

Logical Implications of Tumor Cell Evolution

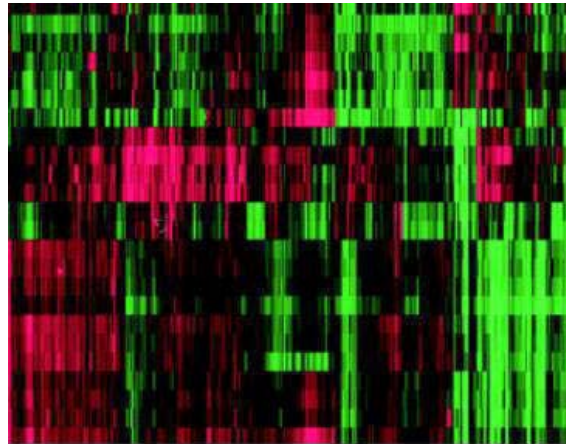
The enormously diverse, stochastic, evolutionary nature of cancer has profound logical implications that sharply define requirements for cure.

Tumor cell evolution limits what can be known about cancer

Consider a patient with metastatic cancer. The patient can have billions of cancer cells spread throughout his or her body. At the genetic and epi-genetic level each cancer cell can be different. It is instructive to ask the question:

What can be known about the patient's cancer cells?

We can experimentally characterize bulk tumor and *identifiable* metastatic lesions. Detailed information can be obtained about the molecular biology of the cells that are examined. Genetic and epi-genetic alterations can be characterized. Gene expression profiles can be identified.



Gene expression profile

A tremendous amount of information can be known about those cancer cells that are identified and examined. However, we generally cannot *identify* all the cancer cells that are present.

There is no logically-sound way to generalize from a sub-set of observed cancer cells to the entire set of all cancer cells present in the patient. Any such generalization is based on the false logic of induction. In addition, since evolution is an unpredictable, stochastic process, it is not possible to formulate a theory that can accurately predict what has evolved or what will evolve.

This is not a trivial academic point. A single cancer cell that is resistant to therapy after forty cell doublings can potentially give rise to a lethal population of one trillion cancer cells.

The following conclusions are inescapable:

- We generally do not know all that has evolved in a patient with metastatic disease.
- We cannot know what will evolve in a patient.
- We cannot have comprehensive knowledge of tumor cell evolution pathways.

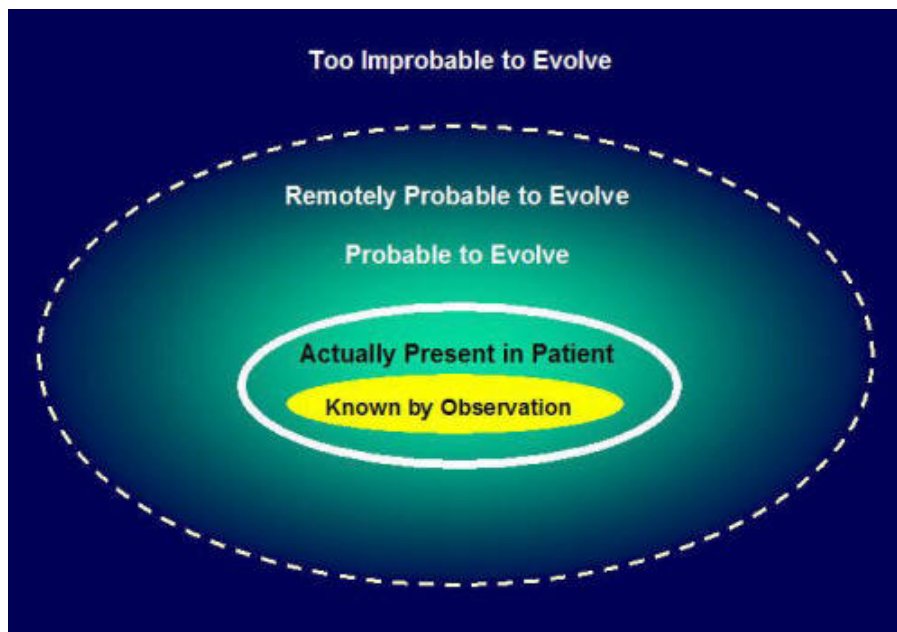
Since only known or knowable properties can be targeted it follows that:

The essential targets of any therapy that can consistently and specifically cure or control cancer must be independent of the pathways of tumor cell evolution.

What population of cells must therapy target to cure or control cancer?

The obvious answer is: all malignant cells in the patient or all tumor stem cells present in the patient. However, things are not so simple. As a matter of deductive logic this answer is false. It presupposes knowledge that cannot be known.

It is instructive to think in terms of *sets* of cancer cells. The following picture represents the universe of all possible malignant cells with all possible genetic and epi-genetic alterations.

The Universe of all Cancer Cells

The set of cancer cells actually present in the patient is contained within the white oval. This set changes with time. The changes are stochastic and predictable only to the extent that the set will (almost always) remain inside the dashed oval.

The set of cells that are actually known by observation are contained within the yellow oval and can also change with time. Not all cancer cells that are actually present in the patient are known or knowable by observation (except in cases of localized disease).

As the distance from the set "Actually Present" increases, the cells become increasingly less probable to evolve. The probability value is 1 inside the white oval and approaches 0 at the dark blue periphery. The exact probability function or distribution is both unknown and unknowable.

Inside of the dashed line is the set of all cancer cells that could realistically evolve in a patient. This set is fixed and does not change with time. [i] Outside the dashed oval is the set of cells that are just too improbable to evolve in a patient.

Except in trivial cases, it is not possible to know by observation or accurately predict by theory the content of the white oval. The content is the output of an enormously diverse, stochastic, unpredictable evolutionary process. The formulation of a theory that can consistently predict the unpredictable is a logical contradiction. Consequently, the content of the white oval is generally unknowable and is not a suitable target.

By contrast, in principle, we can formulate a "*well-corroborated scientific theory*" that defines the set of all malignant cells that could realistically evolve. [ii] (The simplicity or complexity of the theory is for the moment not the issue.)

It follows as a matter of logic that the smallest target population sufficient for the cure or control of cancer is the set of all malignant cells that could evolve.

The hypothesis that any cancer cell present in the patient will be a member of the set is falsifiable, but in practice will always hold true as explained below. This is not the case for any "knowable" set of lesser size.

This set is the smallest knowable set of cancer cells that is comprehensive. By comprehensive we mean the set contains all the cancer cell types that are actually present and that actually will evolve in the patient. Therapy that targets a smaller set will fail. This is an extremely important point.

Terms like "*remotely probable to evolve*" and "*that could evolve*" are ill defined and nonquantitative. However, when translated into practice these terms acquire meaning.

Since a patient with cancer can have a cumulative tumor cell burden of 10^{12} cells, a 99% cure rate requires (to a first approximation) targeting the set of all malignant cells that have a probability of 10^{-14} or greater of evolving. Since cancer in a patient is a unique singular

event within the history of the universe the underlying probabilities are unknowable. There is only one way to deal with this problem. The target set must be very broad and extend to cover the extreme limits of improbability, where there is near certainty that no malignant cell could evolve that is not a member of the targeted set.

It is because so little can be known about what will evolve that so much must be targeted to cure or control cancer.

Individual cancer cells with particular genetic and epi-genetic alterations are like microscopic pixels in the big picture. We cannot know and cannot target the almost unlimited number of individual pixels. They are irrelevant. What matters are the properties of the entire set of all cancer cells that could evolve. The entire set is the required target to cure or control cancer.

The logically required target for the cure of cancer is an abstract set of cancer cells.

The required target is the set of all cancer cells that could evolve in the patient. You cannot study it by observation. Most cancer cells in the set have never even existed and never will exist.

Objection

How can you study, let alone target a metaphysical set of cancer cells? It is not even meaningful to talk about cancer cells that don't actually exist.

Response

The answer comes from Karl Popper:

Observation and experiment are not the logical source of scientific knowledge. Scientific knowledge comes from hypothesis, deductive logic and refutation. The role of empirical data is as a means of refutation.

It may seem strange that the logically required target population for the specific cure or control of cancer is abstract. This strangeness accurately reflects the diverse, stochastic, evolutionary nature of cancer. The key is to connect the metaphysical back to the real world by empirical data that can potentially falsify the model. In this sense the abstract set of all cancer cells that could realistically evolve is no different from a scientific theory.

The probabilities that describe the specifics of tumor cell evolution cannot be known

Cancer in a patient is a singular event in the history of the universe. Every patient is different. The cancer cells that evolve in every patient are different. The probability of a singular, one-time event cannot be measured or experimentally determined. Either the event happens or it does not.

The probability of a coin flip giving heads can be experimentally measured by observing the frequency of heads in a very large series of coin flips. You cannot do this for a singular event that happens just once. You cannot measure the probability that a nuclear power plant, bridge or dam will catastrophically fail. [iii] Similarly, you cannot measure the probability that a certain cancer cell will or will not evolve in a particular patient.

Probabilities of singular events are metaphysical. Although, the nature of probability remains incompletely understood, as pointed out by Popper, probabilities do have an objective character that describe "relational properties of the physical world." [1] [2] Indeed, much of modern physics involves the application of the concept of probability to singular events. Einstein and Gibbs independently formulated a solution to this problem based on ensembles that give meaning to probabilities for singular events.

However, the fact remains, the probability that a particular type of cancer cell will evolve in a patient is unknowable. Any function that describes the probabilities of what will evolve must generate output that changes and that has stochastic or random features. This follows from the many different layers of stochastic complexity of tumor cell evolution. Accurate modeling of tumor cell evolution and modeling of the probabilities that different tumor cell types will evolve is an intractable mathematical problem. The bottom line is: probabilities that describe what cells will evolve in a patient with cancer are unknowable.

Near certainty exists at the extreme limits of improbability

When you don't know or can't know the solution to a problem there is a very good approach to follow. Physicists, engineers and mathematicians use it all the time. Look at the extreme cases, the limits. What is so improbable that it will never happen? What is so probable that it will always happen. These are the limits. Surprising, it is at the extreme limits that we can have almost absolute certainty of knowledge. This is how we must approach the problem of tumor cell evolution.

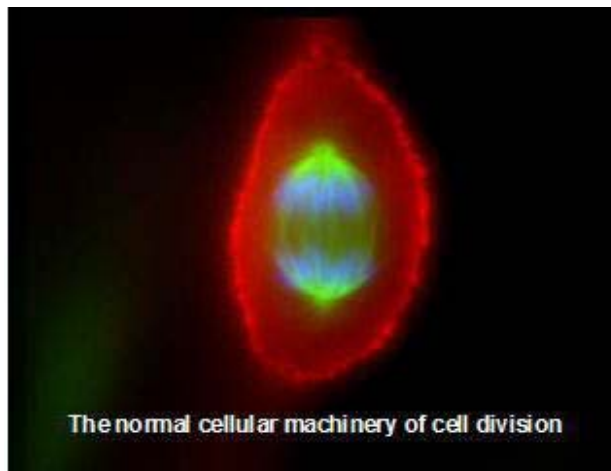
We need to step back from the swirling chaos of cancer and seek firm ground. When dealing with complex stochastic processes, it can be very easy to know with great certainty what will *not* happen. But it can be impossible to know what will happen. This may seem contradictory, but it is not. There is a logical asymmetry between the two. I know with almost absolute certainty that I will not win the state lottery three times in a row. However, I cannot know what the winning lottery number will be. The difference reflects the fact that there are a very large number of ways to lose and only a small number of ways to win. It is only in this sense that we can understand cancer and evolutionary cancer cell populations. We can know what will *not* occur. We can know what will not evolve and we can know what will not evolve with sufficient certainty to formulate a theory of cancer that should be

accurate to more than one part per thousand trillion. Such a theory can tell us how to consistently and specifically cure or control cancer.

What can be known about all malignant cells that could evolve in a patient?

- Cancer cells must engage in malignant behavior, proliferation and invasiveness in an abnormal context. This is just the definition of cancer.
- All malignant cells will use normal cellular machinery to carry out proliferation and invasiveness.

Normal cellular machinery enables cancer



Microtubules are green. Actin is red. Chromosomes are blue.
The Imaging Technology Group, Beckman Institute for Advanced Science and Technology
at the University of Illinois at Urbana-Champaign ©

Cancer cell evolution occurs within the context of extensive, complex, pre-existing cellular machinery. Normal cellular machinery exists that can carry out the hallmark functions of malignancy. [3] This is represented in the biochemistry of activities, such as cell proliferation, DNA synthesis, [mitosis](#), tissue remodeling, wound healing, cell migration, blood vessel formation, and [trophoblast implantation](#) during formation of the placenta. [4] Morley Roberts pointed this out eighty years ago. [5]

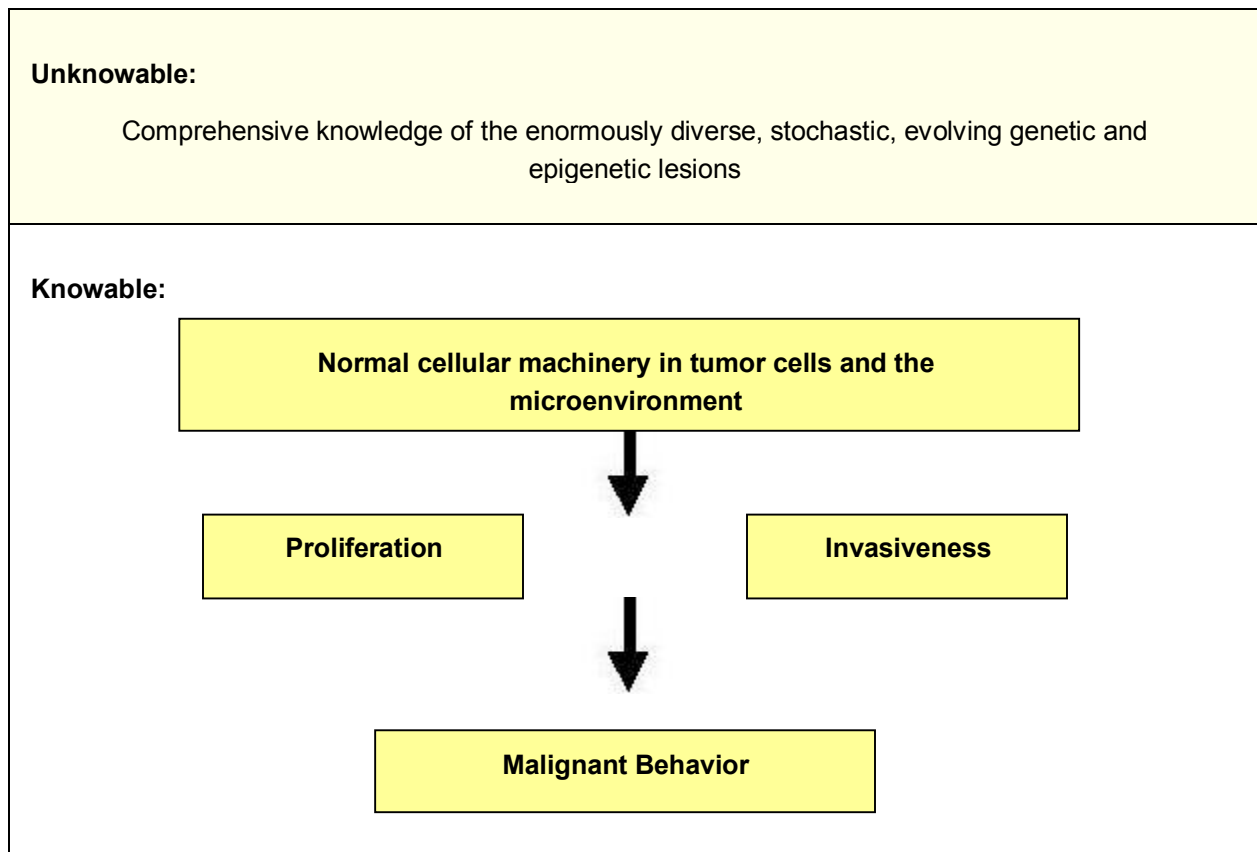
Dr. Robert Weinberg and colleagues demonstrated that the introduction of three oncogenes into human cells is sufficient to transform normal human cells into cancer cells. This means (at least to a first approximation) that all the other machinery needed to form tumors was normal cellular machinery. [6] It is overwhelmingly more probable that cancer cells will use normal cellular machinery than evolve extensive new machinery. Although the “Rules for Making Human Tumor Cells” are encoded by diverse and stochastically evolving genetic and epi-genetic alterations, it is normal cellular machinery that must execute these instructions. [7]

Cancer cells that violate this property have never been described. [iv] The complexity of the requisite interdependent biochemical processes is too great, the joint probabilities too small, and the human life span far too short for a tumor cell to evolve that violates this property. [8] Accordingly, all cancer cells use normal cellular machinery to carry out the biochemistry of malignancy, proliferation and invasiveness. We can be confident this is true based on deductive logic, the requisite complexity of life, Darwin's Theory of Evolution, and basic laws of probability. Like all scientific knowledge this cannot be known with absolute certainty. However, an exception to this rule has never been observed. On statistical grounds we can be confident that it never will be observed. In science this is as good as it can get.

For the almost unlimited random combinations of genetic and epi-genetic alterations, a malignant cell will result only if changes are compatible with normal cellular machinery carrying-out proliferation and invasiveness.

If this condition is not met then the cell is dead end. It may be a tumor cell, but it is not a malignant cell. Only cells that can engage in malignant behavior can sustain the clinical disease of cancer.

What Can and Cannot be Known About Cancer



Footnotes

[i] It is of course dependent upon our choice of what we consider realistically probable, (e.g., one in a thousand, one in a million, one in a billion chance to evolve in the patient)

[ii] The term "*well-corroborated scientific theory*" means a theory that is potentially falsifiable, internally logically consistent, consistent with other well-established "principles of nature" and that resists the severest attempts at falsification. In other words, the theory will be true for any malignant cell ever observed. An exception would disprove the theory. (See the section on the logical structure of knowledge.)

[iii] The probabilities can be estimated.

[iv] This does not imply that a violation will not occur. Such reasoning is inductive in nature and invalid.

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