



Cancer Disease: A New Hypothesis of Interpretation and Therapeutic Approach

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Abstract

The authors propose a new research hypothesis about cancer pathology, starting from the hypothesis of considering cancer as a process of adaptation to changed conditions, which can be internal or external to the organism, with the aim of reaching the survival of the species. The authors, in the present work, put forward an hypothesis which is based on the observation of natural phenomenon, referred to the previously described mutations, some as natural evolutionary phenomena which are genetically transmitted as a result of environmental adaptation (for example the color of the skin), some others, with the same modalities, as pathological phenomena (for example thalassemia), some others as more flexible environmental responses (for example human height in relation with the improved food conditions), some others as immediate responses of the organism in order to defend its own biological integrity and individuality (for example violent anaphylactic reactions which happen as consequences of extraneous proteins introduction).

In the latter category, within the hypothesis put forward by the authors, we find the “event of cancerous modification”. The observation of the organism behavior when there is a noxa which is perceived as a biological risk, produces a response which is related to the perception of the degree of danger of the risk itself, expressed with precise parameters, such as biological reaction intensity, its immediacy, the index of involvement of some organs and apparatuses together, the type of organs and apparatuses involved. The second element is the frequency-intensity ratio of the stimulus during the time.

An occasional but particularly intense stimulation produces an immediate and intense response- reaction, while a low intensity but constant frequency stimulation, produces a slower response, with a process which tends to let the reaction to become chronic. The pathologic evolution of the reaction stimulus-response is therefore related to these parameters and, in particular, the response to a violent reaction can originate a lethal event which is completely the opposite respect to the primary purpose of protecting the biological integrity of the individual; on the other side, a persistent and low intensity stimulus, can originate a chronic inflammatory response, with an evolution which is much slower, but not less dangerous during the time.

Between these two extreme parameters we can situate the event *cancerous modification*.

Cancer is not a Disease

Attacking and destroying cancer

Every natural event can't prescind from nature itself and its working schemes. That is to say that, in case of cancer pathology, nature behaves in such a way: “reacts to an external or internal stimulus of the organism itself by modifying the cellular structure in order to adapt it to the changed conditions”.

Inflammation plays an essential role in cell transformation processes: the inflammatory process is at the base of every mutation. Inflammation intervenes in all the reparative mechanisms, and constitutes, or better includes, the biological switch which regulates the cellular transformation processes. The genetic mechanism heads up the beginning evolution of the single originating cell, its partition and differentiation in cellular lines and in the further development of vessels, organs and apparatuses. The first step of research about cancer causes has to start from this issue.

We go on defining as a “pathological” tumoral process, a process of cellular differentiation which, at the beginning, actually does not have any pathological trait, even if the final result of this cellular adaptation process is a clearly pathological event.

As we know today, there are so many factors which can determine cancer pathology, that they cannot be really considered responsible for a cancer. The expression “Cancer is not a disease”, beyond the “journalistic” title, outlines a concept that we consider essential for the research: cellular adaptation. Cellular adaptation phenomena are common in nature and they are not classified as pathological events but as species evolution events. Species evolution events are not considered as pathological ones, but simply as evolutive adaptation events, which are implemented by nature for a specific species, when some environmental changes happen. Species evolution process is widely observed in nature: just to give an example, the increase in height over generations is a response to the improved environmental conditions (various types of food are more available) which determines a delayed cartilages connection.

This is a natural phenomenon which is a response to a precise objective of nature, which is always the same: species conservation. As we can see, no research is possible and it can bring to an essential assume; the question: which objective is sought by nature? Which is

the objective of a specific natural phenomenon? What nature wants to modify in order to maintain the continuity of species? When environmental conditions get worse (food shortage, etc.) nature let cartilages to connect each other earlier, generating tinier individuals which are able to survive better in adverse environmental conditions.

Another example of natural adaptation is mediterranean sickle cell anaemia phenomenon, which is present in people who have been living for generations in marshy malaria zones. Their red blood cells gradually modified themselves through generations, becoming unsuitable to host malaria plasmodium, so in this way these individuals become resistant to malaria and do not get sick. Anyway these individuals, because of their red blood cells modifications, are exposed to an another kind of pathology.

Starting from these observations, we can see how important is facing “cancer disease” from a different point of view, completely opposed to the present one, which, being affected by the “antibiotic mentality”, which wants to individuate a substance with the aim of selectively destroying that specific tumoral cell. This is the same thing we do when we individuate the appropriate antibiotic therapy using the antibiogram.

Which can be the essential elements of a new research method in oncology? Or, in other words, what determines the carcinogenic evolution of a cell?

- genetic predisposition
- triggering event (induction) in cellular transformation
- activation of the phase change biological switch
- molecular mutations of the cell
- alteration of intracellular relationships, intended as loss of interdependence relationships functional control
- new modified cellular organism working principles

Genetic predisposition is the main research line in the biological area, certainly it is fundamental in order to approach cancer pathology in the right way. We permit to except about the way of interpreting the genetic relevance of cancer evolution.

This is not, as it is commonly believed, a genetic alteration which can determine the onset of a specific tumor pathology (if not, we should be able to make a list of all the genetic alterations for every single tumor pathology) (if we succeed in the common effort of interpreting the role of every single segment of the genetic code) but to attribute to the genetic influence of the characteristics acquired over one or more generations, which can determine or facilitate the activation of that molecular switch which can originate the phase transition, and then cellular modification.

Histopathology Molecular Oncology

The mechanism of cellular modification, as a consequence of a stimulus, happens in two distinct moments

- cellular division
- genetically transmissible genetic modification

Different stimuli, which can be internal (hormonal, etc...) or external (chemical, physical etc...) produce firstly a local modification, which happens in the moment of the cellular division.

The cell, under the continuous pressure of the stimulus, destroys itself or modifies its own genetic patrimony: in this case, the modification can happen in two different directions:

- progressive, low entity, genetic modifications
- in presence of a protracted stimulus, backwards cellular regression goes along the primitive differentiation path, with the attempt of carrying out a total reprogramming, having, as a consequence, the loss of the connections with the adjacent cells.

Phenotype Changes which Distinguish Tumor Cells from Normal Cells

Cancer generates when controls in cellular division do not work properly.

Changes producing an uncontrolled cellular growth

Autocrine stimulation: Most of the cells “decide” if divide or not just as a response to some signals coming from neighboring cells; positive signals stimulate division, negative signals stop proliferation. On the other hand, most tumor cells produce themselves stimulation signals (growth factors) as part of a process called autocrine stimulation, or became insensitive to negative signals.

Loss of contact inhibition: Normal cells stop dividing when touching another cell, as demonstrated by normal cells which, when kept in culture, set up monocellular layers on the bottom of culture plates; tumor cells, which have lost contact inhibition, climb over each other producing layers of many cells. This change in behaviour contributes to set up disorganized masses of cells, which are peculiar in tumors, and are very different from the organized disposition of normal cells.

Resistance to apoptosis: When deprived of growth factors or exposed to damaging agents, such as toxins or X rays, normal cells die. Programmed cell death, or apoptosis, is activated by the expression of some genes of the cell. This mechanism, which prevents cells from proliferating when they should not, and eliminates severely damaged cells, probably is a protection against early stages of cancer. Most tumor cells are much more resistant to apoptosis than normal ones.

Gap junctions’ loss: Normal cells are linked to neighboring ones, through little pores, or gap junctions, which are present in their membranes. Gap junctions allow to transfer little molecules, which are very important in cellular growth control. Most tumor cells have lost such communication channel.

Changes producing genome and karyotype instability

Problems in DNA replication mechanisms: Most of the times cancer origins from cells which lost the ability of duplicating accurately their genome. Cells developed some systems to repair damaged DNA; these systems include enzymatic processes for repairing mismatch and damages which are caused by ionizing radiation and ultraviolet rays. Studies on yeast and bacteria, demonstrated that, in DNA reparation, defective mutant organisms have a highly increased mutation rate. High mutation rates can determine cancer, as shown by the xeroderma pigmentosum hereditary syndrome, which predisposes to skin cancer.

Increase in chromosomal aberrations: Tumor cells karyotype often contains important rearrangements, such as broken chromosomes with some segments attached to other chromosomes (crossing over), multiple copies of single chromosomes, large chromosomal segments deletion and entire chromosomes deletion. All these changes can be detected by chromosomes painting. Several studies confirmed that tumor cells present a reduced accuracy level in replication. For example, normal fibroblasts have an undetectable gene amplification rate (an increased number of copies for a gene) while in tumor cells this rate is very high, 1 for 100 cells. This kind of amplification can improperly activate some of the genes which control cells proliferation.

Although it is confirmed the fact that tumor cells have a higher frequency of chromosomal aberrations, probably just a small fraction of these chromosomal rearrangements brings to a cancer development. For example, solid tissue tumors normally contain many chromosomal aberrations, but many of these are not recurrent in all tumors. However, few rearrangements appear regularly in specific types of tumor. Some examples: translocation of the chromosomes 8 and 14, which has been found in patients with some types of lymphoma and translocation of the chromosomes 9 and 22 which has been found in some types of leukemia.

Changes producing a potential immortality

Loss of cell division limitations: Many normal cells (except stem cells) die spontaneously after a precise number of cell divisions is done. Senescence of normal cells and their natural death is something evident, both in culture and in vivo. Tumor cells instead, can divide indefinitely.

Capability of growing in culture: Cells deriving from tumor cells, can be usually put directly in culture, where they grow well, originating tumor cellular lines suitable for research purposes. Tumor cells instead, do not grow well in culture. This difference between normal and abnormal cells is even more evident in grown up cells, like isolated clones, on Agar, probably because normal cells have to face more genetic changes, respect to tumor cells, to become competent for cellular division in culture.

Reactivate telomerase activity: Most human somatic normal cells do not express telomerase enzyme, and this lack in expressing telomerase prevent them from reproducing efficiently sequences which are situated in telomeres, at the end of their chromosomes. As a consequence of this, after a certain number of cell divisions, telomeres become shorter and shorter until they contribute to cell senescence and cell death. Tumor cells reacquire the capacity of expressing telomerase, a feature which probably contributes to their immortality.

Changes which allow tumor to destroy neighboring tissues and to invade distant tissues

Capability of forming metastases: Normal cells remain within well defined confines. Tumor cells instead often acquire the capacity of invading neighboring tissues and transferring through blood circulation, in order to invade distant tissues. Metastases formation (invading distant organs and tissues) is a complicated behaviour which requests many genetic changes.

Angiogenesis: Once the adult human body has developed, no more new blood vessels are formed, except wound healing. However tumor cells produce a substance that induces blood vessels growth close to them. These new vessels are the mean through which tumor can get new nutrition sources; these vessels are also a sort of emergency exits through which tumor can metastasize.

Eluding immune system surveillance: Human immune system can recognize tumor cells as extraneous agents and attack them, contributing to eliminate tumors before they become big enough to be detected clinically. Patients affected by cancer often have antibodies or T killer cells, which are directed against tumor cells. Tumor cells which succeed to remain alive and to proliferate then develop, in such a way, the capacity of eluding the immune system surveillance.

Stem Cells

The carcinogenesis process starts as a consequence of multiple factors; these factors can be internal or external (carcinogenic), and the organism has some mechanisms acting in the way of neutralizing the carcinogenic factor activity, repairing the damaged DNA or destroying the altered cell. One of these mechanisms is the immune system, which supervises the onset of an identified cancer and destroys it.

But where the phenomenon of “regression undifferentiation” is part of a process which is apparently “normal and recognized” by the organism, finalized to a readjustment to the changed environmental internal or external conditions, therefore without the presence of specific antigens, the immune system does not intervene.

The finding of cancer stem cells to put forward the hypothesis that these cells are the origin of tumor mass formation, its maintenance and its metastatic diffusion.

The stem cells are: a) embryonic stem cells (derived during the blastocystis phase), totipotent, able to become all tissues in the body, b) adult stem cells, derived from umbilical cord, multipotent, that can

just differentiate into some tissues in the body and c) cancer stem cells, which are present in the tumor mass and are apparently related with the adult stem cells.

Cancer stem cells are a small group of cells which are responsible for metastasis and recurrence following an apparent cancer eradication. Cancer is a complex tissue that perfectly follows the same reparation and self-regeneration criteria which characterized sane tissues. Within the hypothesis put forward by the authors, the insurgence of a cancer is a “natural” process, which is started by the organism, through cellular regression and along the original differentiation line, in order to obtain a readjustment to the altered conditions which induced the cancer itself. If the mutation happens through an hypothesized “phase change switch”, the presence of cancer stem cells is the expression of this regression and of the consequent loss of coordination with the adjacent cells, and then the abnormal uncontrolled proliferation.

The adult stem cell is integral part of tissue reparative phenomena, and, the presence of cancer stem cells having the same histological features of the tissue from which they derive, is the expression of this readjustment phenomenon. In this way, the carcinogenesis process appears as an evolution activated by the organism with the same modalities which are considered of its own, along innate and expected adjustment paths, which are perfectly natural and compatible and, above all, not attackable by designated defenses, such as the immune system.

State of the Art: Role of Inflammation

The inflammation process is a phenomenon whose presence in nature constitutes the basis of every reparation process of the organism. The inflammatory response, mediated by lymphocytes, is a response to an underway pathologic process. Every injury, loss of substance or lesion of the organism is cured through a preliminary inflammatory response, which moves the defense mechanisms, activates the reparative processes, and causes a modification in the cellular elements.

Through these modifications every single cell obtains a reparative capacity. The prerequisite of certain cancerous tissue modifications is often an inflammatory process which reacts to a noxa that can be internal or external to the organism.

The induction of a transformation from normal tissue cell into cancerous cell, under the hypothesis put forward by the authors, cannot be considered a pathological phenomenon, but a natural process which is activated by the organism in order to adapt the functions of that organ to the changed chemical, physical, hormonal, environmental conditions internal or external to the organism itself, in order to produce, through a process of cellular differentiation, those modifications needed to make the organism itself suitable to survive. The actual state of the art in the oncology research, is deeply affected by the influence which the actual antibiotic era has on the medical scientific thinking.

This important discovery together with the deep revolution in the therapeutic field, which happened as a consequence of the discovery itself, influenced in a crucial way the oncology research orientation, by addressing it to the antibiotic treatment model.

The organism, if a noxa of various type is present, (chemical, physical, hormonal, biological, etc.) which has enough intensity and duration, activates a cellular nuclear mutation finalized to rearrange the function to the changed conditions which were caused by the noxa.

The state of the art of cancer treatment consists fundamentally on early diagnosis and on the total eradication of the affected part. Similarly, therapeutic treatments of tumor mass ablation, in presence of metastatic lesions, need radiotherapy or chemotherapy, are having results which often do not bring to a definitive solution. Up-to-date tendencies, which consider the introduction of substances that can be selectively captured from cancer cells, with the aim of realizing

a selective and focused destruction of the cells themselves, reveal a parasurgical therapeutic approach which is far from the real objectives of the process which is run by the organism in order to protect and guarantee its own existence.

Research Hypothesis: The Phase-Change Biological Switch

The hypothesis put forward by the authors, is that the organism, while acknowledging information about the chronicity level of the lesion and the inadequacy of the reparative processes, activates a sort of phase-change biological switch, which is suitable to allow the cell to go back over the initial process of differentiation, with the aim of making all the modifications which are suitable to adapt to the changed conditions and to allow the survival. This process, known as evolutionary phenomenon of environmental adaptation, needs long times (many generations: see thalassemia). In the case of cancer, the time which is necessary to the adaptation process and to the needed gene mutations relative to it, is much shorter if compared with the individual average lifespan, and can bring it to an end rather than to the pursued adaptation.

In this perspective, is easy to understand how, even if absurdly, the definition of cancer as a disease does not have any foundation if analyzed with the perspective of nature which is directed to species conservation through the activation of the hypothesized phase-change switch.

Switches of Phase Change Process

We know that a stimulus, which is protracted for a certain period of time, originate a temporary neural modification (in the neural cell); this modification, under the action of a persistent stimulus, can originate a permanent modification, which can be genetically transmitted.

This observation introduces two concepts, which maybe are not new, but we believe they are essential.

- Surprising cell plasticity at molecular level
- The concept of nervous tissue as a neural peripheral organ (epithelial tissue = nervous tissue): epithelium intended not as a covering tissue but as a highly specialized organ which has a close connection with the central nervous system, having the function of neuro modulator.

Let us analyze cell plasticity at molecular level.

The cell, analyzed as a functional interdependent complex, reproduces in an infinitely small setting, the same schema of the whole macroscopic cellular set. In the single cell we find the same functional logic of the complex organism intended as an organized multicellular set. This concept can be easily and logically understood, because we are speaking of a set of functions reproducing a demultiplied specific function of every single cell.

In this way, if the cell differentiation process translated into a highly specific function of the single cell and if such a cell has plastic capacity, if it is intimately modifiable thanks to biological switches which can interfere with the normal cell process of modifying DNA and responding to new needs (= internal or external stimuluses) we have to individuate such biological switches and to find a way to activate or inactivate them, leading the phase transition process Individuating the switches (molecular?) of the phase change process and individuating activation and inactivation mechanisms (molecular?) of them.

Which is the nature of such phase switches? Proteins? Enzymes?

We can hypothesize a biological molecular mechanism as an essential part of cell evolutive process, maybe a residual of that evolutive process (memory?) which has remained latent but able of being reactivated when occurring a chemical, biological, physical stimulus having adequate intensity and persistence.

Cell modification involves DNA, and such a modification (which can also be induced by a virus) has the aim of originating a cell regression phenomenon along the evolutive differentiation path in order to reprogram the cell itself to make it compatible with the stimulus. Undifferentiation, regression, reprogramming phenomena happen together with cell division phenomena and, at this step, activate biological switch function, which reprogram the two new cells originated by the stimulated mother cell.

Let us notice that in nervous system (= nervous cell) cellular regression phenomenon does not happen, because the neuron is a perennial element not subject to cell division (nervous system cancer does not exist). A persistent stimulus (conditioning) is however able to produce a modification of the nervous cell; this modification can be genetically transmitted when the stimulus (conditioning) became persistent enough.

The cell, which during the cell division has seen its DNA modified together with interconnection links with the neighboring cells, progressively unfastens from the functions executed from the organ of which the cell itself is a part; therefore, the cell follows an independent reproduction path according to the new modified DNA schema, giving origin to a tumor mass which, progressively, induces compression or altered substitution of the functions of the organ in which it is located.

Cell Neoplasia and Phase Transition

Correlation between cell neoplasia and phase transition outlines a common mechanism which justifies the assumption which is the object of this paper "cancer is not a disease".

As a matter of facts, from a physical point of view, water, as the temperature varies, became ice or vapor, and these new conditions are not considered pathological differentiations from the initial liquid state. The switch determining the phase transition from liquid to gas (vapor) or from liquid to the solid state (ice) is the temperature: in this case the switch has a physical nature.

Let us make a consideration: at the molecular level we do not speak of physical, chemical or biological state, but we speak of molecular switch; crossing over of molecular elements is the peculiarity which differentiates physical switch from a chemical or a biological one.

The energetic characteristic of a biological switch is very different from the one of a chemical or physical switch, because energy which has developed from its functioning has the same nature of the one derived from the cell unit to which it is referred.

The functioning is anyway particular, it appears as modulated on cell functioning, and intervenes as a response to an internal or external stimulus in a precise moment which is the one in which cell division occurs, and we would say that it is closely correlated with cell division or even that it is an essential part of it; that is to say that the biological switch should be intended to be a protein (enzyme) leading the division itself, because the possible cell DNA modification happens exactly at this stage.

This fact demonstrates that the organism, exposed to any stimulus, such as a physical, chemical, biological one always reacts with a biological response which is typical of the targeted organ using as a phase transition biological switch the process which starts the cell division.

Cell division is a process activated by cell ageing, which responses to precise parameters that transmit accurately characteristics of the cell during chromosomes cross over; the secret of the biological switch operation is in the early stage of cell lines differentiation of a development process realizing one-way precise schemas which maintain the memory of every single stage of the evolution differentiation process.

Maybe we can analyze one interpretative key of the two phenomena, tumor differentiation and cell division, within the stem cells context; stem cell is the only cell remaining totipotent.

Chronical inflammatory state is a particular moment which can intervene as a mediator between the normal cell division state and the cell mutation towards a tumor line. Inflammation is, as a matter of facts, a particular condition of the organism which physiologically intervenes in every reparation process, stimulating cell division, and, as a consequence, tissue regrowth. Within cell regeneration we have to consider the different tissue reparative typology.

Chemical, physical or biological stimulus, which can be internal or external to the organism, can activate the chronical inflammation process, and, through this, it activate a response, which is initially oriented to reparation, but after that, while the inflammatory process became chronic, it is oriented to an attempt of adaptation thorough a cell mutation finalized to readapt the organism to the changed environmental conditions.

A less known fact is that the epithelial tissue, which covers both internally and externally all the organs, is not simply a covering tissue with nerve endings, but, deriving from the same ectodermic embryonal sheet where surrenal glands, retina, organ of Corti in the auditory apparatus originate, should be considered, as the other one, a high specialized organ of the same kind of brain, a real apparatus having neuromodulatory functions, at the peripheral level of the various organs.

Such a consideration about the real function of the epithelial apparatus and its neuromodulatory functions, originates from considering neuromodulation with a different meaning from the one which is commonly used. From this point of view neuromodulation is a linking activity between central nervous apparatus and peripheral nerve apparatus, having information capabilities at central level about what happens peripherally, and regulatory capabilities about every single organ and apparatus functions, through a feedback mechanism.

Within a highly complex and organized system, which continually operates 24 hours a day a complete check up of its every single function, maintaining them under control and intervening to correct possible altered parameters, providing for possible reparation operations which are necessary after altered parameters are precisely and promptly identified.

Organism individuates with absolute precision every alteration, lesion or damage, and promptly activates all the necessary reparation processes.

In the same way, with the objective of individual's preservation, the organism provides to realize all the structural changes which better permit to it to adapt to the changed environmental conditions. This adaptation process has to consider as a physiological consequence which is proper of the organism. Such a plastic capability requests an obliged path which goes through a slow selection process which can operate necessary mutations within useful periods of time. Generational selection means genetic modifications, which through paths which select stronger individuals which are able to generate new strong individuals. All these considerations explain the initial axiom "cancer is not a disease" and, as a consequence, they justify the orientation towards a different research line [1-13].

Research Orientation

In the hypothesis put forward by the authors, the new orientation of oncology research has to be oriented to the identification of the close relationships which exist between brain and peripheral organs, and, in particular, to the feed-back systems, to the directional and actuative properties of the brain, to the differentiation and regression processes of cells, to the mechanisms which allow the recognition of the pathological state of the organs.

A particular attention should be paid, in the authors' point of view, to individuate the phase- change biological switch (which can be a protein or a combination of factors) which, as the authors hypothesized and highlighted, constitutes the decisive key of the cure against cancer and, however, the real objective of a research which, recognizing as many different forms of pathologies as the affected

tissues, is the unique expression of an essential objective, which is, from nature's perspective, the individual's continuous adjustment to the environment: this represents the guarantee of the individual's survival.

Conclusions

This paper represents a strong signal in order to promote a new direction in cancer research: individuating the hypothesized PHASE-CHANGE BIOLOGICAL SWITCH which constitutes the common denominator of a multiple characteristics disease. Experience teaches that often a scientific discovery happens because someone hypothesized its existence a priori.

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