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

(2017): New Cases 1.68 million; Deaths: 600,920

The Demographics of an Ageing Society: Projected 20% Increase in Incidence of 2020 and 30% by 2030
The Complex Biology of Cancer Progression and Treatment Resistance

Escape From Controls for Normal Tissue Architecture

Genome Instability and Emergence of Different Clones

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

Invasion Without Metastasis

- basal cell carcinoma
- glioblastoma

Invasion and Metastasis

- lung
- breast
- colorectal
- prostate
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
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)
Cancer: A Complex Ecosystem of Tumor and Host Dynamics
Cancer: A Complex Ecosystem of Tumor, Host Dynamics and the Effect of Treatment

- Tumor
- Host immune response
- Microbiome
- Treatment ($R_x$)
- Tumor microenvironment
The Path to Precision Oncology:

Superstitions

Symptoms

(Molecular) Signatures

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 Profiling and Classification of Subtypes of NSCLC

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 Molecular Signaling Networks (Circuit Diagrams) and Identification of Targets for Rx Action and How Rx Resistance Emerges

molecular signaling network topologies in health

altered network topologies in disease

Progressive Perturbation and Dysregulation

Clinical Disease and Progression
Cancer as a Complex Adaptive System

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

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

- variation
- selection
- adaptation
- evolvability

"fitness" for selection pressures operating in a particular environment
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 the body’s immune system)
Dynamic Tumor-Host Interactions in Cancer

- **immune elimination**
- **subclinical disease**
- **immune equilibration**
- **clinical disease (primary tumor)**
- **immune escape**
- **(sub)clonal diversification and therapeutic resistance**
- **metastatic disease**
- **increasing tumor burden**
What Makes Cancer So Dangerous and Difficult to Treat?

Dynamic Heterogeneity: Variation, Adaption, & Evolvability

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 Rx
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 (trunk)
  - private mutations (unique to individual patients or individual metastatic lesions in same patient) have occurred later in progression (branch)
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
Cancer as a Complex Adaptive System: The Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones During Progression
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 specific alterations in molecular targets/pathways in cancer cells
- Molecular profiling to ID patients with relevant \( R_x \) targets for improved treatment (precision oncology)

**Immunotherapy**
- (re) Activation of body’s immune defenses to detect and destroy cancer cells
The Principal Challenge in Cancer $R_x$ Therapy

The Co-existence of Multiple Tumor Cell Clones with Varied Susceptibility to Different-$R_x$

$R_x$ - Resistance
Tumor Cell Heterogeneity:
The Omnipresent and Greatest Challenge in Cancer Therapy
Tumor Cell Heterogeneity:
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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 clones that emerge as escape variants driven by the selection pressure of treatment?
  - intrinsic resistance (exist before treatment)
  - acquired resistance (mutations induced by Rx – similar to antibiotic resistance in bacteria)
Design of Cancer Treatments to Hit Multiple Targets

- design a single drug that hits multiple clones and multiple signaling pathways
- very low probability of technical success of creating a single molecule with multi-target pharmacological promiscuity and no off-target effects (toxicity)
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

‘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

$sensitive$

$sensitive$

$sensitive$

$Rx_1$

$Rx_2$

$Rx_2$

$Rx_2$

$Rx_2$

resistant

$sensitive$
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
  - $R_x$ elimination of ‘dominant’ clones allows pre-existing ‘minor’ clones to prosper (intrinsic resistance)
  - direct drug effect to cause mutations and new resistant clones (acquired resistance)
The Need for Rethinking Therapeutic Strategies to Combat Cancer
The Promise of Cancer Immunotherapy
The Therapeutic Challenge of Overcoming Heterogeneity in Tumor Cell Susceptibility to Anti-Cancer Drugs

- moving from classical ‘chemo’ and “targeted” drugs to devise new ways to attack every clone

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

- therapeutic activation of immune responses
  - passive immunotherapy (designer antibodies)
  - active immunotherapy (activation of immune functions)
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
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
Setting the Immune System Free
To Combat Cancer
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)

- **Rx**
  - $Rx_1$
  - $Rx_2$
  - $Rx_3$
  - $Rx_4$
  - $Rx_5$

- **targeted drugs**

- **Cytotoxic T cells**

- **immunotherapeutics**
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**
Overcoming Tumor-Induced Immune Inhibition: Immune Checkpoint Inhibitors
Why Are Some Cancer Types More Responsive to Immune Checkpoint Blockade?

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

**Less Responsive**
- pancreatic
- colorectal (MSI-low)
- ovarian
Immunogenic Versus Non-Immunogenic Tumors

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

- Non-Immunogenic
  - ‘cold’
  - ‘non-inflamed’
  - ‘silent’
  - low mutagenic burden
  - low tumor neoantigen expression
Realizing the Promise of Immune Checkpoint Inhibition

- 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
Immunotherapeutic Strategies to Enhance Immune Responses to Patient-Specific Tumor Neoantigens

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

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

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
Summary and Key Points
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 $R_x$ efficacy (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)
Aspirations for Improved Cancer Treatment

- maximize the efficacy and safety of therapeutic interventions against advanced (metastatic) disease
  - the promise of immunotherapy
- mobilization (reactivation) of body’s immune defenses to detect and destroy all clones
  - how to expand efficacy?
  - is the cost of immunotherapy sustainable?
Cancer as a Multi-Dimensional Dynamic Interaction Between Multiple Complex Adaptive Systems

- individual risk patterns
- tumor subtypes and different progression patterns and Rx responses
- systems for care delivery and outcomes

- germ line predisposition
- environmental carcinogens
- lifestyle
- precision oncology
- new standards for care
- access to care
- cost of care
- quality of care
Future Challenges in Cancer Care

The Demographics of an Ageing Society And Projected Increased Cancer Incidence

Infinite Demand Versus Finite Resources: The Adequacy of Clinical Infrastructure and Economic Sustainability

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

Complex Clinical, Scientific, Economic, Ethical and Legal Issues