Medical Hypotheses

Could Cancer be a Physiological Phenomenon Rather Than a Pathological Misfortune?

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Abstract—The hypothesis presented here is that cancer is not a phenomenon where the normal functions of the human body break down (like diabetes mellitus or renal failure) but rather a well planned and well coordinated physiological response (similar to the inflammatory response). 'Cancer initiating genes' are presumed neoplastic DNA sequences involved in sensing genome deterioration, consequently enhancing preservation. This genetic trait, different from the concept of oncogenes, actively triggers the neoplastic transformation once genome deterioration is sensed. This self destructive, altruistic phenomenon, obviously devastating to the organism, is nevertheless shown to be a possible mechanism of natural selection. The survival advantage of cancer initiation is discussed using both the concepts of group selection and gene selection.
Natural selection, the driving force of evolution, is believed to operate solely on the basis of phenotype differences among individuals. In this paper cancer is hypothesized to be a mechanism that directly scrutinizes the gene contents of the individual, therefore representing natural selection based on genotype differences.

Introduction

Cancer is generally regarded as representing a deterioration of the normal physiological functions of the body. On the question of why cancer strikes only certain individuals at certain times, various contributing factors have been mentioned such as viruses, deficiency of the immune system and external environmental factors. This article assumes a more direct causal explanation relying on an evolutionary rationale.

Goal oriented phenomena

First, let me introduce a key concept, 'goal oriented behavior'. When appreciating the wonders of nature, we realize that anatomy and physiology are both tailored to achieve distinct purposes. Although the term goal oriented behavior strikes the ear as teleological, it should rather be understood in the following way: Nature, through endless steps of evolutionary selection, has constructed functions intended to achieve specific goals. For example, the lack of a nucleus in

the red blood cell and the local release of chemotactic factors secondary to an infectious process. Goal oriented behavior can also be understood as adaptation.

Goal orientation scale

Goal oriented behavior represents one end of a scale, whereas randomness, chaos and chance represent the opposite extreme. Various phenomena can be placed along the scale. A simple example illustrates the idea: opening a closet, turning on the water tap and leaving the room is a random unpurposeful combination. On the other hand, shutting the main power supply, climbing on a chair and unscrewing a lamp should definitely be regarded as a goal oriented combination. Notice that the steps in the second example are not more complex, but rather the combination and the order are crucial.

Basic rules for determining a behavior as goal oriented

The following assumptions are made:

1. It is not the steps, but rather the combination of steps that determines the degree to which a function is goal oriented.
2. The larger the number of purposeful steps, the smaller the chance for a behavior to be random.

The following features, if found in the behaviour at question, imply a higher goal oriented score:

*   The behavior is efficient in performing the goal.
*   The goal accomplished by the behavior is set to happen at an expected predetermined time.
*   Each single step is specific and unlikely to have been triggered by mere chance.
*   Two or more different behaviors are simultaneously triggered to achieve a similar goal. Such a coincidence strengthens each behavior's goal oriented score as opposed to a situation in which each behavior is observed alone.

Goal oriented phenomena in biology

1. A complex and goal oriented function in biology is not likely to be derived from a single step mutation, but rather as a stepwise and extremely slow process. This is due to the infinitely small statistical probability of such an event to occur. As an example, it would be impossible to pre-sume that a single generation leap could produce through mutations a creature with a totally different circulatory system, involving the simultaneous appearance of thousands of mutations.
2. Any function that is both goal oriented and widespread must be derived from extensive and long term evolutionary selection and therefore must possess a survival advantage.
3. Any goal oriented and complex function in biology, especially when it appears uniformly in all individuals of the species, must be genetically coded and appear as a sequence in the DNA. This is due to the fact that evolution can only be related to DNA, which is the only known link between consecutive generations of the species.

Cancer DNA

It is hypothesized that the human genome contains sequences for coding the various features specific to each tumor type. The observations leading to this hypothesis are: Neoplastic transformation in different individuals repeats itself over and over again in a relatively predictable and similar fashion. Each tumor subtype can be defined by:

1. A specific histological pattern.
2. A relatively predictable clinical course.
3. Features specific to each tumor type, such as tumor specific antigens and specific excreted factors. Of major interest are those which were not present in the previously normal cell.

How is it possible to extrapolate valid information from the histological architecture about clinical course, invasiveness, aggressiveness, prognosis, chances of metastasizing, unique antigens presented by the tumor, and many other parameters that are predicted by pathologists?

The repetition of each cancer subtype (in different individuals) and the distinction between manifestations of different tumors can hardly be attributed to randomness since each function is extremely complex and definitely gene related.

Cancer as a goal oriented phenomenon

The simultaneous activation of a huge repertoire of mechanisms all different in pathogenesis, but known to be favorable to a fast growth of the tumor, with a simultaneous active decline of the normal body functions leads to the conclusion that cancer is a goal oriented phenomenon. Of main interest are those fea-

tures expressed by the cancer cell which were not present prior to the transformation. If we accept the final goal to be death of the organism, then a logical scheme can be noticed in the pathogenesis of the disease.

Following are examples of the different mechanisms through which the neoplastic cell actively manipulates, weakens and ultimately causes death of the organism:

1. Modulating the antigenicity of cancer cells in order to evade the host immune system. Examples include: blocking and enhancing antibodies, specific nonresponsiveness in an otherwise immune competent host (1).
2. Secretion of growth factors that contribute to tumor blood supply and growth capabilities. (for example: transforming growth factor which allows anchorage independence).
3. The ability to lose normal cell division suppression (for example: loss of contact inhibition).
4. The cell's ability to disregard outside signals, such as partial elimination of receptor portion in the case of the epidermal growth factor receptor which lacks an extracellular portion.
5. The various paraneoplastic syndromes serve to weaken the body through hormonal and other yet to be defined ways.
6. The ability to metastasize and the ability of the secondary tumor to survive in a different and hostile surrounding. Note that active processes underline this ability, such as secretion of various connective tissue dissolving factors enabling invasiveness.
7. Weight loss in the presence of an enlarging tumor mass, fatigue, fever and other systemic features of the tumor are not just passive consequences but most probably the result of active mechanisms, requiring gene expression.

The complexity of each of the above functions, the numerous different mechanisms simultaneously triggered, all serve a common goal of destroying the individual's homeostasis. This leads to the presumption that a non random, well defined and intentional mechanism is involved.

This differs from type insulin dependent diabetes mellitus (IDDM) which is also a multi target disease, but, as opposed to cancer, is not a goal oriented phenomenon. Diabetic manifestations are all the result of a primary dysfunction, a localized lesion of the insulin secreting cells.

One known theory which tries to explain the pathogenesis of cancer states that many of the phenomena acquired by the tumor are secondary adaptations favoring survival and clonal expansion. The monoclonal cell line shows a pattern of increased adaptability through natural selection of mutationally different cancer cells. By this an evolutionary microcosm is presumed to exist inside every cancer host. Two difficulties arise with this theory:

a. Cancer, from transformation till death of the organism, involves a limited number of generations which makes this complex adaptation unlikely.
b. Even more difficult to explain is how totally unconnected evolutionary systems give rise to similar outcomes. The conventional explanation is that a similar surrounding should always result in an identical evolutionary end product, when let run again and again. This explanation ignores the randomness in evolution and also cannot explain why certain features are unique to only specific tumor types.

Evolution within cancer

If cancer stems from DNA sequences present in the genome, the rules of evolution must apply to these sequences as well. What follows is that cancer DNA is probably constantly changed by mutations. The cancers known to exist today are those that succeeded in surviving through natural selection.

I presume malignant tumors to be more complex than benign cancers in terms of both their manifestations and goal orientation. Through evolutionary processes it is possible that new subtypes of cancer may emerge in the future, some of which may be more aggressive, owing to their increased complexity and goal orientation.

Cancer exists in simpler forms of life. It is possible that cancer in humans is on a higher level of organization then the cancer of more primitive life forms, just as the respiratory system of humans is more complex than the equivalent in insects. It is possible that the evolution of cancer can be traced back by comparing manifestations of the disease in more primitive life forms.

Group selection as a rationale for cancer

Group selection (2) deals with 'traits that are selected against at the individual level' (3). Different evolutionary principles and driving forces rule group selection (4) as opposed to individual selection. In the

classic evolution (5) the fit survives. In group selection it is only the next generation (rather than the individual itself) that counts. The sole importance of any individual is only as a vector for passing its genes to the next generation.

Passing the genome is not enough, since it does not imply evolution but merely preservation. The mere existence of the individual is not the sole justification for passing one's genes.

Group selection in insects

The following example from a certain insect specie demonstrates, rather dramatically, how the forces of group selection and individual selection, pull in opposite directions.

The male of the praying mantis (6), a cockroach-related insect, only reproduces (ejaculates) while the female chops its head off and feeds on the remains. This behavior is presumed to be genetically determined (and not just a tradition) since physiologically the male ejaculates efficiently only while participating in such a ceremony.

We can understand this behavior in the following way: the male, after reproducing, serves no purpose but to compete for the same limited resources of food against following generations. Furthermore, his flesh can serve to nourish the female (6), providing its future offspring a better chance for survival. This trait, although shortening considerably the male's life span, serves as an advantage from the view point of group selection.

Group selection in humans

A healthy female has the potential to become pregnant some 20 or more times. The limiting factor for the number of offspring, is the caring, protecting and feeding of the next generation. In this context we realize that every existing offspring is directly taking the place of a potential baby that awaits birth. This is a genetically determined limitation implanted in our genes. So long as the newborn is breast-feeding the prolactin secreted in the mother acts as a birth control mechanism. As soon as breast feeding is stopped, the next pregnancy can occur.

Group structure

In the context of limited resources, offspring with inferior genes may take the place of better offspring, weaken the adaptability of the species and represent

an evolutionary disadvantage. It is presumed that the larger the number of offspring, the better the adaptability.

Apart from being a gene vector, a second role of the individual is caring for the next generations. In the setting of a group, the individual's chance for survival is directly influenced by the strength of the group. More important for this discussion, the number and health of the offspring depend much on the group structure. Therefore I deduce that it is not only the personal gene pool which contributes to survival but also the composition of the group.

The ratio of workers to non workers in a group is limited by food supply made available by the workers. In a hypothetical prehistoric tribe the larger the number of working hands, the larger the number of offspring that can be supported. Non workers are not only children but also the sick and the old. It would be an advantage for the tribe to possess a genetic quality that limits the age of an individual.

Comparing two tribes

Consider the following example: let us compare two isolated tribes, where the resources of each tribe are limited by nature and by the amount of working hands available. The first tribe is led only by the principle of individual selection in which the fit survive.

In the second tribe each individual contains a genetic mechanism which enables detection and elimination of those individuals showing genetic inferiority defects (especially in pre-reproductive individuals) and also detection of old age. When comparing these two tribes after a number of generations, we will most probably find that the second tribe is composed of a larger number of healthy and competent individuals.

The organization of the human population given in this example is one of the isolated tribes, since human evolution occurred mainly in prehistoric era. The last few thousand years and their new social structure have probably contributed little to the process of evolution.

Kin selection (7), was introduced to explain the survival advantages of altruistic behavior in nature. Cancer can be viewed as such an altruistic phenomenon, where one member of the tribe sacrifices himself in order to increase the chance for survival of his kin.

The triggering mechanism

We now arrive at the most difficult aspect of the theory, namely why does cancer strike only certain individuals. This theory assumes an active triggering

mechanism, one which intentionally sets off the destructive process only when certain conditions have been met. Previously, an assumption was made that an evolutionary advantage exists if two specific subgroups of the population are actively removed. One group is the older population, the other is composed of the genetically inferior.

Cancer in the post-reproduction age

With respect to aging, it is presumed that a drift in the integrity of the genome is sensed by the cancer DNA sequences. Once a massive deterioration is spotted in any body cell, the triggering mechanism activates the neoplastic transformation in that specific cell.

Cancer in the pre-reproductive age

With respect to the pre-reproductive individuals having an inferior genome, the matter is a little more complex. The neoplastic transformation is a single cell event (almost always involving somatic cells) so a question is raised: why should a somatic inferiority bother the genome pool when it is only germ cells that directly effect evolution?

A somatic cell deterioration raises the probability that this individual contains a defective genome, defective in the sense that the genome has not succeeded in preserving its contents. By deterioration, a massive change in the contents is implied and not just a few spot mutations. By omitting this individual from the general gene pool, while still in his pre-reproductive period, a possible contamination is eliminated, one that would otherwise demand many generations of natural selection to remove.

This contamination stems from two reasons: first, this individual carries poor preservation qualities that may be passed down to following generations. Second, any of the genes passed on may be severely damaged or even useless. Notice that passing such qualities (such as a highly damaged recessive gene) does not necessarily prevent the offspring from existing but directly leads to contamination of the general gene pool and reduces the fitness of future generations.

It is possible to unite the pre-reproductive and post-reproductive groups if we take into consideration the assumption that as the individual becomes older, a gradual and irreversible deterioration of the genome is expected. Through the action of both internal and external factors it is presumed that a drift in the integrity of the genome is age dependent.

Certain known cellular mechnisms antagonize the drift in the integrity of the DNA contents. Probably the most understood are the DNA repair enzymes intended for reversing mutations. The repair enzymes are obviously not fool proof.

Genome integrity screening mechanisms

The means through which the cancer DNA senses that a deterioration in the genome has occurred is probably extremely complex. The following simplified examples demonstrate the feasibility of such a function using known qualities of human DNA.

1. Detection of base substitutions: highly repetitive DNA (satellite DNA) are well known sequences found in DNA of humans and other species. These identical sequences appear in up to millions of copies scattered throughout the genome. A hypothetical enzyme may simultaneously stroll along two DNA molecules (or distant parts of the same molecule) comparing such homologous sequences. When mismatches beyond a certain amount are detected, the neoplastic transformation starts. Alternatively, the hypothetical enzyme itself may serve as a template to sense the integrity of a satellite sequence.

2. Detection of deletions or insertions: much of the human DNA is composed of non coding sequences, among these are introns scattered throughout genes. Parts of these sequences may be sites recognized by enzymes that roll over DNA in a way that familiar sequences are met at exact distances apart. When such sequences are shifted out of their correct position, it implies that deletion or insertion must have occurred.

The sequence of events

Neoplastic transformation is presumed to be a relatively common event but only rarely does it reach a clinical stage. Only in those individuals with a high rate of cell transformation, who also show immunological insufficiency, a clinically apparent cancer may result. The above combination of obligatory multiple transformations and a weakened defense response favors cancer in those hosts with a generalized genetic inferiority rather than those manifesting an isolated single cell accident.

The following summarizes one possible sequence of events:

1. Constant random changes (mutations) appear in the DNA of cells due to: aging (possibly through free radicals), external factors such as radiation or viruses (Epstein-Barr virus for example) and internal factors such as spontaneous mutations or dysfunction of the DNA repair mechanisms.
2. A triggering device constantly observes if a threshold of changes has been reached. Specific important and sensitive regions are probably monitored more closely.
3. When a threshhold is reached, a neoplastic transformation which is specific to the involved cell type is triggered.
4. Anti neoplastic mechanisms, basically the immune system, struggle to eliminate the neoplastic transformed cell.
5. Deficiency of the immune system together with a high rate of simultaneous transformations raises the chance for the formation of a clinically apparent tumor. The single cell-tumor mass leap is basically a statistical event with probability ruled by the factors mentioned above.
6. Once the neoplasm is in the clinically apparent stage, it will run its predetermined course, untouched by the organism's defense mechanisms.
7. Multiple well synchronized destructive features, both local, systemic and distant, all serve to achieve the final goal being death of the organism.

It can be asked why the triggering mechanism does not simply kill the genetically compromised cell rather than eliminating the whole organism? The explanation is that evolution is not concerned with the well being of the individual, but rather with the gene pool of the species.

The triggering mechanism can be of low specificity and sensitivity and still have an evolutionary advantage. It is hardly a drawback, from an evolutionary point of view, if the mechanism is activated by mistake so long as it eliminates proportionally more inferior genomes than normal ones.

Diversity of cancer subtypes

In trying to explain the diversity of tumor types and their specificity to the precursor cell the following is speculated: the same factors leading to differentiation in each and every cell, also affect the neoplastic sequences during normal differentiation processes. As a result, the non repressed segments within the cancer sequences show diversity when comparing different cell types. In addition, since every cell has undergone considerable normal differentiation in the pre-

neoplastic period it is presumed that different tissues expose different non suppressed genes as a substratum for the cancer sequences to manipulate.

Consequently, the tumor type is directly related to the specific cell that has undergone the neoplastic transformation, where each cell can only manifest a very limited repertoire.

Is evolution compromised?

Mutations are considered the sine qua non of evolution. Without mutations evolution could not take place. In this thesis cancer DNA is proposed to be a mechanism encouraging preservation and therefore antagonizing mutations. How can this dilemma be settled, taking into account that the cancer mechanism is assumed to have an evolutionary advantage?

While mutations are the driving force of evolution, it is preservation that lets it all happen. Only through extremely accurate replication mechanisms can otherwise unavoidable deterioration be held back.

Various observations have led to the fact that mutations are not incorporated into different parts of the genome at an equal rate (8). Some DNA portions show extreme preservation when comparing different species. Such an example is the presence of an identical DNA sequence found in drosophila, frogs and humans (9).

It is presumed that the genetic alterations expected to take place for evolution to function at its best are not equal when comparing different areas of the genome. For the sake of simplicity, we can separate the genome contents into two levels of information. The parts showing fast evolution include most of the structural genes, whereas the parts showing slow evolution include information relevant for DNA structure and function. The genes for DNA structure and function include genes responsible for the DNA→RNA→protein flow of information.

A good analogy from the world of personal computers is the difference between hardware and software. It is claimed that software represents the faster rate of evolution whereas the hardware and the system functions represent the slower rate. Software evolution is extremely rapid, so that numerous coexisting programs are constantly introduced into the market competing with each other. The simultaneous existence of numerous variants is the hall mark of this evolution. The slower rate of evolution includes the hardware and system aspects of the computer. As opposed to software, strict uniformity must exist in the system and hardware. An advance in the system portion of the computer (for instance switching the binary code into a tertiary one, changing the size of the

floppy disc) could hardly be of commercial value unless the whole system is upgraded as well, otherwise this change would directly lead to loss of all existing functions.

An example for such a hardware DNA sequence exists, one which is highly preserved in phylogenetically diverse organisms. The initiation site for transcription of protein coding genes by RNA polymerase II contains a consensus sequence: showing only minor variations among highly diverse organisms (10). It is undoubtedly necessary to possess such an initiation site in the genome, but the similarity of these DNA sequences throughout large intervals of evolution leads to the conclusion that some active selection mechanisms underlies this conservation.

To summarize, although the cancer triggering phenomenon is intended to achieve certain rigidity of the genome, it selectively preserves those portions belonging to the hardware and system functions. Otherwise an unavoidable deterioration would eventually occur.

The unavoidable principle of natural selection

How did the cancer trait survive the laws of natural selection and become eternally fixed as part of the common gene pool?

Individuals possessing the cancer mechanism are spared the waste of energy related to natural selection of mutations in conserved aspects of the DNA. Individuals not possessing such a mechanism are constantly forming offsprings with mutations in these areas, offspring which are doomed. It can now be appreciated that such a mechanism favors healthier offspring and faster spreading of one's own genes.

Selfish genes

A slightly different evolutionary rationale for cancer DNA can be derived from the concept of natural selection on the gene level (11). Genome deterioration implies that the affected genes are not passed down any more, since these genes have been changed. Furthermore, the changed genes will compete in the next round against the original ones. Those selfish genes who obtained a mechanism for eliminating such deterioration (through destruction of the whole organism) are the ones that have succeeded in being passed on untouched throughout evolution. Natural selection on the other hand has restricted only certain genes to possess such a mechanism, because preserving these specific genes did not jeopardize the flexibility of the specie in the ever changing surrounding. One possible

example for such genes are those related to the synthesis of the four nucleotides.

Further thoughts

1. The entity of 'cancer family syndrome' is a hereditary trait of cancer tendency. This may arise from hyperactivity of the cancer triggering mechanisms or an inheritable unstableness of the genome. Alternatively, this trait may actually represent a more efficient cancer DNA, one which will eventually spread out to encompass the entire human race.

2. The presumed cancer sequences are not necessarily grouped together on one chromosome, but may appear as interrupted fragments spread throughout the DNA. These fragments may include oncogenes, which are well established cancer related sequences. Chromosomal translocation zones may represent key zones in the cancer DNA rather than random weakness spots (translocations such as the Philadelphia chromosome in CML). Is it possible that the neoplastic translocations, as opposed to the conventional belief that translocations give rise to cancer?

3. A large group of acquired hyperplastic type disorders are known to predispose to malignant transformations (1). Among the many examples are: chronic cervicitis, ulcerative colitis, cirrhosis of the liver, Paget disease of bone and leukoplakia. These conditions are characterized by regeneration and massive cell division. DNA is probably most vulnerable to accidents during replication and mitosis. When cells are dividing rapidly and repeatedly in excess of the normal capabilities of the DNA preservation mechanisms, it is logical to assume that the chances of genome deterioration increase. This may explain the association between the hyperplastic conditions mentioned above and the increased risk of malignant transformation.

4. The theory presented in this article assumes the primary cancer DNA to be completely and entirely devoted to genome integrity screening and triggering the neoplastic transformation. This is due to the complexity and the high goal orientation shown by these sequences. A large number of cellular oncogenes have been identified as participating in various normal cellular functions (12, 13). These oncogenes may actually be substratum, secondary genes activated by the cancer initiating genes.

5. Present day cancer strikes mainly at ages much higher than the life expectancy 1000 years ago. The explanation may be that the ability to efficiently preserve DNA contents was gradually increased through the selection pressure of cancer triggering. This has led to an increased age of average neoplastic transformation. The 20th century, through prolongation of life expectancy unwrapped the unavoidable age dependent DNA deterioration and consequently raised cancer prevalence.

Conclusions and implications

The hypothesis presented in this article presumes cancer to stem from activation of specific sequences in the genome which I have termed cancer initiating genes, these sequences being an independent function within the genome.

Hypothetically speaking, elimination or damage to these initiating genes, should irreversibly deprive the cell's ability of ever engaging in a neoplastic transformation (unless these genes are reintroduced). It should therefore be possible to produce cells which have been deprived of the ability to form cancer, no matter what future provocation they will encounter.

These cancer initiation genes may explain both the repetitive nature of each cancer subtype in different individuals and the extremely high goal orientation presented by the neoplastic phenomenon.

Two advantages for survival of the species stem from cancer initiating sequences:

1. Preservation is a prerequisite for evolution. Cancer sequences provided, indirectly, a common gene pool with less tendency of deterioration. This stabilization provides better chances for survival.
2. Through natural selection of specific individuals within the group, cancer, indirectly, increases the group survival and consequently the survival of following generations.

Implications of cancer DNA

1. Better understanding of the pathogenesis of cancer may be derived from pinpointing specific sequences coding for the various subtypes of the disease.
2. 'Neutral genetic changes without phenotypic consequences are invisible to Darwinian processes of selection' (14). In present day concepts, no natural selection is even hypothetically assumed possible on a genotype level.

The 'cancer initiating genes' thesis presented here, assumes that natural selection may also take place on the level of genotype variance. This hypothesized cancer mechanism derives its existence from a phenotypal advantage (clinically apparent tumors triggered in susceptible individuals) but, ultimately functions as a genotype screening mechanism.

Acknowledgements

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