A Changing Paradigm: Cancer Metastasis as the Target

From www.dslrf.org

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What are we going to cover today?

This is more an opinion piece than a scientific talk

**Review**
What is cancer?
How is it the disease typically attacked?

**Metastasis**
What is it?
Why change to attack metastasis?
How does metastasis work, putative targets
Example: Novel therapy to fight metastasis
What is Cancer?

1. A genetic disease (but not necessarily inherited)
2. Unregulated cell growth
3. Begins as a ‘Primary’ (definition for solid tumors)
4. May metastasize (more on this later!)
5. Defined by tissue of origin
6. Typically heterogeneous
7. Typically de-differentiated
8. Absolutely requires a blood supply (more later!)
10. Typically difficult to treat because it is our cells gone awry (low therapeutic index); contrast to bacteria e.g.
Report: Cancer will be No. 1 killer in U.S.

March 11, 2014

WHO predicts 'imminent human disaster'

1. In 16 years, cancer will become the leading cause of death in the United States, surpassing heart disease, according to a new report from the American Society of Clinical Oncology. The number of new cancer cases is expected to increase nearly 45% by 2030, from 1.6 million cases to 2.3 million cases annually.

2. Fifty years ago, only a handful of "minimally effective" treatments for cancer existed, according to the report. Today, there are more than 170 FDA-approved anti-cancer drugs.

3. Two-thirds of Americans now live at least five years after a cancer diagnosis, up from about half in the 1970s (finding earlier??)

4. Taking these future patients into consideration, the oncology society expects demand for oncology services to grow 42% by 2030. Yet the number of oncologists is expected to grow only 28%, leading to a shortage of more than 1,400 physicians.
Characteristics of Cancer Cells

1. Lose contact inhibition and communications with other cells
2. Many genetic alterations
3. Deregulated from inhibitory pathways, so...
4. Higher metabolism, glucose usage, oxygen usage
5. Grow when detached (loss of anoikis: w/o a house))
6. Oncogenes mutated and ‘activated’ (gas pedal)
7. Tumor suppressors ‘lost’, e.g. LOH (brakes)
8. Become drug resistant (windows closed)
9. Immortalized, i.e. they lose ability to undergo apoptosis (never breaks down)
10. Often overexpress tumor-specific proteins
11. Dedifferentiate, i.e. go backwards, e.g. loss of ER/PR
How is Cancer Typically Treated?
Chemotherapy: Kill cancer cells
Radiation: Kill cancer cells
Surgery: Remove cancer cells/organ

How is it not typically treated?
Prevention
Early Detection

The latter two historically not a high priority in NCI budget! Getting better though....
The vast majority of research on cancer has focused on:

- Killing cancer cells (but not normal cells; therapeutic index)
- Finding novel molecular tumor markers (to increase the therapeutic index)
- The development of novel chemotherapeutic agents
- Elucidating the cellular pathways and how they go awry in cancer cells (more later.....)
- Determining the genetics of cancer
- Improving the technology of detection
- The development of cellular and animal models of human cancers
The scientific community has published to date **3,374,693** (as of 10/24/16) articles in the last 50+ years with regards to Cancer....

...and yet all those papers and ‘discoveries’ changed the overall mortality by less than 10%....and for some cancers less than 1%, so....

Research into killing the tumor is not the whole story....
FACT:
More people (85%) die of metastasis* than any other reason in cancer-related deaths.....

*Metastasis: Displacement, from Greek: Meta (next), and Stasis (placement/stoppage)

The spread of cancer cells from the primary site to adjacent or distal sites.
Is metastasis random?

Do cells just break off from a primary tumor, float away, and wherever they land, start to grow?

Partly, yes, mostly no. One million cells per gram of tumor break off and float away per day....but only 0.01% (100) ever end up growing somewhere else. Why?
“Nothing in Biology is random, there are only processes we don’t understand. Metastasis, is, in fact, a highly regulated process every step of the way.”

Isaiah J. Fidler, D.V.M., Ph.D.
Director, Metastasis Research Laboratory
R. E. Smith Distinguished Chair in Cell Biology
Professor, Department of Cancer Biology
The University of Texas MD Anderson Cancer Center

Author of 604 peer-reviewed articles

2013 American Cancer Society Medal of Honor for Basic Research

“To say this honor is richly deserved is an understatement. Dr. Fidler wasn’t just in on the ground floor of metastasis research, he was instrumental in building it.”

Ronald DePinho, M.D., President, M.D. Anderson Cancer Center
In the mid 1960s, Dr. Fidler asked a simple question: “If cancer cells are so aggressive, why do scientists have to inject a million cells into a lab animal to get a single tumor?”

He injected 100,000 traceable melanoma cells into mice and observed their travels and activity. “The cells reached every organ in the body.”.....but after several weeks all died except a few hundred that reached the lungs, where metastasis took hold.

“A (cancer) cell just reaching an organ wasn’t enough to establish metastasis.”

Metastasis arises from 0.01% of tumor cells.
Is this confirmation of the **Seed and Soil Hypothesis**?

**Yes!**

**Seed and Soil Hypothesis:**
Developed by Dr. Stephen Paget, a 19th century British physician. Analyzed hundreds of autopsies of cancer patients and found patterns of metastasis to other organs. Published in first issue of Lancet in 1892.

Tumor cells are like seeds and organs are like soil, and only when the right seed lands in the right soil will metastasis survive and thrive.
What are sites of cancer metastasis?

Bladder → Bone, Liver, Lung
Breast → Bone, Brain, Liver, Lung, Spine
Colorectal → Liver, Lung, Peritoneum
Kidney → Adrenal gland, Bone, Brain, Liver, Lung
Lung → Adrenal gland, Bone, Brain, Liver, Other Lung
Melanoma → Bone, Brain, Liver, Lung, Skin/Muscle
Ovary → Liver, Lung, Peritoneum
Pancreas → Liver, Lung, Peritoneum
Prostate → Adrenal gland, Bone, Liver, Lung
Stomach → Liver, Lung, Peritoneum
Thyroid → Bone, Liver, Lung
Uterus → Bone, Liver, Lung, Peritoneum
Some Characteristics of Metastasis

1. Tumors contain a heterogeneity of cancer cells with varying genetic changes and metastatic capability
2. Tumors contain host cells: epidermal, endothelial, immune....
3. Metastasis favors the survival and growth of a few subpopulations of tumor cells that pre-exist within the tumor
4. Metastasis favors unique interactions (cross-talk) of host cells in particular host tissues and capable tumor cells.
Dr. Fidler, with his wife Dr. Margaret Kripke, then showed the heterogeneity of tumor cells:

They took a parental tumor, extracted individual cells, grew each up into a clone, and inoculated them into mice.

Most caused no metastasis, a few caused identical tumors to the parent, and a very few caused massive metastasis. Tumors are heterogeneous. Why? Massive genetic instability.
The clonal selection model of metastasis suggests that the cell populations in the primary tumor with all of the genetic prerequisites required for metastatic capacity are the subpopulations that metastasize.

Talmadge J E, and Fidler I J Cancer Res 2010;70:5649-5669
Halftime Take-Home Messages:

1. Metastasis: Stochastic (Random), Sequential, Selective....3 S’s.
2. A tumor’s heterogeneity means cells are already in the tumor with varying capabilities to metastasize.
3. The more metastatic cells mutate more, and more rapidly.
4. Killing cancer cells, aiming primarily at the primary site, does not usually cure cancer or save the patient.
5. “The heterogeneity of metastatic cancer cells means that single-agent targeted therapies will fail against metastatic disease” (I. Fidler).
6. Metastasis occurs by targeted growth at specific organ tissues depending on (a) tissue of origin, (b) genetic changes in the tumor cells, and (c) host factors......
7. Metastasis is clonal
8. Metastasis involves unclear interactions with host cells

Let’s look at metastasis.....
THE METASTATIC CASCADE

1. TRANSFORMATION
2. ANGIogensis
3. MOTILITY & INVASION
4. ARREST IN CAPILLARY BEDS
5. ADHERENCE
6. EXTRAVASATION INTO ORGAN PARENCHYMA
7. RESPONSE TO MICROENVIRONMENT
8. TUMOR CELL PROLIFERATION & ANGIogenesis
9. MULTICELL AGGREGATES (lymphocytes, platelets)
10. EMBOLISM & CIRCULATION
11. TRANSPORT
12. METASTASIS OF METASTASES

From I. Fidler
Any of the steps in the metastatic cascade can be rate-limiting....

i.e. if a cell fails at any step in the cascade, the metastatic process stops....

Putative new targets??
The best studied metastatic target to date is **Angiogenesis**

**Angiogenesis:** the physiological process through which new blood vessels form from pre-existing vessels.

Tumors need a blood supply in close proximity to thrive. Dividing tumor cells are usually within 75µm of a nearby blood vessel, while apoptotic tumor cells are >160µm from a blood vessel. Oxygen can usually diffuse no more than 120µm in tissue.

Normal blood vessel growth AND tumor blood vessel growth can be induced through proangiogenic cytokines, e.g. VEGF
What happens to a tumor or metastasis that plants in the right location and starts to grow, but does NOT have a close blood supply? It can’t grow larger than the size of a pea. WHY?....Math.

Formula for surface area of a sphere: $4\pi r^2$
Formula for volume of a sphere: $\frac{4}{3}\pi r^3$

A sphere with a radius of 5mm has surface area of 314 mm$^2$, volume of 523 mm$^3$; Ratio ($V/SA$): 1.66

A sphere with a radius of 25mm has surface area of 7854 mm$^2$, and volume of 65434 mm$^3$; Ratio: 8.33

Thus the surface area of the tumor cannot bring in enough food and expel enough waste to accommodate interior cellular growth: RESULT is central tumor necrosis.
So, in theory, if we could stop angiogenesis of new tumors or metastatic growths, we could limit their size to a pea.

*Changing paradigm: make cancer a chronic disease of small tumors which never grow instead of an acute disease which grows and kills the host.*

How do we stop angiogenesis?
Judah Folkman, M.D.  
Father of Angiogenesis as Cancer Promoter  
Harvard trained surgeon

Discovered that all tumors maximally grew to same size without blood supply, so how do they get a blood supply to grow larger??
VEGF

Vascular Endothelial Growth Factor

Signalling Pathways
Complicated (!)
Redundant
Cascading Regulation
Tyr Phos Regulation
Feedback Regulated
Begins with Receptor

Good place to start:
Block ligand
So.....
Diversion:
Quiz in 5 minutes: know all the names of the molecules, how they are regulated and which amino acid residues are phosphorylated, their expression in the cell cycle, which are upregulated and downregulated in cancer, and which are linked to human diseases.....essay questions only!
VEGF

“Vascular endothelial growth factor (VEGF) is a signal protein produced by cells that stimulates vasculogenesis and angiogenesis. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate. VEGF's normal function is to create new blood vessels during embryonic development, new blood vessels after injury, muscle following exercise, and new vessels (collateral circulation) to bypass blocked vessels. When VEGF is overexpressed, it can contribute to disease. Solid cancers cannot grow beyond a limited size without an adequate blood supply; cancers that can express VEGF are able to grow and metastasize. Overexpression of VEGF can cause vascular disease in the retina of the eye and other parts of the body. Drugs such as bevacizumab can inhibit VEGF and control or slow those diseases. They are important signaling proteins involved in both vasculogenesis (the de novo formation of the embryonic circulatory system) and angiogenesis (the growth of blood vessels from pre-existing vasculature).”

(Wikipedia)
VEGF and Cancer

- VEGF expression is a poor prognostic indicator in breast cancer
- Decreased overall survival and disease-free survival in tumors which overexpress VEGF
- Mechanism suspected to be angiogenesis of tumors
- Tumor cells, like normal cells, detect low Oxygen and produce a transcription factor, HIF, hypoxia inducible factor, which induces synthesis of new VEGF
VEGF: A Central Mediator of Colorectal Cancer Angiogenesis

Environmental factors
(Hypoxia, pH)
Growth factors
(EGF, IGF-1, HGF)

Genes involved in tumorigenesis
(p53, src, ras)

Binding and activation
of VEGF receptor

Endothelial cell activation

Survival/Permeability
Proliferation
Migration/Invasion

ANGIOGENESIS
How is VEGF signalling attacked?
Let’s look at Bevacizumab (Avastin).

- Monoclonal antibody (Mab) which binds VEGF
- Approved by FDA in 2004
- Can show therapeutic efficiency in halting cancer growth and thus metastasis, but removal of the drug causes restoration of growth and spreading of cancer.
- Licensed to use in colorectal, lung, breast (outside US), glioblastoma (US only), kidney, and ovarian cancers.
- First clinically available anti-angiogenesis inhibitor in the US.
Does it Work?....Pros and Cons

- Binds to VEGF and prevents VEGF binding to receptor 😊
- Clinical trials ongoing, but in patients adds 2-4 months of life...😊 or 😞
- At a cost of $80,000 to $100,000/year!!! ....😞
- Needs to be given in perpetuity to continue inhibition (i.v. every 14 days)...😊
- Also works on normal vasculogenesis and angiogenesis...😞
- Side effects: high blood pressure, higher risk of bleeding, bowel perforation 😞
BOTTOM LINE: WE AREN’T THERE YET....We need new pharmaceuticals, lower costs, less side effects, longer survival improvement. It has NOT turned out to be the panacea, but it has hope.

GOAL: Make Cancer a chronic disease!