multiple independent mutations

- First clonal expansion
- Second clonal expansion
- Multiple parallel clonal expansions
“Dot Means a New Form”
Charles Darwin Sketch of Speciation (Early 1850s)

DAR 205.5.184r. Syndics of the Cambridge Library
Timing of mutational events

- ‘Early events’ present in clones in both primary tumor and metastases

- Private mutations (unique to individual patients or individual metastatic lesions in same patient) likely have occurred late(r) in progression
Phylogenetic Tree of Clonal Branching in Two Glioma Patients

From: B. E. Johnson et al. (2014) Science 343, 189
red= shared between initial and recurrent lesions;
green= not shared between initial and recurrent lesions
Branched Evolution and Phenotypic Diversification of Tumor Clones and Subclones
The Clonal Dynamics of Malignant Tumors

- frequent finding of presence of a dominant clone (>50% tumor cells) and multiple subclones at minor frequencies in the primary tumor

- clonal diversity at metastatic sites typically lower than in the primary tumor
  - analogous to an evolutionary bottleneck
  - clonal selection by the ‘fitness’ requirements needed to achieve all steps in the metastatic cascade
The Selection Bottleneck (Selection Sweep) in Metastatic Dissemination

- dominant clone and spectrum of lower frequency clones
- zonal localization of individual clones
- selection bottleneck for ‘fitness’ to complete multiple steps needed to successfully metastasize (note: often not the dominant clone the primary tumor)
- selection for clonal phenotypes with preferred fitness for growth in specific organs?
- further clonal diversification within individual metastases
Cancer as a Complex Adaptive System

- major gaps in knowledge about the triggers of ‘emergence’ of increasingly dangerous tumor cell phenotypes during cancer progression
  - immune evasion, metastasis, Rx resistance
Genome Instability

- progressive accumulation of mutations and other chromosomal abnormalities
- do major shifts in tumor aggressiveness depend on ‘macromutations’ rather than gradual accumulation of mutations?
Macromutation in Cancer

Genome Doubling

- faulty cell division

Copy Number Variations

- duplication of chromosome regions (shown)
- deletions and translocations (not shown)
Macromutations in Cancer

- gain and loss of entire chromosomes
- genome doubling due to faulty cell division
- indels (insertions/deletions): copy number variants
  - sections of chromosomes duplicated, deleted or moved (translocated)
- major structural changes but must still be compatible with cell survival
- potential driver for major changes in tumor aggressiveness and clinical risk?
  - metastasis?, recurrence?
Macromutations in Cancer

- genome doubling as a ‘buffer’ to tolerate macromutations
- back up copy of every chromosome
- “healthy” (unaltered) chromosome sustains expression ‘housekeeping genes’
- “aberrant” chromosome drives new behavior created by altered molecular signaling arising from the macromutation
- copy number variants can affect the function of a large set of genes
What is the unit of selection in cancer progression?
Stem Cells and the Growth Dynamics of Normal Tissues

- embryogenesis
- organ regeneration (limited in mammals)
- post-natal cell turnover in different body tissues/organs
- tissue repair
asymmetric division of self-renewing stem cell

stem cell

unlimited replicative capacity for self-renewal

1st daughter

限

2nd daughter

transit-amplifying cell (precursor for differentiated cell progeny)

limited replicative capacity
Replicative Self-Renewal

stem cells: unlimited but highly controlled division potential

asymmetric division sustains stem cell population and pool of progenitor and differentiation committed cells with limited number of cell divisions (terminal differentiation)
Replicative Self-Renewal

- loss of control circuits that limit the number of cell divisions as hallmark feature of cancer

- does every cancer cell have potential to generate clones with metastatic ability and unlimited replicative capacity or are only a specific population of stem-like cancer cells (CSCs) endowed with this capability?
Cancer Originates and is Maintained by Mutations in Tissue Stem Cells

Asymmetric Division of Cancer Stem Cell

Self-renewing Cancer Stem Cell (minor component of tumor mass)

Progenitor and Differentiated Progeny Tumor Cells From Mutated Stem Cell (tumor bulk)
All Initiated Cells Have Potential for Unchecked Replication and Progression to Malignancy

Tissue Specific Stem Cell

Progenitor and Differentiated (P/D) Progeny

Cancer Initiating Mutation(s) in P/D Cell

Tumor Progression and Eventual Emergence of Metastatic Clones ( )
The Cell-of-Origin in Cancer

- balance of evidence shifting to cancer stem cell (CSC) model
Expression of ‘Differentiated Features’ in Tumors

<table>
<thead>
<tr>
<th>Benign Tumors</th>
<th>Malignant Tumors</th>
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<td></td>
<td><strong>Low Grade/High Differentiation</strong></td>
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![Image of Benign Tumors](image1.png)

![Image of Malignant Tumors](image2.png)

![Image of Malignant Tumors](image3.png)
normal SCs and CSCs appear to exhibit greater radio- and chemo-resistance

- slower reproductive cycling versus progenitor/differentiated lineages
- faster DNA repair and suppression of apoptotic pathways
- higher expression of free radical scavenging pathways to limit damage by reactive oxygen species (ROS)
- greater hypoxic survival via activation of HIF1α and HIF2α pathways and shift to glycolytic metabolism (versus oxidative phosphorylation via Krebs cycle)
what determines the proportional fractions of self-renewing stem cells and progenitor and differentiated lineages?

- in different tumor types?
- in different patients with same tumor subtype?
- in metastases versus the primary tumor?
- in response to Rx?
Cancer Stem Cells (CSCs) Markers

- **CD 133+**
  - glioma, colon cancer
- **CD444, CD24**
  - breast cancer
- **ALDH+**
  - pancreatic cancer cells
- **suggested role for activation of Hedgehog and Hippo pathways**
Why Understanding the Altered Patterns of Molecular Signaling Networks and Clonal Diversification in Different Cancers and Cancer Subtypes is Fundamental to More Rational Approaches to Diagnosis and Treatment
Emergence of Drug Resistance to Targeted Therapy in Melanoma

Initial Rx-Response to Targeted Rx

Rx-Resistance via Alternate Molecular Signaling Pathway (Network Redundancy)

Circumvention of Rx-Resistance Requires Multi-site Blockade of Connected Signaling Pathways

B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)
Implications of Different Cell-of-Origin Models for Cancer on Therapeutic Strategies

• can only stem cells seed metastases with subsequent expansion of the tumor cell population in metastases by proliferation of their P/D progeny?

• do all drug-resistance (Dr) phenotypes arise in stem cells and subsequent expression in their P/D progeny?
Evolution of Drug-Resistant Phenotypes ($r_1, r_2, r_3$) in Cancer Stem Cells and Sustained Expression in Their Progenitor/Differentiated Progeny

Mixture of stem cells and P/D progeny with Rx susceptibility and stem cells with different Rx resistance mutations and expression of same resistance phenotypes in their P/D progeny.
Evolution of Drug-Resistance (D') Phenotypes in P/D Cell Compartment Independent of Stem Cell Phenotype

- Evolution of resistance phenotype to Rx
- D' P/D Cells will continue to generate tumor bulk for the lifetime of their proliferation limit
The Stem Cell to Progenitor/Differentiated Fate Pathway is Not One Way

- drug-resistant (D\textsuperscript{r}) progenitor (P) cells reacquire stem cell like properties with result that next wave of P/D progeny will carry same D\textsuperscript{r} phenotype

- does Rx selection pressure increase the prospect of reacquisition of stem cell properties by P/D cells?
The Stem Cell to Progenitor/Differentiation Fate Pathway is Not One Way: Implications for Drug-Resistance

<table>
<thead>
<tr>
<th>Stem</th>
<th>S</th>
<th>S</th>
<th>S</th>
<th>S^r</th>
<th>S^r</th>
</tr>
</thead>
<tbody>
<tr>
<td>P/D</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>progeny replication</td>
<td></td>
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<tr>
<td>proliferation limit?</td>
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</table>

- acquired D^r in P/D (most likely P) cell (■)
- reacquisition of S phenotype by D^r-P cell
- new S cell now carries D^r phenotype (■)
- D^r phenotype now expressed in all P/D progeny from this S^r cell
The Need for a Better Conceptual Understanding of the Fundamental Differences in the Behavior and Clinical Risk Posed by Different Tumors and Tumor Subtypes
The Need for a Better Conceptual Understanding of the Biology of Cancer Progression and Clinical Risk

- indolent disease likely to cause little to no harm
- consequential tumors with major clinical risk (metastasis) if not treated
- drivers of progressive metastatic disease (macrometastatic disease)
- mechanisms of tumor dormancy (micrometastatic disease) and recurrent disease
The Need for a Better Conceptual Understanding of the Biology of Cancer Progression

- Cancer still perceived (and treated) as a diagnosis with lethal consequences if left untreated.
- Clear evidence of indolent tumors and use of screening programs has resulted in increased incidence.
  - Certain breast and prostate subtypes as prototype examples.
- Emerging view that the term ‘cancer’ should be reserved for tumor subtypes with reasonable likelihood of lethal progression if untreated.
  - “Consequential tumors”
  - Mitigate the “over diagnosis-over treatment” dilemma.
Intrinsic Differences in Tumor Biology and Risk
L. J. Esserman et al. (2013) JAMA 310, 797

diagnostic separation of indolent and consequential
tumor subtypes arising in the same organ

- breast, prostate, lung and bronchus
- screening increases overall incidence of tumor
detection (all subtypes)
- earlier detection reduces mortality from
consequential lesions
- increased detection of indolent lesions
predisposes to overtreatment
- need for new biomarkers and diagnostic tests
to reliably distinguish indolent (watchful
waiting) from consequential lesions with
metastatic potential (require Rx intervention)
Intrinsic Differences in Tumor Biology and Risk

consequential cancers but largely slow growing

- colon, cervix
- screening reduces incidence of lethal tumors due to early detection and removal of precursor lesions

consequential cancers characterized by a fraction of highly aggressive tumors and difficulty of identification by screening

- thyroid
- melanoma
## Change in Incidence and Mortality of Cancers (1975-2010) (Surveillance, Epidemiology and End Results Data)

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<thead>
<tr>
<th></th>
<th>Incidence per 100K</th>
<th>Mortality per 100K</th>
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<tbody>
<tr>
<td></td>
<td>1975</td>
<td>2010</td>
</tr>
<tr>
<td>Breast(^c)</td>
<td>105.07</td>
<td>126.02</td>
</tr>
<tr>
<td>Prostate</td>
<td>94</td>
<td>145.12</td>
</tr>
<tr>
<td>Lung and bronchus(^d)</td>
<td>52.26</td>
<td>56.68</td>
</tr>
<tr>
<td>Colon</td>
<td>41.35</td>
<td>28.72</td>
</tr>
<tr>
<td>Cervical</td>
<td>14.79</td>
<td>6.71</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4.85</td>
<td>13.83</td>
</tr>
<tr>
<td>Melanoma</td>
<td>7.89</td>
<td>23.57</td>
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</tbody>
</table>

**Notes:**
- **Over-diagnosis/over treatment of indolent lesions:**
  - Breast
  - Prostate
- **Consequential slow growing tumors:**
  - Lung and bronchus
  - Colon
- **Screening expands incidence of indolent lesions but limited impact on aggressive subset of tumors:**
  - Thyroid
  - Melanoma

Adapted From: L. Esserman et al. (2013) JAMA 310, 798
Cancer as a Complex Adaptive System

Mutation, Genomic Instability and Clonal Diversification

Heterogeneous Clonal Phenotypes

Robustness

Adaptability

Clonal Fitness

Evolvability

Host-and Rx-Mediated Selection

Increasing Scale of Perturbations in Molecular Signaling Networks and Increased Probability of Metastasis and Drug Resistance
Tumor Cell Heterogeneity and Core Challenges in Cancer Diagnosis and Treatment

- improved prediction of how molecular signaling networks are altered and most likely “escape” pathways that would confer drug resistance/immune evasion
- new minimally invasive methods for longitudinal monitoring of clonal dynamics with tumor progression
- more agile therapeutic regimens to reflect changing clonal dynamics and earlier detection of emergence of drug-resistant clones

confronting the complexity of clonal heterogeneity and metastatic disease
Implications of Cancer as a Complex Adaptive System for the Development of More Effective Diagnostics and Treatment

**Weeks 11 and 14**

- current treatment practices and limitations
- confronting the tumor cell heterogeneity problem
- emerging treatment strategies and the particular promise of immunotherapy
- the time, cost and complexity of development of new diagnostics and therapies to achieve FDA approval and marketing