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The Hallmarks of Cancer: Applications to Cancer Medicine?

Douglas Hanahan

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Cancer is a disease of extraordinary complexity, in terms of genetics, pathology, prognosis, and response to therapy.

**How can we rationalize this complexity?**

**Are there common principles underlying this daunting diversity and complexity?**
A hypothesis for rationalizing the complexity of cancer

• Disparate cancers share fundamental qualities
A hypothesis for rationalizing the complexity of cancer

• Disparate cancers share fundamental qualities

• This daunting complexity merely reflects different solutions to the same challenge:

  cancer cells must surmount multiple barriers and roadblocks used by the organism to prevent expansive cell proliferation, some of which differ from organ to organ
A hypothesis for rationalizing the complexity of cancer

Posed by Douglas Hanahan and Robert Weinberg in 2000
What are hallmarks of cancer?

The **hallmarks** are **acquired functional capabilities**, that allow tumors to

-- *do something active*

-- *do things that normal cells should not*

-- *typically, to do them chronically, rather than during the carefully orchestrated activities of cells and organs in the body*
The first hallmark

Sustaining proliferative signaling
The second hallmark

Evading growth suppressors
The third hallmark

Resisting cell death
The fourth hallmark

Enabling replicative immortality
The fifth hallmark

Inducing angiogenesis
The sixth hallmark

Activating invasion and metastasis
And, in 2011, two emerging hallmarks

Deregulating cellular energetics
And, in 2011, two emerging hallmarks

Avoiding immune destruction
How are these hallmark capabilities acquired?

Via Enabling Characteristics

**Enabling Characteristics** are not functional capabilities per se, i.e. they are not actions performed by cancer cells and cancerous lesions.

Rather, **Enabling Characteristics** are consequential effects that facilitate acquisition of the hallmark capabilities.
An enabling characteristic for acquiring hallmarks

Genome instability and mutation
A second enabling characteristics for acquiring hallmarks
A related realization: tumors are not bags of cancer cells but rather outlaw organs
Tumors are composed of an assemblage of cell types that communicate and collaborate.
Multiple normal cell types are recruited to become components of tumors, helping to provide hallmark capabilities.
Stromal cells functionally contribute to multiple hallmarks

Cancer-Assoc.
Fibroblastic Cells

Infiltrating
Immune Cells

Angiogenic
Vascular
Cells

Sustaining
proliferative
signaling
Enabling replicative immortality
Cancer-Assoc. Fibroblastic Cells

Deregulating cellular energetics
Stromal cells functionally contribute to 7 of 8 hallmarks

Hanahan & Coussens (2012) Cancer Cell
Yet, the basis remains the cancer cells, now including variable populations of 'cancer stem cells' - whose corruptions are being revealed by genome re-sequencing and charting the epigenome.
The disease is regulated in part by the integrated signaling circuit of the cancer cell
Plus an even bigger network: the signals transmitted between the various cells of the tumor microenvironment.
Hallmarks of Cancer: Applications to Cancer Medicine?

• The hallmarks conceptualization is helping to rationalize the wealth of new mechanistic data forthcoming from the cancer research community

• Are there applications of the concept to treating human cancers?
Therapeutic applications: all of the hallmarks are being targeted

- EGFR inhibitors
- Cyclin-dependent kinase inhibitors
- Immune activating anti-CTLA4 MAb
- Telomerase Inhibitors
- Selective anti-inflammatory drugs
- Inhibitors of HGF/c-Met
- Inhibitors of VEGF signaling
- PARP inhibitors
- Pro-apoptotic BH3 mimetics
- Aerobic glycolysis inhibitors
- Sustaining proliferative signaling
- Evading growth suppressors
- Deregulating cellular energetics
- Resisting cell death
- Genome instability & mutation
- Inducing angiogenesis
- Activating invasion & metastasis
- Enabling replicative immortality
- Avoiding immune destruction
- Tumor-promoting inflammation
Typically, therapeutic targeting of individual hallmark capabilities produces initial responses and clinical benefit, followed by relapse to progressive disease.

The reality check: Targeting individual hallmark capabilities is not working so well.
Remarkable, but often transitory responses in patients with metastatic melanoma treated with the B-Raf inhibitor vemurafenib.
Targeting individual hallmark capabilities is not working so well

including:

vemurafenib
erlotinib, et al
bevacuzimab
sunitinib, sorafenib, et al
Hitting individual hallmarks even harder, at multiple nodes
An alternative approach

Co-targeting multiple hallmarks
Perhaps, by co-targeting multiple hallmarks, it will be more difficult for tumors to adapt, resulting in more enduring responses.
For example, combining vemurafenib and ipilimumab in melanoma—clinical trials are ongoing.
Genetically engineered mouse models of human cancer have been used to elucidate cancer mechanisms, and contributed to the formulation of the hallmarks concept.

Mouse models of human cancer are increasingly being used to test new cancer therapies.
Using mouse models in pre-clinical trials to guide clinical trials

Pre/Co-clinical trials in mice modeling a human cancer

Tuveson & Hanahan 2011
Efficacy in mouse model motivates clinical trials

Pre/Co-clinical trials in mice modeling a human cancer

Tuveson & Hanahan 2011
Pre/Co-clinical trials in mice modeling a human cancer

(1)

Efficacy in mouse model motivates clinical trials

(2)

Positive clinical results support drug approval,
PFS, OS

(3)

Tuveson & Hanahan 2011
Pre/Co-clinical trials in mice modeling a human cancer

Positive clinical results support drug approval, e.g. in PNET: everoimous, sunitinib

Discordant clinical results and resistance motivate refined co-clinical trial designs

Tuveson & Hanahan 2011
A case study in PNET

- Preclinical trials in a mouse model of human PNET predicted clinical benefit of sunitinib and rapalogs, and have motivated clinical trials in this tumor type.

- Sunitinib and everolimus are the first new drugs approved by the FDA and European regulatory agencies for treating human PNET in 25 years.

- But, in both mouse and human PNET, the responses are limited in duration.
Adaptive - Evasive Resistance

Tumors in sunitinib-treated PNET mice become more invasive, growing diffusely by co-opting normal tissue vessels.
Initial efficacy, followed by development of adaptive/evasive resistance to anti-angiogenic therapy

Angiogenesis inhibitors evoke adaptive resistance mechanisms, including

- revascularization mediated by other proangiogenic growth factors
- perivascular accumulation of proangiogenic myeloid cells
- heightened invasion and metastasis (hallmark switching)
An e.g. from the Hanahan lab: co-targeting angiogenesis and resistance to apoptosis (& metabolism?)

- EGFR inhibitors
- Cyclin-dependent kinase inhibitors
- Immune activating anti-CTLA4 MAb
- Telomerase Inhibitors
- Selective anti-inflammatory drugs
- Rapamycin
- Sunitinib
- PARP inhibitors
- Inhibitors of HGF/c-Met
- Resisting cell death
- Genomic instability & mutation
- Deregulating cellular energetics
- Sustaining proliferative signaling
- Evading growth suppressors
- Avoiding immune destruction
- Enabling replicative immortality
- Tumor-promoting inflammation
- Inducing angiogenesis
- Activating invasion & metastasis
• Sunitinib targets the angiogenic hallmark

• The mTOR inhibitor rapamycin targets the cancer cells in this tumor type (PNET), increasing apoptosis (and possibly impairing metabolic reprogramming)
Preclinical trials to assess the combination

Defined-endpoint Regression Trial

Rapamycin/Sunitinib Regression Studies

- 0.0009*** 13W TP vs Rapamycin/Sunitinib simultaneous
- 0.005** 13W TP vs Rapamycin/Sunitinib 2D stagger
- 0.040* 15W vs Sunitinib
- 0.019* Sunitinib vs Rapamycin/Sunitinib stagger
- 0.0012** Rapamycin vs Rapamycin/Sunitinib simultaneous
- 0.020* Rapamycin/Sunitinib 2D stagger vs simultaneous

Tumor Burden (mm³)

<table>
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<th>13W TP</th>
<th>15W TP</th>
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Status and implications of the preclinical trials

• In a defined endpoint ("Regression") trial, the combination has added benefit with no short term toxicity issues

• Survival trials are showing modest benefit - perhaps limited by longer-term sunitinib toxicity -> switch to a second generation VEGFRi such as axitinib or tivozanib?
Acknowledgements – Unpublished Results

Liz Allen
Hanahan Lab, ISREC@EPFL
• The hallmarks concept is helping to integrate ostensibly diverse mechanisms of cancer

• There may be value in applying the conceptual framework to treating human cancers
An aside: we are developing a new multi-institutional cancer center in Lausanne
A partnership involving three institutions with complimentary skillsets

- The Cantonal/University Hospital and Medical Research Campus
- The Epalinges/Biopole Bio-Medical Research Campus (Immuno-biology, Cancer, etc)
- The Ludwig Institute Center at UNIL
- The Center of Integrative Genomics (CIG)
- The Swiss Institute for Bioinformatics
- ISREC
- Bioengineering
- Chemistry
- The Center for Biomedical Imaging (joint w/UNIL)
An open position: Division Chief of Medical Oncology

CHUV/UNIL Department of Oncology
Dr George Coukos

Medical Oncology
  - Melanoma
  - Breast/GYN
    - Lung
    - Brain
    - H&N
    - GI
    - GU
    - Sarcoma
  - Radiation Oncology
  - Hematology/BMT
  - Immunotherapy
    - Developmental Therapeutics
      - Tumor Processing Facility
      - Cell & Mol Analytical Platform
      - GMP Facility
      - IND Group
      - Research Nursing
      - Phase I/II Unit
      - Data Management
  - Molecular Oncology

Ludwig Cancer Research Center

Immunology
Immune Engineering

Molecular Oncology
The End

Thank You