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 in USA

Deaths: 595,000 (2017)
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
Hallmarks of Cancer

- Self-sufficiency in growth signal
- Insensitivity to anti-growth signals
- Limitless replicative potential
- Tissue invasion & metastasis
- DNA damage stress
- Mitotic stress
- Oxidative stress
- Metabolic stress
- Proteotoxic stress
- Sustained angiogenesis
- Evading apoptosis
- Evading immune surveillance
Invasion and Metastasis: The Start of the Deadly Phase of Cancer Progression

- Basal cell carcinoma
- Glioblastoma
- Lung
- Breast
- Colorectal
- Prostate

Invasion Without Metastasis

Invasion and Metastasis
Cancer as a Complex Adaptive System
Cancer: A Complex Ecosystem of Tumor and Host Dynamics

- Tumor
- Host immune response
- Tumor microenvironment
Cancer: A Complex Ecosystem of Tumor, Host Dynamics and the Effect of Treatment

- Tumor
- Host immune response
- Microbiome
- Tumor microenvironment
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
Dynamic Complex (Adaptive) Systems: Exhibit Behaviors Created by Constantly Changing Patterns of Interactions Between the Components of the System

- weather/climate
- stock markets
- geopolitical/national security
- predator-prey relationships
- epidemics/pandemics
- disease pathogenesis
Evolvability and Emergence: The Hallmarks of Complex Systems

• new properties emerge from the interactions of simpler units (molecules, cells, organs, organisms)

• 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 Path to Precision Oncology:

Superstitions

Symptoms

Common sites and symptoms of Cancer metastasis

- **Brain**
  - Headaches
  - Seizures
  - Vertigo

- **Respiratory**
  - Cough
  - Hemoptysis
  - Dyspnea

- **Lymph nodes**
  - Lymphadenopathy

- **Liver**
  - Hepatomegaly
  - Jaundice

- **Skeletal**
  - Pain
  - Fractures
  - Spinal cord compression

(Molecular) Signatures
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)**
Understanding Emergent State Shifts in Molecular Signaling Networks and Identification of Triggers of $R_x$-Resistance ($R_x$)

- 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)
Cancer as a Complex Adaptive System

The Behavior of All Complex Biological Systems is Defined by Darwinian Evolution
“It is not the strongest of the species that survives, not the most intelligent, but most responsive to change.”
Darwinian Evolution

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

- selection by variation
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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)
What Makes Cancer So Dangerous and Difficult to Treat

Adaption, Evolvability and Dynamic Heterogeneity

Emergence and Adaptive Evolution of Tumor Clones With Different Properties During Tumor Progression
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 \( R_x \)
Genetic and Functional Drivers of Different Large B Cell Lymphomas

From: A. Reddy et al. (2017) Cell 171, 481
Evolution and Phenotypic Diversification of Tumor Clones and Subclones
Mapping the Dynamics of Clonal Evolution in the Progression of Malignant Tumors: Clonal Branching

- 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 later in progression
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
Lineage Trees and Clonal Diversification in Tumor Progression

- normal DNA replication error rates $10^{-6}$ per cell/generation
- tumor DNA replication error rates $10^{-2}$ per cell/generation
Cancer as a Complex Adaptive System: The Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones During Progression
Clonal 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
The Biological Complexity of Cancer and the Design of Treatment Strategies

- successful surgical removal of primary before metastatic spread tumor (except malignant brain tumors)

- targeting metastatic disease and circumventing $R_x$ resistance
  - subclinical disease with evidence of 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
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

B = 15 weeks $R_x$ (vemurafenib)

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

Darwinian Evolution and Selection of Resistant Phenotypes

- **antibiotics**
- **antivirals**
- **antimalarials**
- **insecticides**
- **herbicides**
- **pesticides**
The Principal Challenge in Cancer $R_x$ Therapy

The Co-existence of Multiple Tumor Cell Clones with Varied Susceptibility to Different-$R_x$
Flying Blind:
Historical “One-Size-Fits All” $R_x$ Approaches to Cancer Therapy
Molecular Profiling and Classification of Subtypes of NSCLC

Distribution of Kinase Fusions Across Primary Tumor Sites and Rationale for Use of Mutation Specific $R_x$ in Fusion –Positive Patients

Molecular Profiling of Cancer

Adapted from: M. Cieślak and A. M. Chinnaiyan (2018) Nature Reviews Genetics 19, 93
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 versus specificity
  - very low probability of technical success
‘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
Understanding Emergent State Shifts in Molecular Signaling Networks and Identification of Triggers of $R_x$-Resistance ($R$)

- **Emergence ($E$)**
  - dynamic molecular signaling network topologies
  - new network topologies to bypass $R_x$-vulnerable pathways

- Intrinsic resistance (pre-exist prior to $R_x$)
- Acquired resistance ($R_x$ as selection pressure)

$R^1, R^2, \ldots, R^n$
Mapping Molecular Signaling Pathways and Networks in Tumor Progression and Treatment
Mapping Molecular Signaling Pathways and Networks in Tumor Progression and Treatment
Redundancy and Robustness in Molecular Signaling Networks: The Biological Foundation of $R_x$ Resistance
Design of Cancer Treatments to Hit Multiple Targets

- multi-drug combinations
  - patient tolerance of side effects
  - cost
- high probability that $R_x$-resistant variants will eventually emerge
- $R_x$ acts as a selection pressure to generate $R_x$-resistant ‘escape’ clones
  - direct drug effect to cause mutations and new resistant clones (acquired resistance)
  - $R_x$ elimination of ‘dominant’ clones allows pre-existing ‘minor’ clones to prosper (intrinsic resistance)
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 “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)
Antibody-Drug Conjugates for Cancer Therapy

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

- direct destruction of tumor cells with or without \( R_x \) 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) or suppress anti-tumor immune defenses (immune checkpoint inhibitors)
Antibody Therapy in Cancer by Targeting Tumor-Specific Neoantigens

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

- 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
Balancing The Body’s Immune Response

- Excessive activation
- Excessive suppression

Optimum defense

Autoimmunity
Chronic inflammation
Life-threatening activation:
- Sepsis
- Organ failure
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
The Immune System and Host Defense

- recognition of diverse ‘non-self entities
  - infectious agents, parasites, cancer
- ‘rapid on’ (and memory of past encounters)
- ‘switch off’ when the threat is eliminated
- without efficient down-regulation (“off”) unchecked
  activation of immune system is dangerous
  - acute overdrive: sepsis and shock
  - chronic overdrive: inflammation, autoimmunity,
    increased cancer risk, neurodegeneration
Immune Checkpoint Controls

health

- preventing uncontrolled activation of immune system

cancer

- cancer cells send molecular signals to switch off immune system
- cancer cells ‘hijack’ host tissue cells and other immune cells (Tregs, MDSCs) to switch off immune system and inhibit infiltration of killer T cells into the tumor
Immunoevasion by Tumor Cells

- 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
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)

- **targeted drugs**
  - $Rx_1$
  - $Rx_2$
  - $Rx_3$
  - $Rx_4$
  - $Rx_5$

- **immunotherapeutics**
  - Cytotoxic T cells
Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Restoration of Effective Immune Surveillance

- **Tumor clones**: $Rx_1$, $Rx_2$, $Rx_3$, $Rx_4$, $Rx_5$
- **Tumor neoantigens**: $NA_1$, $NA_2$, $NA_3$, $NA_4$, $NA_5$
- **Cytotoxic T cells**: $NA_{n1}$, $NA_{n2}$

- **Rx-resistant clones/ Rx refractory disease**

- **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

Adoptive Cell Therapy TILs, TCRs, CARs

Immune Checkpoint Inhibitors in Cancer Treatment

Antibodies to CTLA4

Antibody to PDL-1 or PD-1
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

- **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
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’

**Non-Immunogenic**
- ‘cold’
- ‘non-inflamed’
- ‘silent’

- high mutagenic burden
- high tumor neoantigen expression
- low mutagenic burden
- low tumor neoantigen expression
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
Realizing The Promise of Cancer Immunotherapy

- wide variation in $R_x$ response rates
  - only 20 - 40% positive responses in the most responsive tumors
- lack of diagnostic tests to predict responder vs. non-responder patients
- will I/O combinations increase response rates?
- cost
The Ethics of Hype and Hope
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
Understanding the Complex Ecosystem of Constantly Changing Tumor and Host Interactions

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

- Localization of immune cells/soluble mediators and impact of $R_x$

- Balance of stimulatory and suppressive factors
Cancer As a Complex Adaptive System

- cancer as multi-component, 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) to escape destruction by body’s immune defense and $R_x$
- clonal heterogeneity and phenotypic diversification pose formidable challenges for successful treatment
Cancer $R_x$: Ugly Realities

- 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 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
  - mobilization (reactivation) of body’s immune defenses to detect and destroy all clones
Realizing The Promise of Cancer Immunotherapy

- wide variation in $R_x$ response rates
  - only 20 - 40% positive responses in the most responsive tumors
- lack of diagnostic tests to predict responder vs. non-responder patients
- will I/O combinations increase response rates?
- cost
The Future Landscape for Cancer Care

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

Complex Clinical, Scientific, Economic, Ethical and Legal Issues