Cancer as a Complex Adaptive System: cancer progression, evolutionary dynamics and implications for treatment

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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 to Promote Progression
- Invasion and Metastasis
- Emergence of Drug-Resistant Clones
Invasion and Metastasis: The Start of the Deadly Phase of Cancer Progression

basal cell carcinoma

Invasion Without Metastasis

glioblastoma

colorectal

lung

breast

Invasion and Metastasis

prostate
Central Themes in Cancer Biology

- cancer as a multi-dimensional ecosystem involving complex interactions between cancer cells and host systems
- genotoxic insult(s), mutations and genomic instability as drivers of initiation and progression
- 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
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 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
- Complicated System
- Complicated System
- Complicated System + Complexity (Human Error)
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)
The Ubiquity of Complex Adaptive Systems in Nature:

- Host-Pathogen Interactions
- Physiological Regulatory Networks
- Genome Regulatory Networks
- Signaling Network Dysregulation in Disease
The Ubiquity of Complex Adaptive Systems in Nature:

The Behavior of All Biological Systems is Defined by Darwinian Evolution
Darwinian Evolution

- selection by variation
- adaptation
- evolvability
- “fitness” for selection pressures operating in a particular environment
Evolution and Phenotypic Diversification of Tumor Clones and Subclones

- **Initiating mutation**
- **First clonal expansion**
- **Second mutation**
- **Second clonal expansion**
- **Multiple independent mutations**
- **Dynamic clonal diversification**
Cancer as a Complex Adaptive System:
The Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones During Progression
Understanding the Disruption of Molecular Information Networks in Disease

encoded information and expression as cell-specific signaling networks

patterns of information flow within signaling networks

stable networks and information fidelity (health)

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

- Black Swans
- dislocations
- tipping points
- irreversible cascades

- phase shifts
- perturbations
- inflection points
- unintended consequences

- critical thresholds
- bifurcations
- trigger points

Emergence ($E$)
Wagner Parsimony Profiling of Intratumoral Clonal Heterogeneity in 11 Lung Adenocarcinomas and Different Trunk (Blue), Branch (Green) and Private (Red) Branches

From: J. Zhang et al. (2014) Science 346, 256
Tumor Cell Heterogeneity: The Greatest Obstacle to Curative Cancer Therapy
The Extravagant Landscape of Genomic Alterations in Cancer (Cell 2012, 150, 1107 and 1121)

- “malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for therapeutic ‘cure’ and development of new Rx
Intratumor Genetic Heterogeneity in Multiple Regions of Primary Clear Cell Tumor and Three Metastases (Perinephric and Chest Wall) in RCC

From: M. Gerlinger et al. (2012) NEJM 366, 883
The Principal Challenge in Cancer Rx Therapy

The Co-existence of Multiple Tumor Cell Clones with Varied Susceptibility to Different-Rx
Molecular Profiling and Classification of Subtypes of NSCLC

Tumor Cell Heterogeneity: The Omnipresent and Greatest Challenge in Cancer Therapy
Tumor Cell Heterogeneity:
The Omnipresent and Greatest Challenge in Cancer Therapy
The Problem and The Challenge

- how to hit multiple tumor clones?
- how to hit multiple tumor clones at multiple anatomic sites of metastatic disease?
- how to hit each new variant clone that may emerge as an escape variant driven by the selection pressure of treatment?
Design of Cancer Treatments to Hit Multiple Targets

- design a single drug that hits multiple clones and multiple signaling pathways
  - pharmacological promiscuity
  - very low probability of technical success
Design of Cancer Treatments to Hit Multiple Targets

- multi-drug combinations
  - patient tolerance
  - cost
- high probability that Rx-resistant variants will eventually emerge
- Rx as selection pressure to generate Rx-resistant ‘escape’ clones
Targeted Therapeutics and Cancer

Molecular Subtyping and RX Targets

Initial Rx-Response to Targeted Rx

Rx-Resistance via Redundant Molecular Pathways

B = 15 weeks Rx (Zelboraf®)

C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)
‘Compensatory’ Pathways in Molecular Signaling Networks and Evolution of Drug Resistance

Linkage (Connections) Between Different Signaling Pathways Offers a Major By-Pass Mechanism for Cancer Cells to Develop Rx Resistance
Redundancy and Robustness in Molecular Signaling Networks: The Biological Foundation of Rx Resistance
The Urgent Need for New Diagnostic Tests and Molecular Profiling Tools for Improved Monitoring of Tumor Progression

From ‘Static Snap Shot’ at Initial Diagnosis to Dynamic Monitoring of Clonal Population Changes
Tumor Profiling and Adjustment of Treatment Selection to Reflect Changes in Clonal Composition

- initial diagnosis (‘static snapshot’)

- longitudinal profiling during treatment for earlier detection of emergence of drug-resistant clones

- more agile shifts in Rx regimen to reflect changing clonal dynamics driven by Rx selection pressure(s)
Anticipation-Based Chemotherapy in CLL

Fine Needle Aspiration (FNA) Biopsy

Minimally-Invasive Profiling
(Blood/Other Body Fluids)
Detection of Tumor-Associated Biomarkers in Blood: ‘The Liquid Biopsy’

- cell-free tumor nucleic acids
  - DNA, miRNAs
- circulating tumor cells (CTC)
- exosomes
Flying Blind: “One-Size-Fits All” Rx-Guidelines Ignore New Knowledge of Cancer Subtypes and Clonal Dynamics in Tumor Progression
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly
Confronting the Clinical, Economic and Human Toll of Cancer

595,000
Knowing When to Stop!

“Insanity is doing the same thing over and over again and expecting a different result.”

Albert Einstein
Performance Comparison for New Anti-Cancer Drugs Approved 2002-2014 for Top Ten Pharmaceutical Companies

Gains in Progression-Free Survival (PFS) and Overall Survival (OS) for 71 Drugs Approved by the FDA From 2002 to 2014 for Metastatic and/or Advanced and/or Refractory Solid Tumors

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PFS median 2.5 months

OS median 2.1 months

From: T. Fojo et al. (2014) JAMA Otolaryngology–Head & Neck Surgery 140, 1225
Recognition of the Need for New Approaches to Cancer Treatment

- current clinical strategies for treatment have not kept pace with advances in understanding the biology of cancer

- cancer is a complex adaptive system with dynamic properties shaped by Darwinian Evolution
  - variation (clonal diversity)
  - adaptation and evolvability (selection pressures)
  - immunoevasion and Rx-resistance (fitness)
Cancer Treatment Challenges

Chemotherapy
- lack of specificity
- impact on replicating normal cells (gut, b. marrow, hair follicles)

Targeted Agents
- highly specific for altered molecular targets in cancer cells
- lack of efficacy against target-negative clones

Drug Resistance
- intrinsic (pre-existing before Rx begins)
- acquired (resistant clones selected by Rx regimen)
The Urgent Imperative to Develop New Treatments to Circumvent Clonal Heterogeneity

- harnessing the cognate (detection) and destruction (killing) capabilities of the body’s immune system

- therapeutic targeting of neoantigens expressed on tumor cells
  - passive immunotherapy (designed antibodies)
  - active immunotherapy (activation of immune functions)
Passive Immunotherapy With Anti-tumor Antibodies
Passive Immunotherapy
With Anti-tumor Antibodies

- direct destruction of tumor cells with or without “Rx warhead”
- tag tumor cells for destruction by immune cells
- block host tissue stroma signaling pathways that promote tumor proliferation (anti-angiogenesis Mabs)
- restricted physical access to target tumor cells
- antigen-deletion clones escape destruction
- how to develop Mabs against the diverse neoantigens expressed by tumor cells (heterogeneity)
Immunoevasion by Tumor Cells

- “stealthy” tumor cell strategies that reduce detection and/or killing by body’s immune defenses
- avoiding detection
  - loss or masking of abnormal tumor cell surface proteins recognized by antibodies, NK cells and/or killer T lymphocytes
- suppression of the host immune system
  - tumor signaling to activate regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) that suppress action of anti-tumor killer T cells
Setting the Immune System Free to Combat Cancer
The Promise of Immune Checkpoint Modulator Therapy in Cancer Therapy

Pembrolizumab and Therapy of Metastatic Melanoma in President J. Carter

Saturation TV Advertising
Activation of Anti-tumor Immune Functions

Relentless Emergence of New Tumor Cell Clones During Tumor Progression and Immune Evasion versus Activation of Host T Lymphocyte Clones to Kill (Neo)Antigen-Specific Tumor Clones

Clone Wars
Recognition of Neoantigens (NA) by Cytotoxic (Killer) T Cells

- NA-1
- NA-2
- NA-3
- NA-4
- $N_{A}$

clones

Cytotoxic T cells
The Promise of Immunotherapy: Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Restoration of Effective Immune Surveillance

- **Rx-resistant clones/tumor neoantigens**
- **Cytotoxic T cells**

**Rx drugs**

1. **Rx_1**
2. **Rx_2**
3. **Rx_3**
4. **Rx_4**
5. **Rx_5**

**Targeted drugs**

- **NA_1**
- **NA_2**
- **NA_3**
- **NA_4**
- **NA_5**

- **Rx refractory disease**

**Adaptive evolution of immune response and expanded cytotoxic T cell responses**
Cancer Immunotherapy

Activating receptors
- CD40L
- OX40
- 4-1BB (CD137)
- CD27
- CD28
- TCR
- TCR

Inhibitory receptors
- CTLA-4
- CT6
- PD-1
- TIM3
- LAG3

Agonist
- Dacetylumab
- Chi Lob 7/4
- CP-870893

Antagonist
- Lucatumumab
- Ipilimumab
- Tremelimumab
- αPD-1
- Nivolumab
- Pembrolizumab
- Pidilizumab
- AMP-224
- αPD-L1
- Avelumab (MSB0010718C)
- MED14736
- MEDL3280A
- BMS-936559

Agonistic antibodies
- MED16469
- Urelumab (BMS-663513)
- PF-05082566
- Varilumab (CDX-1127)
Why Are Some Cancer Types More Responsive to Immunotherapy?

**More Responsive**
- melanoma
- NSCLC
- bladder
- renal
- head and neck

**Less Responsive**
- pancreatic
- colorectal
- ovarian
Immunogenic Versus Non-Immunogenic Tumor Microenvironments

**Immunogenic**
- ‘hot’
- ‘inflamed’
- ‘stimulatory’
- high mutagenic burden
- high tumor neoantigen expression

**Non-Immunogenic**
- ‘cold’
- ‘non-inflamed’
- ‘silent’
- low mutagenic burden
- low tumor neoantigen expression
Estimates of Likelihood of Neoantigen Expression Based on Somatic Mutation Prevalence in Different Tumor Types

Molecular ‘Smoking Signature’ in NSCLC and PFS in Patients Treated with Pembrolizumab

From: N.A. Rizvi et al. (2016) Science 348, 124
Immunotherapeutic Strategies to Enhance Immune Responses to Patient-Specific Tumor Neoantigens

**Immune Checkpoint Modulation**
- Induce tumor cell destruction
- Provide checkpoint blockade

**Cancer Neoantigen Vaccines**
- Identify potential neoantigens
- Create synthetic vaccine (RNA, DNA, peptide)
- Provide in combination with adjuvant and checkpoint blockade

**Adoptive Cell Therapy TILs, TCRs, CARs**
- Identify potential neoantigens
- Induce or expand neoantigen specific T cells
- Provide in combination checkpoint blockade

Cancer Vaccines

- far greater technical challenge than most antimicrobial vaccines
- antigenic variation in different tumor cell clones plus inter-patient variation (personalized vaccines)
- how to identify the best combination of antigens as vaccine candidates
- high probability of antigen-negative/deletion variants and tumor relapse
- analogy with the still unsuccessful quest for a HIV vaccine
  - same problem: massive antigenic heterogeneity due to rapid evolution of new viral quasi-species
Activated (Immune) Cell Therapy (ACT) for Cancer

- capture, expand and re-infuse unmodified tumor-infiltrating lymphocytes (TIL)

- genetic engineering of killer lymphocytes with new T cell receptors (TCRs) to enhance tumor cell detection and killing
Engineering Killer T Cells for Cancer Therapy

- Killer T cells harvested from cancer patients
- Harvested cells genetically engineered in vitro to express T cell receptor(s) (TCRs) or chimeric antigen receptors (CARs) that recognize tumor antigen(s)
  - TCR/CAR genes delivered by viral vectors
  - TCRs must be genetically matched to the patient's immune type
- Challenge of creating TCR/CARs for diverse neoantigens
- Cost and complexity of ‘individualized’ therapy
Is Widespread Adoption of Immunotherapy Economically Feasible?

- direct Rx cost
- indirect care cost
- escalating cost of combination regimens (> $200K)
- extravagant cost of cell-based therapies ($500K - $1.5 million)
- complex clinical management challenges and compatibility with community oncology services
The Future Debate on Cancer

Demographics of an Aging Society and Increased Cancer Incidence

Cost of Care

Complex Clinical, Scientific, Economic, Ethical and Legal Issues
Genetic Testing Helps Oncologists Target Tumors and Tailor Treatments

- AML
- An 18 month journey to remission
- 3 approved drugs, 2 investigational drugs
- 2 stem cell transplants
- $4 million dollars

Evan Johnson sits on a terrace at the Mayo Clinic Hospital, Methodist Campus in Rochester, Minn. during the summer of 2014.

From: Winslow, R. (2016) Cancer Treatment's New Direction. WSJ
Summary and Key Points
• cancer as a complex adaptive system

• clonal evolutionary dynamics as a complex interplay between tumor (evasion) and host (detection/destruction) activities

• the evolution of clonal heterogeneity is the core problem in curative cancer therapy
Aspirations for Improved Cancer Diagnosis and Treatment

- maximize the efficacy and safety of Rx interventions against advanced (metastatic) disease
  - circumventing variability in tumor cell clones to the selected Rx regimen (overcoming the heterogeneity problem)
  - dynamic monitoring of changing clonal dynamics during treatment for faster detection of drug-resistant clones and more agile, anticipatory shifts in Rx regimen
Cancer Rx: Ugly Realities

- in the majority of cancers the efficacy of single therapies is either short-lived or completely ineffective

- mutations that confer Rx resistance may pre-exist prior to treatment (intrinsic resistance) or arise as de novo mutations conferring selective survival during treatment (acquired resistance)
Cancer Treatment

- how to design new strategies to hit multiple clones and every new clonal variant that emerges
- the promise of immunotherapy
  - leveraging the detection and destruction capabilities of the host immune system
  - reactivation of immune system following suppression by tumor
  - highly promising early results but long term evaluation needed to assess risk of relapse due to immuno-evasive clones
  - value of new combinations of drug and immunotherapies?