The Atavistic Model of Cancer: evidence, target-the-weakness strategies and radiotherapy

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Therapeutic implications of the atavism model

Targeting Cancer's Weaknesses

Not It's Strengths

Therapeutic implications of the atavism model
Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors

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Abstract
The genes of cellular cooperation that evolved with multicellularity about a billion years ago are the same genes that malfunction to cause cancer. We hypothesize that cancer is an atavistic condition that occurs when genetic or epigenetic malfunction unlocks an ancient ‘toolkit’ of pre-existing adaptations, re-establishing the dominance of an earlier layer of genes that controlled loose-knit colonies of only partially differentiated cells, similar to tumors. The existence of such a toolkit implies that the progress of the neoplasm in the host organism differs distinctively from normal Darwinian evolution. Comparative genomics and the phylogeny of basal metazoans, opisthokonta and basal multicellular eukaryotes should help identify the relevant genes and yield the order in which they evolved. This order will be a rough guide to the reverse order in which cancer develops, as mutations disrupt the genes of cellular cooperation. Our proposal is consistent with current understanding of cancer and explains the paradoxical rapidity with which cancer acquires a suite of mutually-supportive complex abilities. Finally we make several predictions and suggest ways to test this model.
"Natural selection occurs in neoplasms because (epi)genetic mutations generate heritable variation, and some mutations confer a selective advantage or disadvantage on the cell. All the hallmarks of cancer lead to the differential reproductive success of a clone."
(Merlo et al 2006)

Cancer evolves during the lifetime of the patient.

Selection acting on (what is usually assumed to be) random variation produces the acquired capabilities of cancer.

Somatic mutation model

Atavistic model

Natural selection occurs in neoplasms because (epi)genetic mutations damage regulation of otherwise repressed adaptive capabilities. These adaptive capabilities, when derepressed, show up as the hallmarks of cancer.

Cancer evolved ~ billion years ago and it is derepressed during the lifetime of the patient.

The capabilities of cancer are reacquired atavisms.

acquired

reactivated
start making leg suppressor (absent in other tetrapods)

Hind Limbs in a Whale Embryo

~30 Mya atavism produced by leg suppressor alteration, or "derepression of leg program"

abnormal atavistic leg

development of a whale
continuous cascade of maturing cells
(embryogenesis, tissue maintenance, wound healing,)

normal vestigial pelvic girdle

terminally differentiated cells of different cell types and different organs,
Development of cancer is a continuous cascade of maturing cells (embryogenesis, tissue maintenance, wound healing) that can produce atavistic cells, which are abnormal and can lead to cancer. Tumor suppressors are absent in basal metazoans and damaged in cancer, and alterations in these tumor suppressors can produce cancer. The development of cancer begins at ~1 Gya when maturation block but not proliferation block produces a cascade of immature cells, such as leukemia. Normal vestigial appendix and terminally differentiated cells of different cell types and different organs are also shown in the diagram.
non-differentiated cells → differentiated cells

Lineweaver & Schwartzman 2003 (Pace 1997)
Valentine 2004?
E. coli

Methanogens

Archaeae

Eubacteria

cyanobacteria

alpha proteobacteria

organelles

karyogenesis

spirochete

flagella, basal bodies, mitotic spindles

stem eukaryotes

nucleated cells

organelles

mitochondria

LECA

Mitochondria

Bikonts

Plastids

Protostomes

Radiata

deuterostomes

Bilateria

Holozoa

Unikonts

0.8

1.0

1.4

1.6

human

evolution of everything
Each layer of capabilities is built on and depends upon the earlier layers.

- **Earliest evolved capabilities common to LUCA**
- **Stem eukaryote capabilities**
- **LECA capabilities**
- **Multi-cellular metazoan capabilities**
- **Vertebrate capabilities**
- **Mammalian capabilities**

Evolution of multicellularity
The Onion Model of differentially protected, conserved genes.
Atavistic model has therapeutic implications

Current therapeutic treatments predominantly target what cancer cells, and all cells, have deeply embedded in their genomes -- cellular proliferation. It may seem rational to treat a proliferative disease with antiproliferative drugs however, after ~4 billion years of evolution (the first ~3 billion of which were the largely unregulated proliferation of unicellular organisms) cellular proliferation may be the most protected, least vulnerable, most redundant and most entrenched capability that any cell has. The redundant and robust supports for cellular proliferation are ~2 billion years older than the many layers of recent differentiation and regulation that evolved with multi-cellular eukaryotes.
cancer as a castle-without-a-moat

normal cell

therapeutic strategy: exploit the absence of the moat:
attack with fierce non-swimming warriors
they will drown when they try to attack normal cells
Some ABC pumps are heavily implicated in multiple drug resistance.
All ABC pumps did not evolve at the same time.
Some are older, some are newer. Identify which is which.
Prediction of the Atavistic Model: in cancer cells the newer ones will be
damaged and down-regulated compared to normal cells.
The older pumps will be up-regulated and responsible for cancer's abilities.
This seems to be true at the ~ 2 sigma level.
Therapy: identify the specific strengths of the new ones..ie they are
more efficient at pumping out X. Attack cancer cells with X.
If these new pumps are missing in cancer, then cancer cells won't be able
to pump out X. And they won't be able to mutate their missing pumps back
into existence. And normal cells will be able to deal with X.
The Human ATP-Binding Cassette (ABC) Transporter Superfamily

Dean, Rzhetsky & Allikmets, 2001, Genome Research

Gottesman et al 2002
Multidrug Resistance in Cancer: Role of ATP-dependent Transporters,
Nature Reviews Cancer, 2, 48-58
The evolution of multicellularity over billion years has led to the development of immune system capabilities. Initially, prokaryotes evolved into multi-cellular metazoans, followed by vertebrates. Mammalian immune system capabilities have developed the most recently, with adaptive immune responses becoming more prominent.
Targeting Cancer's Weaknesses (not its Strengths): Therapeutic Strategies of the Atavistic Model.

by Charles H. Lineweaver, Paul C.W. Davies & Mark Vincent

...a therapeutic strategy for targeting cancer: design challenges that can only be met by the recently evolved capabilities no longer functional in cancer cells. One example of an exploitable weakness of cancer is the absence of an effective adaptive immune response in immunosuppressed tumor environments. This leaves tumor cells more vulnerable than healthy tissue, to pathogenic attack. Such a target-the-weakness therapeutic strategy has a broad application and contrasts with current therapies that target the main strength of cancer: cell proliferation.
Recipe for targeting the weakness.
The weakness is the absence of adaptive immunity in the tumor environment.

a) Identify a highly effective vaccine that protects the host organ (and the body in general) from a specific virus, bacterium or parasite that targets the host organ.

b) Vaccinate the patient (or verify that the patient has been previously vaccinated)

c) Inoculate the affected organ (specifically the tumors in the organ) with the disease-causing infectious agent at a dosage that will allow the vaccine-primed adaptive immune system to protect normal cells but, because of tumor immunosuppression, will be less able to protect tumor cells from the disease.

This therapy should be most effective in cases of strong immunosuppression. The more advanced the cancer, the more immunosuppressed the patient and the more difference there is between normal and tumor cells in terms of communication with the adaptive immune system. Thus, this therapy may complement standard cancer immunotherapies which are least effective in highly immunosuppressed patients.

In the case of metastasis: modify the approach of Quispe-Tintaya et al (2013). After vaccination against *Listeria*, an inoculation with *non-attenuated Listeria* is carried out. TAMs should be preferentially susceptible to attack from the *Listeria*, but normal macrophages at wound-healing sites will be relatively well-protected by the adaptive immune system. Since non-attenuated *Listeria* is not just the carrier but also the killer, *Listeria* reproduction increases its effectiveness with time.

No dilution of the killing agent (= radiation).

This is not Coley, BCG or immunotherapy.
The goal is not to induce an adaptive immunity response against the tumor. The infectious agent is not attenuated.
billion years now

earliest evolved capabilities common to LUCA

stem eukaryote capabilities

LECA capabilities

multi-cellar metazoan capabilities

vertebrate capabilities

mammalian capabilities

most damaged in low grade cancer

evolution of multicellularity