Cancer as a Complex Adaptive System: Cancer Progression, Evolutionary Dynamics and Implications for Treatment

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Confronting the Clinical, Economic and Human Toll of Cancer

- New Diagnoses: 1.2 million/year
- Deaths: 595,000 (2016)
The Complex Biology of Cancer Progression and Treatment Resistance

- 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

Glioblastoma

Invasion Without Metastasis

Lung

Breast

Colorectal

Prostate

Invasion and Metastasis
Cancer: A Complex Ecosystem of Tumor and Host Dynamics

- Tumor
- Host immune response
- Tumor microenvironment
Cancer: A Complex Ecosystem of Tumor and Host Dynamics

- Tumor
- Immune response
- Microenvironment
- Microbiome
- \( R_x \)
Cancer as a Complex Adaptive System
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
Aging Support Structure
Wrong Glide Path

Complicated System
Complicated System
Complicated System + Introduced Complexity (Human Error)
Complex (Adaptive) Systems: Exhibit Different Behaviors Created by Different Patterns of Interactions Between the Components of the System

- weather/climate
- stock markets
- internet/DOSA/hacks
- geopolitical/national security
- epidemics/pandemics
- disease pathogenesis
Evolvability and Emergence: The Hallmarks 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)
Medical Progress: From Superstitions to Symptoms to Signatures
Precision Medicine and Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection
Precision Medicine: 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)
The Behavior of All Complex Biological Systems is Defined by Darwinian Evolution
Darwinian Evolution

- selection by variation
- adaptation
- evolvability
- “fitness” for selection pressures operating in a particular environment
Darwinian Evolution

- selection by variation
- adaptation to selection pressures in a particular environment
- evolvability
- "fitness" for selection pressures in a particular environment
3E’s: The Interplay Between Cancer and the Body’s Defense Mechanisms

- elimination
- equilibrium
- escape
3E’s: The Interplay Between Cancer and the Body’s Defense Mechanisms

- elimination (detection, surveillance and destruction)
- equilibrium (cancer cells present, but contained)
- escape (breakout and evasion of destruction by body’s immune system)
Mapping Tumor Heterogeneity: Zonal Variation
“malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations

disturbing implications for therapeutic ‘cure’ and development of new $R_x$
Intratumor Genetic Heterogeneity in Multiple Regions of Primary Clear Cell Tumor and Three Metastases (Perinephric and Chest Wall) in RCC
Charles Darwin’s Sketch of Speciation (1837)
What Makes Cancer So Dangerous and Difficult to Treat

Dynamic Heterogeneity

Emergence and Adaptive Evolution of Tumor Clones With Different Properties During Tumor Progression
Evolution and Phenotypic Diversification of Tumor Clones and Subclones
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
Wagner Parsimony Profiling of Intratumoral Clonal Heterogeneity in 11 Lung Adenocarcinomas and Different Trunk (Blue), Branch (Green) and Private (Red) Branches
Cancer as a Complex Adaptive System With Emergent Properties

- unknown but different patterns of environmental exposure and genotoxic insults as triggers of tumor initiation and progression
  - different individuals
  - different tissues
  - different patterns of mutations generate different clonal phenotypes (heterogeneity)
Heterogeneity: The Ubiquitous Challenge in Cancer Diagnosis and Treatment

- (epi)genetic and phenotypic changes in tumors arising in different cell types
  - inter-patient heterogeneity
  - intra- and inter-lesional heterogeneity in the same patient
  - effect of $R_x$ on clonal composition
- profiling heterogeneity
  - clinical presentation and progression
  - response to $R_x$
  - cellular heterogeneity (multiple clones)
  - molecular network heterogeneity (different signaling circuits in different clones)
Understanding Emergent State Shifts in Molecular Signaling Networks and Identification of Triggers of $R_x$-Resistance ($R$)

- Dynamic molecular signaling network topologies
- New network topologies to bypass $R_x$-vulnerable pathways

Emergence ($E$)

- Intrinsic resistance (pre-exist prior to $R_x$)
- Acquired resistance ($R_x$ as selection pressure)
Targeted Therapeutics and the Omnipresent Problem of $R_x$ Failure Due to Emergence of Drug Resistance Clones

Molecular Subtyping and $R_x$ Targets

Initial $R_x$ - Response to Targeted $R_x$

$R_x$ - Resistance via Redundant Molecular Pathways

A

B = 15 weeks $R_x$ (vemurafenib)

C = 23 weeks $R_x$ and emergence of $\text{MEK1}^{C121S}$ mutant

Cancer as a Complex Adaptive System: The Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones During Progression
The Principal Challenge in Cancer $R_x$ Therapy

The Co-existence of Multiple Tumor Cell Clones with Varied Susceptibility to Different-$R_x$
The Biological Complexity of Cancer and the Design of Treatment Strategies

- successful surgical removal of primary tumor assumed (except brain tumors)

- targeting metastatic disease and circumventing $R_x$ resistance
  - subclinical disease with evidence probability of metastatic spread (neoadjuvant and adjuvant $R_x$)
  - advanced disease with clinically evident metastases
  - minimal residual disease and tumor dormancy (long term reoccurrence)
Three Generations of Cancer Therapeutics

**cytotoxic agents ("chemo")**
- no selectivity for cancer cells versus dividing normal cells (gut, bone marrow, hair follicles)

**targeted agents**
- $R_x$ designed to inhibit one or a few molecular targets/pathways altered in cancer cells
- molecular profiling to ID patients with relevant $R_x$ targets

**immunotherapy**
- (re) activation of body’s immune defenses to detect and destroy cancer cells
Flying Blind: Historical “One-Size-Fits All” $R_x$ Approaches to Cancer Therapy
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly

Molecular Profiling and Classification of Subtypes of NSCLC

Challenges in Cancer Therapy

- molecular classification of cancer subtypes with defined molecular alterations
  - how to select right $R_x$ for right patient

- alterations in multiple molecular targets and pathways
  - how to design rational combination therapies

- ongoing clonal diversification with tumor progression and effect of $R_x$ on clonal evolution
  - how to destroy multiple clones and/or stop clonal evolvability

- selective targeting of cancer cell multiplication versus protection of cell division and multiplication needed for production of normal cells (gut, bone marrow, hair)
  - how to minimize adverse events on normal cells
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 $R_x$-resistant variants will eventually emerge
- $R_x$ as selection pressure to generate $R_x$-resistant ‘escape’ clones
  - direct drug effect to cause mutations and new resistant clones
  - $R_x$ elimination of ‘dominate’ clones allows pre-existing ‘minor’ clones to prosper
‘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 $R_x$ Resistance
Redundancy and Robustness in Molecular Signaling Networks: The Biological Foundation of $R_x$ Resistance
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

From: T. Fojo et al. (2014) JAMA Otolaryngology–Head & Neck Surgery 140, 1225
Knowing When to Stop!

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

- Albert Einstein
The Therapeutic Challenge of Circumvention of Tumor cell Heterogeneity

- moving from classical ‘chemo’ and newer targeted agents to devise new ways to attack every clone
- harnessing the cognate (detection) and destruction (killing) capabilities of the body’s immune system
- therapeutic targeting of neoantigens expressed on tumor cells
  - passive immunotherapy (designer antibodies)
  - active immunotherapy (activation of immune functions)
Passive Immunotherapy With Antibodies
Antibody-Drug Conjugates for Cancer Therapy

A. Beck et al. (2017) Nature Reviews 16, 315
Monoclonal Antibodies (Mabs) Immunotherapy for Cancer

- direct destruction of tumor cells with or without “Rx warhead”
- tagging tumor cells for destruction by immune cells
- blocking tumor cell signaling pathways to halt proliferation (anti-EGFR Mabs)
- blocking host tissue stroma signaling pathways that promote tumor proliferation (anti-angiogenesis Mabs)
Antibody Therapy in Cancer

- intrinsic limitations
- Mab or bi-specific Mabs target only one of the many neoantigens expressed by different clones
- high probability or Mab-resistant clones emerging in similar fashion to resistance to targeted anti-cancer drugs
Immunoevasion by Tumor Cells

● “stealthy” tumor cell strategies
  – 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
Balancing The Body’s Immune Response

- autoimmunity
- chronic inflammation
- life-threatening activation:
  - sepsis
  - organ failure

- excessive activation
- excessive suppression

- optimum defense

- HIV
- cancer
- radiation
- corticosteroids
- aging
- predisposition to infections
Setting the Immune System Free to Combat Cancer
Host Immune-Tumor Interactions

Clone Wars

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
Therapeutic Strategies for Circumvention of Clonal Diversity in Malignant Tumors: Single Target Drugs (Rx) versus Immunotherapeutics (Irx)
Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Restoration of Effective Immune Surveillance

Tumor clones

- $Rx_1$
- $Rx_2$
- $Rx_3$
- $Rx_4$
- $Rx_5$

Rx-resistant clones/
Rx refractory disease

Tumor neoantigens

- $NA_1$
- $NA_2$
- $NA_3$
- $NA_4$
- $NA_5$

Cytotoxic T cells

- $NA_n1$
- $NA_n2$

adaptive evolution of immune response and expanded cytotoxic T cell responses
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**
- Identify potential neoantigens
- Induce or expand neoantigen specific T cells
- Provide in combination checkpoint blockade

Immune Checkpoint Inhibitors in Cancer Treatment

From: September 2016 biopharmadealmakers.nature.com
Immune Checkpoint Inhibitors in Cancer Treatment

CTLA4 inhibitors

- **Ipilimumab**
  - Brand name: Yervoy
  - Developing company: Bristol-Myers Squibb
  - FDA-approved indications: unresectable or metastatic melanoma; adjuvant therapy for stage 3 melanoma

PD1 inhibitors

- **Nivolumab**
  - Brand name: Opdivo
  - Developing company: Bristol-Myers Squibb
  - FDA-approved indications: unresectable or metastatic melanoma, metastatic NSCLC, advanced RCC, Hodgkin lymphoma

- **Tremelimumab**
  - Brand name: N/A
  - Developing company: MedImmune, the biologics arm of AstraZeneca
  - FDA-approved indications: none yet; in phase 3 trials

- **Pembrolizumab**
  - Brand name: Keytruda
  - Developing company: Merck & Co.*
  - FDA-approved indications: unresectable or metastatic melanoma, metastatic NSCLC, recurrent or metastatic HNSCC

PDL1 inhibitors

- **Atezolizumab**
  - Brand name: Tecentriq
  - Developing company: Genentech/Roche
  - FDA-approved indications: urothelial carcinoma

- **Durvalumab**
  - Brand name: N/A
  - Developing company: MedImmune, the biologics arm of AstraZeneca
  - FDA-approved indications: none yet; in phase 3 trials

- **Avelumab**
  - Brand name: N/A
  - Developing companies: Merck KGaA and Pfizer
  - FDA-approved indications: none yet; in phase 3 trials

From: September 2016 biopharmadealmakers.nature.com
Why Are Some Cancer Types More Responsive to Immunotherapy?

More Responsive
- melanoma
- NSCLC
- bladder
- renal
- head and neck
- colorectal (MSI-high)

Less Responsive
- pancreatic
- colorectal (MSI-low)
- 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
Immunotherapy for Cancer

- far greater technical challenge than most antimicrobial vaccines
- antigenic variation in different tumor cell clones plus inter-patient variation
- 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 quasispecies
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 patients 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
Cancer Treatment’s New Direction: Genetic Testing and Tailored Treatments

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

From: Winslow, R. (2016) Cancer Treatment's New Direction. WSJ
Summary and Key Points
- cancer as a complex adaptive system
- understanding clonal evolution during tumor progression and treatment
- 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 effective therapy
Understanding the Complex Ecosystem of Constantly Growing Tumor and Host Interactions

- Lineage and subtype
- Clonal heterogeneity
- Mutagen burden
- Neoantigen profile

- Complex non-immune cell contributions to suppressive environment
- Localization of immune cells/soluble mediators and impact of $R_x$
Cancer As a Complex Adaptive System

- cancer as multi-component, multi-dimensional ecosystem involving complex interactions between cancer cells and host systems over extended time periods
- genotoxic insult(s), mutations and genomic instability as drivers of cancer initiation and progression
- relentless evolution of genomic and phenotypic diversity (tumor subtypes and clonal heterogeneity)
- adaptive evolution of tumor cell clones to diverse selection pressures (fitness)
- clonal heterogeneity and phenotypic diversification pose formidable therapeutic challenges
in the majority of cancers the efficacy of $R_x$ therapies (except immunotherapies) is either short-lived or completely ineffective

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

mutations are typically present in multiple pathways

intrinsic and/or acquired mutations in non-targeted pathways can enable ‘by-pass’ signaling circuits that ensure tumor cell survival and ever-broadening resistance $R_x$ spectrum
Aspirations for Improved Cancer Treatment

- how to maximize the efficacy and safety of therapeutic interventions against advanced (metastatic) disease
  - circumventing variability in tumor cell clones to the selected $R_x$ 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 $R_x$ regimen
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 immunoevasion clones
  – value of new combinations of drug and immunotherapies?
  – affordability?
How Much Is a Miracle Worth?
The Future Landscape for Cancer Care

Demographics of an Aging Society and A Major Expansion in Cancer Cases

Defining Treatment Value: Cost, Quality-of-Life and Outcomes

Complex Clinical, Scientific, Economic, Ethical and Legal Issues

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