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REVIEW AND HYPOTHESIS

Cancer is the Reactivation of Abort Mechanisms from Embryogenesis in Later Stages of Life

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Abstract. **Cancer is the reactivation of mechanisms from embryogenesis which were originally used for detecting defects or malfunctions in the developing fetus by spontaneously aborting fetuses with chromosomal abnormalities. Cancer remobilizes and reactivates those mechanisms to fulfill its specific purpose which is the termination of the organism. This is in my opinion the genuine purpose for the 'growth till death of the organism' process as seen in cancer. The cancer process starts with the altering of the status of a distressed 'detection cell' from mature to immature which activates the uncontrolled growth mechanism. I suspect that this cell signaling alters specific embryogenic genes for this purpose.**

The most important feature is the blocking or disrupting of the highly regulated intracellular control processes. Because of the disruption of the internal cell cycle mechanism the distressed 'detection cell' will continue only as a growth and proliferating machine which is facilitated by mechanisms which support and stimulate this goal. These are the so called cancer superpowers. These detection cells are the initiators of the cancer process. A network of these special kinds of cells monitor when an organ or tissue has reached its mature form and size. I assume they also monitor the homeostasis in the cellular micro environment of the constituent parts of the organism.

Another example of the use of mechanisms from embryogenesis is metastases which show striking similarities with the mechanisms used in the fertilization process by sperm cells. I suspect that the mechanisms of metastases are triggered by expressing embryonic sperm genetic complements in specific cancer cells.

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1. Clinical Observations in Cancer Research

This essay seeks to review the literature that discusses a cell-centered view concerning the origin of cancer, which is different from the gene-centered view of cancer origin. Here I will focus on discussing and developing some of the new viewpoints rather than dwelling on what might be potentially wrong with some of the current dogmas in cancer research. There are excellent articles and books written in which it is made quite clear about some of the shortcomings [1].

What is clear in the cancer literature is that the big question still remains unanswered, i.e., what is the origin of cancer? It is generally assumed that a better understanding of this question would lead to a better understanding of many of the mysteries of the cancer process. A workable theory of cancer also has to explain both why it is predominantly a disease of old age and why we do not all die from it, as it was stated in a Scientific American article [2].

In cancer research it is well established that a cell must acquire several extraordinary features to be malignant. It is generally agreed by the cancer research community that five or six different regulatory systems must be perturbed in order for a normal cell to grow as a cancer. Robert Weinberg and William Hahn published the following characteristics that all life threatening cancers exhibit [3,4].

1.1. Marks of malignancy: The six diabolical superpowers of cancer

1. Growth even in the absence of normal 'Go' signals.
2. Most normal cells wait for an external message before dividing. Cancer cell often counterfeit their own pro-growth messages.
3. Growth despite 'stop' commands issued by neighboring cells. As the tumor expands, it squeezes adjacent tissue, which sends out chemical messages that would normally bring cell division to a halt. Malignant cells ignore the commands.
4. Evasion of built-in autodestruct mechanisms, halting apoptosis. In healthy cells, genetic damage above a critical level usually activates a suicide program. Cancerous cells bypass this mechanism, although agents of the immune system can sometimes successfully order the cancer cells to self-destruct.
5. Ability to stimulate blood vessel construction, angiogenesis. Tumors need oxygen and nutrients to survive. They obtain them by co-opting nearby blood vessels to form new branches that run throughout the growing mass.
6. Effective immortality. Healthy cells can divide no more than 70 times. Malignant cells need more than that to make tumors. So they work around systems- such as the telomeres at the end of chromosomes-that enforce the reproductive limit.
7. Power to invade other tissues and spread to other organs, metastasis. Cancers usually become life-threatening only after they somehow disable the cellular circuitry that confines them to a specific part of the particular organ in which they arose. New growths appear and eventually interfere with vital systems.

In an attempt to formulate a unified theory about the origin of cancer, it is crucial to look beyond mundane genetic mutations, signal pathways, and molecular signatures. It is also important to explain how the so called cancer superpowers fit in this new hypothesis on the origin of cancer. Other important topics and observations in the cancer literature are listed in this section.

1.2. Popular conceptions of cancer

Many of the traditional assumptions and popular conceptions of cancer such as multi-step carcinogenesis may need adjustment in order to formulate a more useful and better explanatory theory of the origin of cancers. Until recently, it was common knowledge to attribute all the ma-

lignant features of a cancer cell to its aberrant genetic changes or signal pathways because of the prevailing belief that they are operative and responsible for its malignant behavior. Many of the previous and current scientific objectives and methods may be missing the mark because the cancer targets which have been aimed for are either wrong or irrelevant and because the hypotheses cancer researchers have adopted have been misguided or misleading. It is also a well established fact that spontaneous mutations are unlikely to cause the initiation and progression events that lead to most invasive, metastatic neoplasms [5]. To support this conclusions are the observations that on several occasions, cancer targets have been detected in normal or nonmalignant cells. An example of cancer targets occurring in normal-appearing tissues is the phenomenon of field defect [6].

1.3. Reactivation of embryonic genes

A recurring theme in cancer is that embryonic genes or pathways normally turned off in adult tissues are according to current dogma mistakenly turned back on in cancer. Carcinogenesis seems to resurrect preexisting but dormant signaling networks or pathways that had been active during embryogenesis. It is established that during malignant transformation innumerable embryonic markers, pathways, and processes resurface during malignant progression. One cannot help but notice that the same biologic properties that facilitate embryonic development also favor malignant transformation [7].

1.4. Stem cell theory of cancer

In cancer research the latest hot topic is the stem-cell origin of cancers. On the surface, it seems that a malignant cell and a stem cell are simply mirror images of each other. There appears to be malignant potential in every stem cell and stem cell potential in every malignant cell. According to the theory of a stem-cell origin of cancers, when a stem cell converts to a cancer cell, the cancer cell retains many stem-cell features. This is in stark contrast to the prevailing view that a mature cell transforms into an immature malignant phenotype by acquiring mutations. The stem cell theory predicts that the current obsession with cancer genetics will shift to stem-cell targets [8]. However, this theory also assumes a random mutation in a stem cell as the initial step in the cancer process, which is actually not a real departure from the original unsuccessful gene mutation dogma.

The common theme between my view and the stem cell theory is a cell-centric rather than a gene-centric outlook when considering the origin of cancers, and the appreciation of the vital importance of the microenvironment around cells and how a malignant cell may be influenced by its neighboring cells and its immediate niche. The difference with my hypothesis is that in my view specific so called differentiated somatic 'detection cells' can become cancer cells by reactivating abort mechanism from embryogenesis, which makes it unlikely that stem cells are the origin of cancer cells.

2. What Is Cancer?

Cancer is an evolutionary process or program with a set of mechanisms that will be triggered by a so called disrupted 'detection cell' when for a prolonged period a specific threshold of certain stressors are exceeded in the cellular microenvironment of the constituent parts of the organism. This evolutionary process evolved in multi-cellular organisms to terminate organisms when sustained unviable conditions were detected in the external cellular environment. Besides the major concepts in evolution and nature such as: reproduction, growth, ageing and death, we have to include the process of what we call cancer. The concept of reactivation of evolutionary mechanisms within the life-span of an adult organism is not fully acknowledged in biology at present.

My main thesis is that the cancer process

remobilizes and reactivates existing mechanisms in the specific organs and tissues to fulfill its intentional purpose which is 'to grow the organism till death'. Cancer is reactivating embryological processes which were originally used in embryogenesis for detecting defects or malfunctions in the developing fetus by spontaneously aborting unsustainable variations of the fetus. Spontaneous abortion, also known as miscarriage, is the expulsion of an embryo or fetus due to accidental trauma or natural causes before approximately the 22nd week of gestation. The most common cause of spontaneous abortion during the first trimester is chromosomal abnormalities of the embryo/fetus, accounting for at least 50% of sampled early pregnancy losses [9]. For this reason, the idea that most clinical miscarriages reflect the adaptive functioning of an evolved mechanism of quality control is now widely accepted [10].

I hypothesize that the rejection of a fetus with chromosomal abnormalities occurs via the same 'growth till death' mechanism which is reactivated in the cancer process. Detection cells in the constituent organs and tissues monitor the extra cellular environment to check whether it is viable for the normal cell cycle to take place. If it is contaminated for certain period of time with excess levels of specific stressors, the abort mechanism is switched on in the distressed detection cell. This termination or rejection process is in my opinion the genuine purpose for the 'growth till death of the organism' program only in later stages of life, as seen in cancer. I assume that when a malignancy arises, homeostasis in the cellular micro environment is violated.

In the cancer literature, it has been noted that more than 100 types of what we have summarily grouped together as 'cancer' arise from all sorts of tissues. I hypothesize that, contrary to the cancer dogma, all of them are subjected to the same underlying program. According to the proposed hypothesis, cancer is from the perspective of the disrupted detection cell an intentional mechanism. The cancer process serves a specific purpose and it is not a random process which progressively accumulates genetic mutations as commonly is assumed by most cancer researchers.

I contend that the recurring theme to solve the mystery of cancer is that most if not all of the intriguing properties of malignancy can be traced to the remobilizing or reactivating of mechanisms used in the rejection or termination of unsustainable forms of the developing organism in embryogenesis. Reactivating implies an intentional rather than a spontaneous action and suggests a deliberate manipulation of the genetic code or expression.

2.1. The initiator of the cancer process

In embryogenesis the development of an organism is closely monitored by the cells in the constituent organs and tissue. I assume that the assembly of an organism is monitored by a network of 'detection cells' to determine whether the living conditions and homeostasis of the micro environment is sustainable for cell division. Another important feature of these networks of detection cells is the monitoring and signaling to determine when constituent parts of the organism have reached their adult form and size. This is a signaling cascade in a network between cells within specific organs and tissue and of course between them as well in order to build and assemble a healthy biological sustainable organism.

What happens in cancer is that signals are generated by a distressed detection cell when it is surrounded by an excess of specific stressors and thereby creating a hostile environment with the result that this environment is perceived as not sustainable for this organ or tissue. After specific periods of exposure to excess levels of stressors the only mechanism a distressed detection cell can resort to in such conditions is to activate the abort mechanism by which the mature status of the cell is switch to that of an immature cell. This feat is accomplished by switching on embryonic genes via cell signaling. I contend that activating embryonic genes to start the

growth mechanism is one the few deliberate gene mutations in the cancer process. Most cancers occur in adult cells, that is why the mechanisms that confirm the mature status of a cell are switched off in order to start the growth till death mechanism by mimicking an immature cell. This process is similar to how it is done in embryonic stages of development when an immature cell will never reach its mature state when the conditions are not viable.

I contend that these so called 'detection cells' are the initiators of the cancer process. Nature must have enable these networks of special cells to monitor the living conditions in the cellular micro environment of constituent parts of the organism, not only in embryogenesis but also in later stages in the life of the organism. The logical conclusion is that these 'detection cells' must be quite robust because an organism cannot afford to be terminated by every disruption at cellular level. That is why these cells are more susceptible to internal micro environmental disruptions than from direct external stressful exposure.

In my opinion cancer in all its forms is an evolutionary well-established process which evolved to tackle a specific problem which is the deliberate process of terminating the organism when 'detection cells' of its constituent organs and tissues have detected that the microenvironment of the detection cell is contaminated or that the homeostasis is disrupted.

2.2. Reactivation of abort mechanisms from embryogenesis

The evolutionary trick applied by a detection cell in distress is to convert its internal control system to an immature state via cell signalling. The biological implication of this immature status is that the specific detection cell is triggered to grow to reach its mature state or mark which is blocked or disrupted in the abort and cancer program. The cell is now locked in a permanent loop of immaturity and will indefinitely continue to grow.

I assume that a certain level of stressors (e.g., aberrant hormones or stress signals) is exceeded in the cell microenvironment whereby the stressors are not perceived as familiar versions of well known substances. Consequently, the receptors on the distressed detection cell surface will trigger the termination or abort pathways which will mobilize the well known cancer super powers. An important distinctive feature is that this termination process overrules the apoptosis mechanisms which are subordinate to the abort or termination mechanisms. Apoptosis seems to be more restricted at cellular level while the cancer or abort program is targeting the organism itself.

As discussed earlier the conversion to an immature status by the distressed detection cell is done via cell signalling whereby embryonic genes are switched on. The converted 'immature cell' will start to grow and the cancer process is initiated. By mimicking an immature state this disrupted adult detection cell will start growing again. One of the next steps in the cancer program is the proliferation of this distressed cell, which is a separate mechanism, is done by disrupting or blocking the strictly regulated internal cell cycle which will cause asymmetric cell divisions. Asymmetric cell division in this situation is the uneven distribution of chromosomes between two daughter cancer cells. These consecutive asymmetric cell divisions will create bewildering amounts of genetic variations in the copies of the distressed detection cell, which has become a tumor by now. The production of a wide variety of phenotypes in the daughter cells of the cancer tumor is actually the purpose of cancer cell proliferation. Their goal is to survive in as many circumstances as possible in order to terminate the organism. All in all what is monitored in adult cancer is a replay of mechanisms used when an unsustainable form of a developing organism is spontaneously rejected or terminated at an embryonic stage.

Many of the malignant properties (e.g., dormancy, drug resistance, immunity) associated with cancer cells are the effect of this reacti-

vation by the distressed detection cell. Additional mutations in the same pathways that regulate these vital functions are redundant or unnecessary for the formation of cancer. Only a few critical mutations, which I already mentioned are actually pivotal during carcinogenesis and are sufficient to push a distressed 'detection' cell into the ways of a cancer cell.

2.3. Why cancer happens in old age

The main problem from a cell perspective is the disruption of the homeostasis of the cellular microenvironment. Most organisms are programmed to maintain a certain form of Homeostasis—control, balance and organization—in their cell system. In old age this micro environmental balance seems to be a more difficult problem to maintain than at a younger age because of deterioration and wear and tear of the overall human organism. I suppose that in old age the specific stressors or substances are not discarded appropriately from the microenvironment of the distressed detection cell.

The removal of harmful substances from the cell environment becomes probably inadequate in old age. As a result of old age certain harmful substances accumulate for a longer period of time in the detection cell microenvironment. These events are unnoticed at an organism level but can be permanent stressors at a cellular level and in time the 'detection cells' will trigger the cancer process with the well known observed characteristics and ultimately terminating the organism. Such a 'detection cell' doesn't have to be a stem cell to perform this specific task because all the characteristics of cancer can be explained with the mobilizing and reactivating of existing embryonic mechanisms used in later stages of life by differentiated somatic cells.

3. How to Understand the Mechanisms of the Cancer Process

In biology the formation and construction of the human organism, actually every complex organism is very strict and conservative in order to reach the complex and properly functioning living creature. Sexual reproduction also enforces conservation of a species specific karyotype because embryonic development depends on absolute chromosomal conformity and coherence.

Karyotype is the number and visual appearance of the chromosomes in the cell nuclei of an organism that define each species. Thus, healthy cells are strictly bound to predetermined characteristics and specific cellular programming of the organ or tissue of which the cell is a part of. Aberrant or deformed cells or wrongly distributed chromosomes in an embryonic phase are not viable and unsustainable variations will be aborted. Cancer cells on the other hand are not bothered with these strict rules. However, it is surprising that cancer researchers do not seem to recognize the similarities between these observations.

3.1. Gene mutations and aneuploidy

In cancer research it is observed that in every form of cancer individual genes are mutated, but also entire chromosomes which are made up of thousands of genes are mixed up, copied, broken and put back together structurally different or even missing [11]. What the proponents of both the gene mutation theory and the chromosome mutation theory are missing is that they are monitoring the effects of the same process. As already mentioned, these observations are the effects of the reactivated abort program from embryogenesis.

In biology, it is a fact that embryonic development depends on perfect chromosome conformity and coherence. Cancer cells on the other hand are not bothered with these strict rules. Proponents of the chromosomes mutation theory argue that the karyotypes of solid tumors are always aneuploid, a state in which an abnormal number of chromosomes more or less is present in the nucleus. This means that the tumors have gained or lost fragments or even entire chromo-

somes. These kinds of tumor chromosomes will code for and produce a wild number of proteins. Such disruptions of genes and chromosomes composition will lead to a disrupted production of enzymes, which are also intended for recovery and removal of damaged DNA. According to these researchers these mutations will lead to the destabilisation of the cell and control structure. This also includes the most complex regulated group of proteins in a cell, and thereby the most vulnerable, the mitotic spindle apparatus that divides chromosomes during cell division. Although these observations are correct, aneuploidy is not the initial step in the cancer process. The first step in most cancer processes is the conversion of a distressed mature cell into an immature cell via activating specific embryonic genes.

3.2. Proliferation of cancer cells

The confusion among cancer researchers, who support the gene theory, is that in cancer cells of the same cancer tumors, different combinations and variations of genes and chromosomes are observed. They assume that because of the variations in genes and chromosomes each tumor cell is a sort of new species. In this view, their inherent instability set individual cancer cell to evolve new traits and behaviours what is better known as a cancer phenotype.

However, I contend that these observations are the effect of the disruptions of the internal cellular control system triggered by the distressed detection cell, which will perform consecutive asymmetric cell divisions in the copies of the distressed detection cell. With asymmetric cell division I mean the uneven distribution of chromosomes between two daughter cancer cells leaving both aneuploid. The very purpose of this asymmetric cell divisions is the creation of uncontrollable numbers of phenotypes in the copies of this distressed detection cell which has become a cancer cell by now. These copies with bewildering and unbridled genetic variations are capable of developing all sorts of characteristics or behaviours in order to survive in all kinds of hostile environments in the organism it has to shut down. With this mechanism the copies of the distressed detection cell will be able to reach all the crucial organs and tissues of the organism and terminate its biological functions. Just as this mechanism is used when unsustainable forms of the developing embryo/fetus are detected. This proliferation strategy is the intentional purpose of the activated detection cell in distress. In my view this is the most crucial element of the 'growth and proliferation till death' mechanism of cancer. In contrast, healthy cells are strictly bound to predetermined characteristics and specific cellular programming of the organ or tissue of which the cell is a part of. Cancer researchers assume that additional disruptions of chromosomes and gene mutations or aneuploid behaviour are the logical sequential progression of cancer. In cancer research it is not contemplated that genetic disruptions could be the effect of the deliberate close down or disruption of various internal cellular control systems via cell signalling by a distressed detection cell. The enormous variability of cancer cells and multiplicity of phenotypes is the reason why cancer is an incomprehensible disease when monitored from the gene theory perspective.

3.3. Asymmetric cell division

The concept that asymmetric division or uneven distribution of chromosomes in two daughter cancer cells is pivotal for carcinogenesis and is consistent with the observation that cellular aneuploidy is an early acquisition in many tumors. A high form of aneuploid behaviour seems to support a sign of aggressive growth during abnormal growth of cancer tumors [12]. Clinical practice recognizes that certain histological features are associated with bad behavior of a tumor. Current clinical practice also assumes that those tumors tend not to be uniform and no universal rules seem to govern their dispositions. To overcome such shortcomings a set of convenient criteria are used to

correlate histological features with clinical outcomes. Such as: the high mitotic rate, atypical mitosis or vascular invasion. My explanation is that the level of detected stressors by the so called 'detection cell' determines how many systems are closed down or disrupted in the internal cellular control system. The level of stressors in the cellular micro environment determines the variations in aneuploid behaviour. Thus the number of effected mechanisms in the internal cell control systems determines whether a tumor has an indolent or aggressive character.

In summary, the aneuploid behaviour is the result of deliberate disruptions or halting of some of the important mechanisms in the internal cell control structures. Disruptions of several intracellular control functions, such as in the mitotic control mechanism are observed in certain types of leukemia in children. With this example in mind, it is conceivable that certain types of cancer are not fatal because not all crucial internal cellular control systems have been disrupted or switched off. The functioning of the internal cellular control systems depends on to what extent the extra-cellular environment of the detection cell, of a specific organ, has been contaminated.

3.4. Heterogeneity of cancer

I contend that the heterogeneity of a particular malignancy is determined by different cellular targets (distressed detection cells) in which the genetic changes occur and does not arises from activation of different genetic (i.e., oncogenic) pathways. Just as genetic instability is not the explanation of the formation of cancer. Genetic instability implies randomness but many traits of malignancy are actually reactivated and passed on from one generation of cancer cells to the next, which suggest a deliberate process is running. The mechanisms discussed in this chapter are in my opinion plausible explanations for the observed heterogeneity and drug resistance of cancer cells.

3.5. Angiogenesis

To facilitate the destruction of the organism and support the 'growth till death' mechanism, the manufacturing of blood vessels in the tumor is stimulated. This so called angiogenesis process is also an important feature in embryogenesis. Once the cancer process is triggered, the unbridled and uncontrolled cell divisions occur at a speed unprecedented in an adult organism. In my view this speed suggests that this process is evolutionary arranged to terminate the development of a fetus or embryo that is in an early stage of development. The termination via uncontrollable growth and proliferation of disrupted cells has to happen quickly before an unsustainable, therefore poorly functioning form, of the specific organism will develop.

Many tumor types that express certain angiogenesis markers: e.g., vascular endothelial growth factor and micro vessel density, in various cancers display a more aggressive phenotype and predict a worse prognosis than the types that do not express them. Therefore, angiogenesis is just as vital in organogenesis in a developing embryo as it is for cancer cells and carcinogenesis in a developing malignancy.

3.6. Immunotolerance

The main premise of my theory is that cancer is the reactivation and mobilizing of mechanisms used during embryogenesis and especially in the termination of unsustainable forms of the developing fetus. This leads to the conclusion that cancer is an innate process and this claim can explain why the human immune system cannot recognize cancer tumors.

A convincing observation to support this claim is a classic example of immunotolerance which is the acceptance of a semi-allogeneic fetus by its mother [13] In many respects, a fetus resembles a neoplasm because, like a malignant tumor, I suspect that fetal and malignant cells may use similar mechanisms to achieve immunotolerance; certain factors that mediate immunotolerance are present in both fetal cells and in

malignant cells. Thus, the presence of certain fetal antigens may be considered equivalent if not identical to tumor-associated antigens. These fetal and tumor-associated antigens are in fact one and the same and play a pivotal role in the immunotolerance of their respective cells. The phenomenon of fetal "microchimerism," or persistence of fetal cells in the mother after delivery, is also a clear indication of immunotolerance. I assume that cancer cells, like fetal cells are endowed with certain biologic properties that prevent them from being recognized and attacked by a normal immune system.

3.7. Metastasis

Another example of the mobilizing of existing embryonic mechanisms in cancer is the metastasis process which shows striking similarities with the mechanisms used in the fertilization process by sperm cells. Sperm cells also have to overcome hostile environments, use chemical signaling to find their goal, have highly activated motility and finally have the capability to penetrate the wall of the female egg which means a capability to penetrate foreign tissue. I suspect that the mechanism of metastasis is triggered by expressing embryonic sperm genetic complements in specific cancer cells [14, 15].

I assume that preferred locations of metastases has to do with the ultimate goal of the 'growth and proliferation till death' mechanism of cancer. I think that organs and tissues are selected during metastasis for their critical function which will speed up and ensure the termination of the organism. The fact that these emmigrating cells manage not to antagonize but instead to collaborate with the local cells has to do with the expression of embryonic sperm genetic complements which favors the fusion with local cells. I also contend that the immature status of metastatic cancer cells is a signal recognized by all cells in an organism about its overall biological condition. To put it more dramatically, once a metastatic cell has arrived at its place of destination its doomsday message will be recognized by all the cells of the constituent organs and tissues. They will comply with its message, which is the termination of the organism by growing till death.

The same ingredients that promote the rejection of an unsustainable fetus and the fertilization by sperm cells: proliferation, mobilization, and migration are now being used in malignant tumor growth, invasion, and metastasis. During organogenesis, embryonic cells are activated as they form various tissues and organs. This process is accomplished by proteolytic enzymes and invasion molecules operating at maximal speed, while autocrine, paracrine, and angiogenic factors work in full gear [16].

These assumptions are supported by the following established characteristics of metastatic cells; these cell types contain the cytoskeletal machinery that allows them to mobilize easily. They are equipped with an array of proteolytic enzymes that permit them to disembark at various destinations seemingly at will. They possess the ability of surviving in harsh, hostile environments. And they are endowed with the fortunate ability to pick the right places to colonize, where there are sufficient supplies and support. These immigrating cells manage not to antagonize but instead to collaborate with the local cells.

3.8. Metastases are not propelled by evolutionary selection

A last remark about metastasis of cancer cells is that this mechanism is unlike clonal selection such as in B-cells in the immune system which evolved to target foreign invaders. In this strategy a B-cell will bind to its cognate antigen and this B-cell will be triggered to proliferate based on the foreign target encountered. Cancer cells on the other hand have only a limited number of innate targets, the potential two hundred human cells, to invade and do not proliferate based on foreign targets. After the initial cancer cell is triggered to start the uncontrollable growth, the next step is the production of a wide

variety of cancer phenotypes in the daughter cells. The purpose of this mechanism is to ensure that there will always be a cancer phenotype to survive and invade any cell encountered in the hostile innate systems. This deliberate mechanism is actually producing random variations of phenotypes in daughter cancer cells. The variability of the cancer cell phenotypes is dependent on the number of disrupted internal cell control systems, which is triggered by the level of contamination of the cellular microenvironment. These evolutionary mechanisms are the reason why there will always be a cancer cell that will survive any form of cytotoxic attack via chemotherapy. That is why I think that selection in evolutionary sense is not the correct description to explain the metastases of cancer cells. Selection is more appropriate to describe the tactics used by B cells in the immune system.

Because it is often the metastasis rather than the primary tumor that ultimately kills, solving the enigma of metastasis is synonymous to defeating cancer. The findings that both drug resistance and metastasis occur early if not at the very beginning of carcinogenesis support my hypothesis of the origin of cancers.

4. Why Not Everyone Gets Cancer

A distinction between internal and external stressors in the development of cancer is not that clear. External stressors which cause persistent tissue damage via inflammation, exposure to excessive sunlight, viruses and infections can cause cancers not because of the external stressors itself but by the counteractions in the microenvironment of the distressed cells to reduce these external irritants. These counteractions to reduce this chronic tissue injury will induce the accumulation of specific cellular stressors which disrupt the homeostasis in the microenvironment of detection cells. In general it will take long exposure of external stressors to cause cancer which is a well established observation in cancer research.

Internal stressors such as in breast, prostate and colorectal cancers are in my view predominately triggered by the influence and force of the unique and complex human cognitive and neuro-endocrine processes which can alter the biological active forms of substances of the endocrine, hematological and metabolic systems. These altered biological active forms of substances will be perceived as stressors in the cellular micro environment of the relevant organs and tissues. This explanation confirms the fact that we actually never can speak of internal stressors in cancer because the human biological systems are always influenced by its environment and they will evolve and adapt or literally perish when applied human behaviour is maladaptive for those biological systems [17].

Although environmental causes explain 95% of the cancer incidence, not everyone is equally sensitive for these environmental pressures. In epidemiology several external risk factors which might influence the development of cancers are known, such as: social, cultural, economic, lifestyle pressures and certain environmental toxins. However not everyone is equally susceptible for those environmental pressures which might cause cognitive and neuro-endocrine deregulation of other biological processes.

The individual physical constitution in terms of hormonal, metabolic and cognitive systems may determine whether an individual will develop certain forms of cancer when exposed to specific sustained environmental pressures. I contend that an organism is able to restore local cellular homeostasis in the short term, but that capacity will deteriorate with age or by excess exposure which is dependent of the physical constitution of the individual. But this is something different than developing spontaneous gene mutations which are responsible for causing cancer which is the current dominant explanatory model. My explanation why some people develop a form of cancer is dependent of the specific personal and environmental circumstances of the individual while the genetic centred proponents assume that cancer is ultimately inevitable. But the 1 in 3 or 1 in 4 statistics refute

this assumption. That is why I claim that only specific individuals who exhibit specific behavior or have to endure specific environmental pressures will succumb to cancer.

4.1. Cancer in children

Cancer in children is not common. Although only about 3% of all cancer deaths in the US are due to leukemia, it represents roughly 50% of all childhood cancers. That is why leukemia is the most common childhood cancer. Unlike leukemia in adults, childhood leukemia is acute in the vast majority of cases. The biologic nature of tumors of childhood is clinically, histopathologically, and biologically distinct from that of adult-onset malignancies. Childhood cancers tend to have short latency periods, are often rapidly growing and aggressively invasive, are rarely associated with exposure to carcinogens implicated in adult-onset cancers, and are generally more responsive to standard modalities of treatment, in particular chemotherapy. Most childhood tumors occur sporadically in families with at most a weak history of cancer [18].

The thesis of this essay is that cancer is the reactivation of abort mechanisms from embryogenesis in later stages of life. From these basic assumptions the following conclusion can be made for childhood cancers and cancer of the blood.

My first conclusion is that these observations seem to suggest that the disrupting substances in the bone marrow of these children are at a distressing level at a young age. Because childhood leukemia is acute in most cases, it seems to indicate that the disruption of the homeostasis of the microenvironment of specific blood cell was already disrupted during pregnancy. From my thesis I derive the conclusion that the physical condition of the mother (hormonal, metabolic, hematological and immunotolerance) is causal in the development of a disrupted homeostasis of the bone marrow of the embryo instead of genetic implications.

Most leukemic cells are immature or in arrested development to become mature. Because the level of disruptions in the cellular microenvironment is already quite severe in childhood cancer, blood cells will remain immature and because of this prolonged immature status the cancer progress will be triggered. Acute forms of blood cancers differ from other types of cancers because blood cells don't have to be converted from a mature cell to become an immature cell which is in my view the start of the cancer process. The initial activation of embryogenic genes to start the cancer process in blood cancers is not necessary. It also means that in blood cancers the cancer process is locked by halting the maturation mechanism of blood cells. The observation that leukemic cells remain immature and proliferate which makes them cancerous confirms my assumption that having a immature cell 'status' is the trigger to start the real cancerous process. The goal of distressed blood cancer cells is to produce as much immature blood cells to terminate the organism. All of this is most likely the result of disrupted local cellular homeostasis in the bone marrow.

Because blood is in contact with virtually all organs and tissues, blood cancers don't have to disrupt as many control systems as in other forms of cancer to execute its termination process. Blood cancers seem to proliferate immature cells, which is a developmental stage in blood, with relatively little phenotypical variation in the blood cancer cells which is what is happening in chronic stages of blood cancers. This changes overtime when the immature cells accumulate inexorably, creating an even more unsustainable microenvironment. This situation will trigger the cells to disrupt more internal cell control systems, which mobilizes other cancer mechanisms and thereby creating more cancer phenotypes. The blood cancer has reached by then an acute stage, which is more difficult to treat.

It should be noted that leukemia and lymphomas of immunophenotypically mature lymphocytes do not necessarily have cells that resemble normal mature lymphocytes cytologically [19]. The cytological characteristics are in

my view crucial to understand the progression of blood cancers.

Another conclusion which is in line with previous statements is that because blood can reach all of the crucial organs and tissues of the organism, fewer internal cell control system need to be disrupted compared with other metastasized cancers. Other types of metastasized cancers have to disrupt more cell control systems to create unlimited amounts of phenotypes in their tumor cells to reach all vital organs and tissue of the organism. This fact, less variability in blood cancer phenotypes can explain why chemotherapy is relatively successful in curing some blood cancers. And it is also the confirmation that there is no such thing as selection in cancer phenotypes which might cause drug resistance. Otherwise drug resistance should be more prevalent in the initial stages blood cancers.

However, in severe cases of acute forms of blood cancers drug resistance is more prevalent which indicates that the contamination or the disruption of the cellular microenvironment is at unsustainable levels. The detection of such a microenvironment will trigger more intracellular control systems to breakdown to speed up termination of the organism. I suppose blood cancers have several specific cell cycle disruptions to promote cell proliferation in order to interfere more intensively in all organs and tissues. In these cases more blood cancer phenotypes will be monitored such as the easy noticeable translocations. The observation that most blood cancers do not form solid cancers indicates that other control systems are blocked in order to ensure termination of the organism. Thereby I assume the deregulation of processes such as blood clotting and apoptosis.

5. Paths to Follow According to the Proposed Hypothesis

Here I discussed a cell-centred view of the origin of cancers. To better appreciate this view, one has to take an evolutionary look at the available data. It is also important to take the complete human organism across its life-span in the equation to understand a complex disease as cancer. A wider perspective is necessary to explain biological processes and complex human behaviour. The reliance on the gene mutation theory as the sole explanatory model will obscure the causal mechanisms of cancer.

Closer examination of the mechanisms during embryogenesis and organogenesis will deliver valuable clues about which specific cells monitor the maturation of organs and tissues. It is also to determine whether the same cells monitor the homeostasis of the microenvironment of the specific organs and tissues. Cancer researchers will have to focus their efforts on tracing the networks of these so called 'detection cells'. The recognition and monitoring of receptors and pathways of the abort or termination program that shut down or disrupt several internal cell control systems of the 'detection' cells are crucial for the understanding of the cancer process. Monitoring the activated mechanisms during a spontaneous abortion of an unsustainable fetus in a model animal will give important clues about the cancer process in the adult organism.

Furthermore, researchers may have to establish what an unsustainable cellular microenvironment is. They have to examine what the substances and characteristics are of both healthy and disrupted homeostasis in all sorts of organs and tissues. Researchers have to focus on the extra cellular environment to figure out what level of these substances cause the activation of the abort mechanism in detection cells. The disruption of the microenvironment of specific detection cells is in my view the cause of every type of cancer. This assumption follows from observations that a healthy cell when exposed to stressors originating from the extra-cellular environment of a cancer cell will also become a cancer cell within a short time. It is also an established fact that exposing cells to external cancer inducing substances is not productive to understand the real causes of cancer. I think by considering this hypothesis these observations will be better

understood.

To understand the mechanisms of metastasis, embryological studies might deliver vital clues about how genetic complements of sperm cells are activated in cancer cells. Once these mechanisms are properly understood and therapies are designed to eliminate the activation of these genes, cancer will be considered a localized phenomenon and no longer a deadly disease.

Once the cancer process is activated it is irreversible. Nature does not have regret functions within the cellular structures. That is why this termination process goes through several stages that in most cases can take many years before the final stage is reached. Cancer research has to determine which internal cell control systems are sensitive for contamination of the cellular micro environment. This may lead to better and more accurate classification of stages in cancer development.

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