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Modulation of Cell-Cell Communication and Epigenetic Mechanisms as a Shared Cellular Mechanism in Diverse Childhood Brain Diseases, Such as Cancer and Autism

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Abstract

While the molecular mechanisms underlying the pathogenesis of diverse childhood diseases are still unknown, both inherited and somatic mutations, as well as a variety of environmental factors, are known to be causative agents in multi-factorial diseases, such as cancers and several neurological and brain diseases. Toxicological mechanisms of mutagenesis, cell death, and abnormal alteration of gene expression during early development, peri-natal, adolescent-, mature- and geriatric- existence can influence homeostatic regulation of cell functions of proliferation, differentiation, apoptosis, senescence, and adaptive functions. With the current strategy to provide better diagnosis, treatments, and prognosis of childhood diseases, including mutations being a main "driver" of "precision" and "personalized" medicine, there is a growing awareness that "epigenetic" mechanisms can, also, play a significant role in childhood diseases. The basic hypothesis to be examined is whether either natural or synthetic chemicals can interfere with cell-cell communication, especially during in utero development, to modulate homeostatic control of adult brain stem cell behavior. Given that adult organ-specific stem cells exist in all of our organs, epigenetic perturbation of stem cell behavior by environmental, dietary, microbiome, pharmaceutical and behavioral factors could provide a unifying mechanism for diverse diseases, such as cancer and autism. Using the apparent differences in childhood brain cancers and adult cancers, a speculation of how both genomic and environmental alterations of epigenetic mechanisms, regulating stem cell proliferation and differentiation via perturbation in cell-cell communication, will be offered as a shared mechanism between cancers and neurological diseases.

Keywords: *Childhood Cancers; Epigenetic Mechanisms; Stem Cells; Multi-Stage; Multi-Mechanism of Carcinogenesis; Gap Junctions; Teratomas; Barker Hypothesis; Gut/Brain Axis; Microbiome, Autism*

Abbreviation

GJIC: Gap Junctional Intercellular Communication

"As we begin to unravel the unique developmental origins and distinct biological drivers of this heterogeneous group of tumors, clinical trials need to keep pace. It is important to avoid therapeutic strategies developed purely using data obtained from studies on adult glioblastomas. This approach has resulted in repetitive trials and ineffective treatments being applied to these children…" [1].

Introduction

Introduction: Differences in the patterns and treatability of childhood and adult cancers

Search for Common Biological mechanisms of widely different clinical childhood diseases

At a time of the explosion of new concepts, molecular methodology and experimental findings, related to a wide range of childhood diseases, such as birth defects, cancers, immunological-, reproductive-, and neurological- diseases, each discipline digs deeper into its domain. As a result, far too often, what is missed is the "shared" underlying mechanism of the pathogenesis of these widely different clinical

manifestations. A common biological process that is shared in all tissues and organs is cell-cell communication, which is needed to maintain homeostatic control of the development and maintenance of normal cell functions of cell proliferation, cell differentiation, apoptosis, senescence, and adaptive functions of differentiated cells.

This "Review" will try to examine how the roles of stem cells, cell- cell communication (both extracellular, intracellular and gap junctional intercellular-communication) and epigenetic mechanisms can affect the development of the pathogenesis of cancers, while suggesting the same mechanisms might influence widely different brain disease, such as Parkinson's Disease, and autism-spectrum disorders [2,3].

Nature of carcinogenesis: roles of mutagenesis and epigenetic mechanisms

While, in general, patterns of the various types of cancer differ from country to country, it is well known that the patterns of childhood cancers seem to differ between childhood and adult cancers within a country [4-6]. In addition, the treatability of childhood cancers appears to be more successful than the same apparent type in the adult [5]. This difference has implied that either the internal childhood physiology might contribute to better efficaciousness of the cancer therapy or possibly the real differences resides in the apparent similar cancers to the therapy.

From the standpoint of the pathogenesis of different classifications of cancers, e.g. teratomas, teratocarcinomas, carcinomas, sarcomas, etc., there might be some clues as to why the childhood cancers might have a different mechanistic basis for their cancers. Taking but one example at this time, the studies of the attributable cancers, due to exposures to the atomic bombs' radiation, childhood cancers appeared relatively early after young children were exposed, whereas, exposed adults had their cancers appear much later [7]. The neutron and gamma radiation of the atomic bombs, while not being very good "point mutagens" [8] or effective "initiators" of animal carcinogenesis [9,10], are known to be efficacious chromosomal mutagens [11]. Yet, even this information about the mutagenicity of ionizing radiation might not explain this phenomenon [12,13].

Mechanisms of Carcinogenesis. The Multi-Stage, Multi-Mechanism Concept of Carcinogenesis

One of the earliest insights to the mechanism of carcinogenesis came from the animal studies that indicated in adult cancers seemed to consist of three distinct operational phases from the first transition of a single normal cell to a cell that seemed to become "immortalized" [14,15]. This step was "irreversible". However, it was not a full blown, invasive, metastatic cancer. This step was referred to as the "initiation" step. Next, this initiated cell could exist in the body during the whole lifetime without ever becoming a metastatic cancer cell. It has been assumed that this operational event *in vivo* was due to a mutational event.

However, it was shown in early studies that, if this initiated cell was exposed to a "non-initiating" agent or condition [16,17], it could be clonally expanded to form benign lesions, such as a skin papilloma, liver enzyme alter focus, a polyp in the colon or a nodule in the breast. This process was referred to as the "promotion" process. Operationally, this process appeared to be interruptible or in some cases, "reversible" [18].

Finally, upon exposure to other agents, a cell in the benign lesion could acquire all the genotypic or epigenetic changes required to attain the "hallmarks of cancer" [19,20]. This phase was the last step in converting the benign lesion to an invasive, metastatic cancer cell, and has been called the "progression" phase [21].

All of these experimental observations in animals were technically "operational", without any firm molecular mechanistic basis. Initiation was initially thought to be a mutagenic event, caused by DNA damage, which led to a mutation in a critical gene related to maintaining "mortality" of that cell. After exposure to a presumed mutagen, this (these) mutated gene(s) allowed the cell to become "immortal". The early work of Land., *et al*. [22], using genetic modification of normal rodent cells with several oncogenes, showed that the first step was to "immortalized" the "mortal" cells. After a few "immortalized" cells were recovered, these cells could be neoplastically transformed with

another type of "oncogene" [22]. These experiments helped to create the prevailing paradigm that the first step of the multi-stage, multi-mechanism process involved the "immortalization" of a normal, "mortal" cell. While, in this case, oncogenes were used to "initiate" the normal mortal cell, it was assumed that radiation and chemical mutagens could act the same manner as the "initiating" oncogene.

Actually, earlier, it was shown that a skin cancer- prone human syndrome, xeroderma pigmentosum, whose cells, *in vit*ro, were shown to lack UV-induced DNA lesions [23], were highly prone to UV induced mutations [24,25]. Later, it was shown that skin cancer cells from these xeroderma patients had mutations in their DNA that were associated with UV lesions [26]. Therefore, mutations could be formed by "errors of DNA repair" that eventually could contribute to cancer. Since skin cancers are the most prevalent cancers and, while all of us get exposed to ultraviolet light, not all of us get skin cancers before we die. However, we all have "initiated" skin cells.

It was later shown that there existed chemicals and conditions, such as growth, wound healing, and compensatory hyperplasia, that contributed to the "tumor promotion" process [27,28]. These agents and conditions were not "initiators" that damaged genomic DNA or produced mutations. These were "epigenetic" agents that could clonally expand, by mitogenesis, an "initiated" cell and could prevent their apoptotic death [29,30]. While still not universally accepted, it was shown that tumor promoters interfered with cell-cell communication [31]. In other words, once a normal cell was "initiated" or made "immortal", it was now surrounded by, and communicating with, normal cells. This communication was mediated by some suppressing signal, secreted either by the normal cell or by direct transfer of some mitogenic suppressing ion or chemical directly through gap junctions [32].

Characteristics of Adult Cancer Cells

One of the early observations, that provided a link between the studies of the "initiation"/"promotion"/"progression" experiments and the role of gap junctions in cell growth, differentiation [33] and apoptosis, was that by W Lowenstein and Kanno [34]. They showed that normal cells controlled growth when "contacted-inhibited", whereas cancer cells, which seemed to lack gap junctional intercellular communication (GJIC), lacked growth control, could not terminally differentiate or apoptose properly. This was also shown during *in vitro* transformation studies [35].

When it was later shown that a powerful skin tumor promoter, phorbol ester, *in vivo*, could reversibly inhibit GJIC [36], but was shown not to be a DNA damaging agent or inducer of genomic mutations, a new concept was introduced in the understanding of the initiation/promotion/progress concept of carcinogenesis, namely, that the underlying mechanism was an "epigenetic" mechanism [37,38]. In other words, in spite of the current idea that mutations are the "drivers" for carcinogenesis [39], it has been argued that the real drivers of carcinogenesis are these epigenetic agents (endogenous growth factors, hormones, cytokines; exogenous agents, such as pollutants, dietary agents, medications, behavioral influences, alcohol, smoking, lack of exercise, etc.) [3,40].

In addition, with the relatively recent introduction of "oncogenes" and "tumor suppressor" genes [41], it is important to determine if these oncogenes and tumor suppressor genes were linked to gap junctional intercellular communication. Several oncogenes, such as ras, src, neu, etc., were shown to down regulate functional gap junction proteins at the posttranslational levels [42]. Moreover, a tumor suppressor gene was shown to restore gap junction function in a gap junctional intercellular communication deficient human cancer cell [43].

These latter observations, linking the lack of gap junctional intercellular communication to cancer cells, suggest a way to characterize adult cancer cells. Conceptually, if cancer cells are characterized by the lack of gap junction function, this phenotype of cancer cells can be the result of (a) the cancer cell having originated from a normal cell that never expressed the connexin genes, therefore, they do not regulate their cell proliferation by GJIC or "contact-inhibition", or (b) the GJIC-deficient cancer cell expresses their connexin genes, but the gap junctions were not functioning because of a posttranslational modification by an oncogene [32]. This distinction of adult cancer cells leads to both the potential origin of the cancer cell and to the differential treatment of these two types of adult cancer cells.

The Link between Epigenetic Mechanisms, Gap Junctional Intercellular Communication, Cancer and Neurological and Brain Dysfunctions

Obviously, the potential link between cancers (childhood and adult), epigenetic alterations, organ-specific stem cells, cell-cell communication and neurological and brain diseases might be viewed as a speculative idea without much scientific evidence. A complex role of gap junctions has been shown in cells of several brain cancers and other neurological disorders [44-47]. However, one of the first chemical toxicants, i.e. DDT, was shown to be a neurotoxicant and a tumor promoter by inhibiting gap junctional intercellular communication [48]. In addition, several known tumor promoters and an oncogene were shown to inhibit GJIC in rat glial cells [44,49,50]. In addition, functional gap junctions were induced in SV40 immortalized human neuronal cells lacking functional gap junctions [51,52]. Estrogens, tumor promoters of human breast cancers [53] and modulator of gap junctions [54], are also physiological modulators of hypothalamus, and have an active role in the CNS regulation of reproduction [55]. Autocrine and paracrine (cytokine) signals coordinate responses of several cell types of the immune system that can promote either pro- and anti-inflammatory effects [56-58]. Growth factors, such as FGF-1, can induce gap junction hemi-channels of astrocytes of rodents and promote the inflammatory responses in acute spinal cord slices [59]. Connexin hemi-channels have been implicated in the initiation and propagation of calcium waves between radial glia during corticogenesis [60].

The link between glial cells and, in particular, astrocytes, is characterized by their usual high expression level of connexins [61], but changes in the expression level have been reported in a depressive context. On the other hand, anti-depressive drugs have been shown to impact the function of connexin43 gap junction channels in astrocytes [62]. Another link between connexin43 in depression and alcoholism, suggests that GJIC and hemi-channel communication are involved in the pathophysiology of these brain disorders [63]. The drug, modafinil, used to treat sleep disorders, narcolepsy and cataplexy, has been shown to increase glial gap junction function [64] and cortical astrocytes [65]. All of these observations, plus many others, led Charveriat., *et al*. [62] to suggest that the connexin-dependent neuro-glial networking as a new therapeutic target.

It has been shown that the induction of GJIC enhances neuronal differentiation of rat neural stem cells [66].

Lastly, the growing evidence links the wide- ranging effects of the gut microbiome on normal physiology [67] and the pathogenesis of cancer [68] and neurodegeneration [69,70]. The probable role of the various cytokines, produced during chronic inflammation and cell death, could modulate stem cell behavior and gap junction function [71-74].

What is the Origin of Adult Cancer Cells?

When an organism, such as a human being, is exposed to a "carcinogen", a single normal cell can be irreversibly "initiated". Although cells within a tumor, while being both genotypically and phenotypically heterogeneous, they were derived from a single cell [75,76]. Therefore, the question has been, "What is the origin of that cell"?; "Could it be an adult organ-specific adult stem cells (the "stem cell hypothesis" [77-81])"; or "Is it a 'de-differentiated' or 're-programmed' somatic differentiated cell [82].

Until relatively recently, human stem cells were only assumed to exist, without having any experimental basis of their biological characteristics. With the isolation of human embryonic stem cells [83,84], and the induced pluripotent stem cell ("iPSc" [85]), some important observations have been made. The "toti-potent" stem cell, i.e., the fertilized egg, when it divides and reaches a blastosphere, the compaction stage, does not have functional gap junctions [86]. It is noteworthy to recognize that these embryonic stem cells, grown under standard condition with "feeder layers", do not differentiate. If these embryonic stem cells had functional gap junctions, they would be "contact-inhibited" by these normal feeder cell cells that do have functional gap junctions. These embryonic cells would, therefore, not proliferate, but either differentiate or apoptosis. This interpretation is further borne out when GJIC-deficient human cancer cells are placed on feeder layers (see Figure 5 in [87]). These single normal stem or cancer cells, when placed on the feeder layer cells, grow into discreet colonies because they lack functional gap junctions.

To provide some evidence that the "de-differentiation" or "re-programming" hypothesis cannot explain the origin of the "initiated" cell, comes from the operational definition of an induced pluripotent stem cells. The original origin of these "iPS" cells was thought to be the normal, "mortal" cells of a primary *in vitro* population of fibroblasts [88]. To determine if these "iPS" cells were truly induced pluripotent stem cells after exposure to the Yamanaka embryonic genes (Oct3/4, Sox2, c-Myc, and Klf4), they had to form "teratomas" when injected back into a syngeneic adult animal.

Now, if this "re-programming" or "de-differentiation" phenomenon is the explanation for the mechanistic origin of cancer cells in adults, why is it that we normally see carcinomas and sacromas, when cancers are formed in adult human beings? If the "reprogramming hypothesis" of cancer was the de-differentiation of a somatic differentiated cell, one should see teratomas rather than carcinomas and sarcomas.

The isolation of several organ-specific human adult stem cells [87,89-94], that supported the "stem cell hypothesis" as the origin of human cancers, came from the neoplastic conversion of a normal human breast stem cell [79]. In addition, other experimental demonstrations seem to support the stem cell origin of cancers [95-97]. In addition, an alternative explanation for the origin of "iPS" cells has been proposed [79, 98-102]. In a primary *in vitro* population of normal skin fibroblasts, there exist a few adult stem cells, expressing the Oct4 gene. When the embryonic Yamanaka genes (Oct3/4, Sox2, c-Myc, and Klf4.) are placed on these cells, only a few cells survive and they have been characterized as expressing the Oct4 gene, in addition to the 'fingerprints" of the differentiated population of primary cells" [103,104]. This has been characterized as a "not perfect re-programing" of the differentiated cells. Alternatively, these differentiated "finger prints" of expressed differentiated cells might simply be the adult stem cell's normal expressed differentiation markers.

The fact that a series of clones, isolated during the neoplastic conversion of normal human adult breast stem cells, demonstrated that (a) the original normal adult breast stem cells expressed OCT4A gene and did not express the connexin 43 gene or have functional GJIC [79]; (b) after exposure to the SV40 large T gene, clones of SV40 –expressing cells were isolated and shown to continue expressing the Oct4A gene, while not having functional GJIC and were, now, unable to differentiate and had an extended life span; (c) when these "immortalized" SV40 adult human, non-tumorigenic cells were, then, exposed to ionizing radiation, a few clones were isolated that gave rise to "weakly" tumorigenic cells; and (d), finally, when a population of these cells were genetically transfected with the C-erbB2/neu oncogene, clones were isolated that gave rise to cells that were highly tumorigenic. Throughout this sequential evolution of a human adult normal breast stem cell, the Oct4A gene remained expressed (it was not "re-programmed"), as well as the GJIC function was never expressed. This experiment has challenged the origin of the "iPS" cells and supported the Stem Cell hypothesis of carcinogenesis.

Another Consequence in the Understanding of Viruses and Human Cancer

While the virus hypothesis of carcinogenesis is almost as old as the Mutation or De-differentiation hypotheses, it was when Dr. Zur Hausen, who was awarded the Nobel prize for linking various viruses to different cancers [105], that there was an acceptance of the role of viruses in some cancers by the scientific community. Yet, no satisfactory explanation as to how the viruses might be integrated into the "initiation", "promotion", "progression" hypothesis of carcinogenesis. The relevance of viruses and cancers, particularly to an explanation of any differences in childhood and adult cancers, relates not only to understanding the mechanisms of carcinogenesis, but to modes of prevention and treatments of cancers.

While the literature related to this issue is extensive and far beyond the objective of this "Review", a few observations might provide some insight to how viruses contribute to the "initiation", "promotion", "progression" concept of human carcinogenesis. If the observations, *in vitro*, showing that the "initiation" step is one by which a normal cell (either an adult stem cell or a "re-programmed" somatic differentiated cell) is converted to stay "immortal" or become "immortal", respectively, some early observations could provide a major insight.

Early studies to try to transform, neoplastically, human fibroblast or epithelial cells failed when using radiation or chemical "carcinogens" [106-108]. This is because the Hayflick cell replication restrictions [109] were not overcome and these physical and chemical "carcinogens" were unable, under those *in vitro* conditions, to "immortalize" "mortal" normal differentiated somatic human cells. Only when primary human cells were treated with a single "oncogene" or "immortalizing" viruses, could one obtain so-called "immortalized" human cells [22], which, subsequently, could be neoplastically transformed. Those viruses, that could convert a mortal cell to an "immortalized" cell, were referred to as "immortalizing viruses".

This might have been a very misleading designation, because there is a completely different interpretation of these observations. When setting up a primary culture of any human tissue, the population of cells from that tissue will contain a few organ-specific stem cells, the finite-limited life span progenitor cells and the terminally-differentiated cells. The few organ-specific adult stem cells are naturally "immortal" until they are induced to terminally differentiate, senesce or to apoptosis. When this population is exposed to the viruses, such as SV40 or the human papilloma virus (or their respective SV40 large T antigen gene or the HPV E6 and E-7 genes), while all the differentiated cells might be infected or genetically transformed, only the few adult stem cells survived and remained "immortal". The "immortalizing" viruses did nothing to "immortalize ' or "re-program" the "mortal" cells (these cells died when the primary culture went through "crises").

These "immortalizing" genes actually rendered non-functional the critical gene products (e.g. p53; RB) needed for differentiation or "mortalization" of the few stem cells [110]. In the opinion of this author, these viruses should be referred to as "Blockage of mortalization" viruses rather than "immortalizing" viruses. When one examines the frequency of the few clones of "immortalized" cells isolated in these studies, they approximate the number of organ-specific stem cells that exists in any primary culture of normal tissue.

If this interpretation is correct, then its relevance to childhood and adult carcinogenesis could be attributed to the fact that one would expect the numbers of organ-specific stem cells to be higher in the young person than in the adult, rendering the "target-size" for the "initiation" event to be greater in the young [111-113]. Therefore, from the perspective of prevention of viral-associated cancers, antibodies, that are being strategically developed and applied (e.g., HPV, hepatitis virus), are reducing risk to cancers later in life [114].

In brief, viruses, by themselves, do not convert a normal cell to an invasive, metastatic cell. In other words, they cannot mechanistically perform all three stages of "initiation", "promotion", and "progression". They can, if this interpretation is correct, prevent the differentiation of normal adult organ-specific stem cells. Depending on the number of these stem cells during the virus infection, will determine the risk of one of these "immortalized" stem cells (an initiated stem cell) to be expanded by any number of promoting conditions or agents to become an invasive and metastatic cancer cell.

Modification of Organ-Specific Stem Cells During in Utero Development and the Barker Hypothesis

This particular issue of modifying organ-specific adult stem cells has to be viewed from the standpoint of speculation because actual experimental demonstration of modifying human organ-specific stem cells, in vivo, has not been done. Yet, several observations, *in vitro*, or *in vivo* animal studies, might be relevant to the understanding of childhood versus adult cancers. First, it is a fact that organ-specific adult human stem cells exist. From the early development of the fertilized egg, a delicate concatenation of differentiation occurs after the one "totipotent" fertilized egg cell starts to divide. As the blastocysts gets larger, the subsequent daughter cells face new micro-environments (less access to oxygen; nutrients, etc.), heart cells, blood cells, muscle cells, neuronal cells, etc. begin to appear. These differentiated tissue cells came from pluri-potent, multi-potent, bi-potent, uni-potent stem cells. Since these stem cells are characterized by their ability to divide either symmetrically or asymmetrically, adult organ-specific stem cells, depending on exterior signals (endogenous or exogenous), there could be an expansion or diminution of these adult organ-specific stem cells in any organ. This might be most relevant during early development, rather than late in life, when organ-size has reached its maximum and heavy constraints are placed on continued cell division in the brain, heart, liver, eyes. etc. (Closed organ systems). On the other hand, there could be continuous cell proliferation, such

as in the skin and gut (Open organ systems) or continuous cell division in the lung, testis (Steady-state semi-closed organ systems). It has been noted that early -life stress (abuse or neglect) has been associated with abnormal hippocampal function in childhood, possibly due to the physiological effects on stem cells [115].

Another example of early life effects on the developing organisms, even between plants and metazoans, is the appearance of tree tumors [116]. This should suggest a fundamental basic common mechanism between different phyla, such as plants and metazoans. Recent examples of modulation of organ-specific adult stem cells in humans and vegetables has been demonstrated [117]. This suggests that if one could increase or decrease symmetrical or asymmetrical division of organ-specific adult stem cells during early development, one could affect the birth defect or teratogenesis frequencies. However, an example has been demonstrated that in utero exposure of the developing embryo-fetus to stressful conditions could be associated with to diseases later in life and led to the Barker hypothesis [118,119]. This was the epidemiological observation of the effect of dietary restriction of the Dutch population during the Second World War [120]. Another came from the Japanese survivors of the two Atomic bombs in Hiroshima and Nagasaki [121]. Among other numerous observations made of these survivors, leukemias were seen after a decade of exposed young survivors, and, equally importantly, the breast cancers seen after multiple decades of exposed young women survivors. The reason a small attributable number of breast cancers to the neuron and gamma radiation was seen is because the background frequency of breast cancers in Japan at that time was extremely low. This was most likely due to the Japanese diet at that time. It was "calorically-restricted", heavy dependent on soy products, vegetables, raw fish, no meat, green tea, and the lack of smoking by women. Caloric resection is known to reduce several chronic diseases [122,123].

Here is where experimental studies, *in vitro*, on human adult breast stem cells might explain these epidemiological findings. The work on human adult breast stem cells showed they were the target cells for breast carcinogenesis [79,124]. This work also showed that "immortalizing" viruses, such as SV40, could maintain the stemness state of these cells [89], while they, by themselves, did not neoplastically transform the cells. However, these "initiated" breast stem cells could be internally promoted with other treatments by expanding these initiated breast stem cells, and not by "re-programming" embryonic genes. Even more informative, has been the demonstration that one of the anti-cancer component of soy products, genistein, could induce terminal differentiation of these normal human breast adult stem cells [125].

Even green tea components, a significant part of the Japanese diet, has been shown to be an anti-tumor promoting agent [126,127]. The lack of cigarette smoke tumor promoting- chemicals [128,129], also, should be considered a part of the low frequencies of breast cancers in the Japanese women, since smoking has been associated with human breast cancer [130].

Given several recent demonstrations that exposure of pregnant animals to "epigenetic" agents, such as bis-phenol A, could modify the gap junction function [131] and the phenotype of coat color of agouti mice [132], the possibility of modifying (increasing or decreasing) adult organ-specific stem cells, depending on concentrations reaching the target organ, the presence or absence of modifying agents, such as melatonin [133], the pharmacodynamics of the chemical agent, one could affect the target size of the initiating event of carcinogenesis or of any adult stem cell- dependent function of that organ. That might be especially related to childhood cancers or other non-cancer-stem cell-dependent function, such as brain-specific functions affected by agents, such as pesticides, that are both a neurotoxicants and tumor promoters, which can inhibit gap junctional intercellular communication in both brain cells and liver cells [49-52].

The Dissection of Teratomas and Carcinomas and Sarcomas In Understanding Childhood and Adult Cancers

While previous assumptions as to the main "drivers" of childhood (and even adult tumors) have been genomic mutations, an extensive review of childhood and adult brain tumors has identified aberrant epigenomes in both types of brain tumors [134]. Since, as discussed above, the role of epigenetic mechanisms in the multi-stage, multi-mechanism process of adult "initiation", "promotion", "progression" during adult carcinogenesis is well established, specifically during the promotion phase. Yet even with these more recent studies of epigenetic changes seen in childhood cancers, incorporation of some early observations, seems to have been missed in these studies.

Critical to what will follow, it has to be made clear that, as Loewenstein postulated [135], cancer cells lack the ability to have cell-cell communication with their normal cell counterparts. What he was studying was that form of cell-cell communication, dependent on functional gap junctional intercellular communication (GJIC). While this was partially correct, there are other broad forms of cell-cell communication involved in growth control, namely extra-cellular secreted form of cell-cell communication [32] and the secretion of extra-cellular vesicles [136], as well as "nanotubes" [137]. Because of some degree of skepticism that exists concerning these last to forms of communication, specifically with regard to their potential roles in carcinogenesis or other diseases, these last two forms of inter-cellular communication will be ignored at present.

This is an important distinction, because, of the phenotypes of the two kinds of cancer cells that are deficient in cell-cell communication, there seems to be two types of cancer cells; (a) those that lack gap junctional intercellular communication because they do not express the connexin genes and have no GJIC, and (b) those cancer cells that do express their connexin genes and have gap junction proteins but are non-functional. Both have the same functional phenotype, in that they are unable to perform cell-cell communication. However, from a very different molecular developmental phenotype, those cancer cells, that never express their connexin genes to perform GJIC, are "embryonic-like", since stem cells appear to lack functional GJIC because they lack expressed connexins [42]. There are other cancer cells that also lack functional GJIC because, while they express connexins, their gap junctions are rendered non-functional by expressed oncogenes, such as ras, raf, src, neu, mos, etc [138]. These cancer cells can be partially differentiated and are not "embryonic-like".

Here is the explanation for this distinction, namely, those that do not express their connexins are stem cell-like, and express Oct4 and drug transporter genes [139], which make them more resistant to radiation and chemotherapy [140]. One has to assume that these stem cell-like tumors are either teratomas that continue to grow as an undifferentiated tumor because of (a) the micro-environment has prevented the normal extra-cellar matrix or secreted factors from their role to induce differentiation; or (b) they were irreversibly "initiated" in that state to prevent their differentiation.

On the other hand, those cancer cells, that are "partially" differentiated ("oncogeny as partially blocked ontogeny" [78]) and have expressed connexins proteins that cannot function as gap junctions, are very different, phenotypically, in that they do not express Oct4 gene and do not express the drug transporter genes. These cancer cells might be more easily treated with conventional treatments.

What follows are a few very important observations that seems to support this interpretation. In human adult colon cancers, it is well known that the tumors that arise from the left side of the colon (the polyp- type or the partially differentiated) are treatable, whereas, those colon cancers, originating from the right side, appear to be non-treatable (flat type)with current therapies [68]. One explanation is that the polyp- type colon cancers, while derived from colon stem cells, were initiated but did partially differentiate by shutting off their Oct4 gene and drug transporter genes, but did turn on their connexin genes to start to differentiate before their gap junction proteins were post-translationally –modified by some activated oncogene [138]. One must treat these tumors, either by surgical ablation or by inhibition of the specific oncogene product, in order to restore GJIC for terminal differentiation to occur or for apoptosis to occur. On the other hand, to treat the flat type in the same manner would be useless. In these cases, treating the "flat-type" with agents, that cause expression of the connexin genes and that would establish function gap junctional intercellular communication, might be the recommended approach with a drug, such as SAHA [141].

As a relevant aside, when the drug, Cis-platin, was discovered [142], it was shown it was not mutagenic, in spite of it being very toxic and being able to induce oxidative stress and form DNA lesions (probably in mitochondrial, not genotypic DNA). One of its most successful uses was shown in testicular cancers, where, after treatment, one notices most of the testicular cancer cells were "differentiated" [143]. That implies the drug acted as an "epigenetic" toxicant, by inducing these germinal-type stem cells to differentiate rather than to die by "normal" cytotoxicity.

The Possible Predominant Role of Epigenetic Mechanisms in the "Initiation" of Carcinogenesis in Childhood Cancers?

Finally, one still needs to provide evidence that childhood cancers could have their origin in epigenetic mechanisms that might explain the different patterns of cancers seen in children and also their relative more successful treatment to control their tumor growth than the same type of tumor in the adult. While from a theoretical point of view, reversing a non-mutagenic origin of the "driver" of childhood cancer would be much easier than treating a non-reversible or mutational "initiation" of a "cancer stem cell", experimental proof the "epigenetic" origin of childhood cancers needs to be demonstrated. Aside from the aforementioned studies suggesting epigenetic origins of cancers in animals does exist and that epigenetic mechanisms do play a role in the multi-stage, multi-mechanism of adult carcinomas and sarcomas, only recently has some important studies linking epigenetic mechanisms involved in explaining the differences in childhood and adult cancer.

One such study, characterized as a "paradox" in the classic "initiation" and "promotion" experimental studies of rodent liver cancers, the protocol of using the same "initiator" of rodent liver cancers, followed by the "promotion" with phenobarbital (an epigenetic-acting drug [144]), in pre-weaned and post-weaned rodents, two very different cancers were found in the pre- and post-weaned rodents [145]. When initiated, but not promoted with phenobarbital, many basophilic adenomas were seen, but when these initiated animals were promoted with phenobarbital most of the basophilic adenomas disappeared, leaving many basophilic preneoplasic lesions. This appeared to show that phenobarbital in the pre-weaned rodents suppressed, not promoted, the basophilic preneoplastic lesions into basophilic adenomas. In the post-weaned rodents, initiated rodents, without exposure to phenobarbital, only eosinophilic preneoplastic lesions were seen. However, when these initiated rodents were treated with phenobarbital, eosinophilic adenomas were seen. This clearly demonstrates that the pre- and post- weaned animals' physiological state conditioned the initiated liver stem cells to responded to this epigenetic-acting drug very differently. In the pre-weaned case, the tumors were classified as aggressive, basophilic type (embryonic-like), whereas those in the latter protocol were classified as eosinophilic –type or partially differentiated.

While these studies did not measure the two types for their expression of Oct4 or drug transporter genes, or functional GJIC, the results suggested that the pre-weaned physiological state, in the absence of the phenobarbital, influenced the stem-like phenotype of the tumors, whereas the post-weaned physiological state, with exposure to the classic rodent tumor promoter, phenobarbital, influenced the promotion of the initiated partially differentiated liver stem cells.

These results have several potential significant implications to childhood and adult cancers. First, the basophilic adenomas appeared after initiation, but without any added exogenous promoter. That means some "endogenous" factor (possibly growth factors, hormones, cytokines) might have promoted the basophilic preneoplastic lesions to become the basophilic adenomas. These endogenous promoters are known to inhibit gap junctional intercellular communication. If phenobarbital was given after initiation in these pre-weaned rodents, this classic tumor promoter of adult adults actually suppressed their conversion to the basophilic adenomas. In other words, the agent that promotes the growth of initiated stem cells in the young organisms is very different from any promoting agent of initiated stem cells of the adult. In addition, the transition of the young organism to the adult causes an internal microenvironment to favor stem cell proliferation to be primarily symmetrical and thereby keeping the initiated stem cell in an undifferentiated state, whereas, the adult microenvironment causes these initiated stem cells to partially differentiate by asymmetric cell division.

Since phenobarbital acts as a tumor promoter by inhibiting gap junction function [144], it suggests these eosinophilic adenomas had expressed GJIG. On the other hand, the appearance of basophilic adenomas appeared in the animals without exposure to phenobarbital, suggesting some endogenous factor blocked a secreted mitotic-inhibited promoter of an initiated stem cell, that had no expressed connexins or functional GJIC, keeping these stem cells in an "embryonic -like" state.

The second implication of these observations is that treatment of a tumor in a young organism with a known agent that promotes tumors in an adult organism might be a preventive or therapeutic means. Alternatively, treating a childhood cancer with agents, such as antioxidants, could block the promoting effect of hormones, growth factors and cytokines (oxidative stress inducing chemicals). This might seem counter-intuitive, but these experiments suggest this strategy.

If this example can be used to carry over to the childhood and adult tumors problem, it might suggest that that the embryonic, fetal and neonatal physiological state can influence whether the un-initiated or initiated stem cell continues to divide symmetrically to form teratoma-like tumors or very aggressive teratocarcinoma tumors. The former being potentially treatable by agents that could cause altered gene expression, whereas the teratocarcinomas type might resemble those with a mutated gene causing the initiation of an organ-specific adult stem cell.

However, in the context of trying to determine a distinction of teratoma cancer cells and those of carcinomas and sarcomas, one can characterize the latter two has having gone through an evolutionary series of mutational and epigenetic changes, in order to attain all the "hallmarks of cancer". That "initiation" step, in particular, requires an irreversible step of a mutation. What about teratomas? Do these cancer cells require transiting from a normal cell through the "initiation"/"promotion"/"progression" phases? Are mutations involved in their formation?

Part of the answer to these questions come from several sources. First, the definition of a teratoma is:

"A type of germ cell tumor that may contain several different types of tissue, such as hair, muscle, and bone. Teratomas may be mature or immature, based on how normal the cells look under a microscope. Sometimes teratomas are a mix of mature and immature cells. Teratomas usually occur in the ovaries in women, the testicles in men, and the tailbone in children. They may also occur in the central nervous system (brain or spinal cord), chest, or abdomen. Teratomas may be benign (not cancer) or malignant (cancer)". [NCI Dictionary of Cancer Terms].

Second, these benign teratoma tumors, by having a mixture of various normal tissues, such as hair and bone, implies they were derived from various organ-specific stem cells, which, in turn, were derived from the embryonic stem cells. These tumors are a mixture of the few embryonic, adult organ-specific stem cells and the resulting differentiated offspring of the organ-specific stem cells. Now, if these teratocarcinomas conform to the "initiation", "promotion", "progression" hypothesis of carcinogenesis, it would be hard to explain two facts of these types of benign teratomas: (a) How did normal differentiation occur to form the various normal differentiated tissues arise in these tumors, if an "initiation" or mutational event occurred that normally blocks terminal differentiation?, and (b) Also, if the "initiation", "promotion", "progression" process was a part of the teratoma formation, then one has to assume, in childhood cancers, the "promotion" phase must have been accelerated compared to the same process in adult cancers. In adults, the process could take many decades. The "initiation "phase (the irreversible conversion of a single adult stem cell) could take place within hours in either the childhood or adult cells.

From experimental studies of teratomas (benign and malignant), it was shown, by using teratocarcinoma cells from a genetically – marked mouse that had been grown as ascites tumors for 8 years, that, when cells from these teratocarcinomas were injected back into a normal blastocyst of another different genetically-marked mouse, a normal mosaic mouse developed and survived, exhibiting tissues composed of both the normal recipient mouse blastocyst and that of the teratocarcinoma [146]. This could not have happened if the original teratocarcinoma had a mutated gene that blocked terminal differentiation. In fact, the results of this study showed, unequivocally, that a non-mutational origin for the formation of malignancy and for its reversal to normal developmental potential. They further hypothesized that the teratocarcinoma cell, when placed back into its "normal" microenvironment, i.e. the blastocyst, rather than the adult microenvironment, the teratocarcinomas stem cell led to a re-establishment of normal gene expression. While "back mutations" can, theoretically, occur, rarely, this phenomenon of back mutations of a "mutated" gene in the teratocarcinoma would not be able to explain the frequent re-establishment of normal gene expression. It is easier to have an epigenetic alteration of the same genes in a number of cells than to back mutate the same gene in all the cells.

The original teratocarcinoma cell must have had some "epigenetic" event that caused its origin. When grown for 8 years as an ascites tumor in adult animals, it remained as a malignant teratocarcinoma. However, when these non-mutated teratocarcinomas cells were placed in its normal micro-environment, normal expression of these cells occurred. Finally, had true malignant carcinoma cells, that had

their origin caused by the initiation, promoter, progression model, where the original stem cell was mutated in a critical gene that influenced asymmetrical cell division or its ability to terminally differentiate, no mosaic animal would have developed. Therefore, this implies that there can be both an "epigenetic" basis for tumor formation in developing embryos or fetuses, as well as mutational origin of tumor formation in adult organs.

The quote by Markert seems to explain this experimental finding [147]:

"Cells interact and communicate during embryonic development and through inductive stimuli mutually direct the divergent courses of their differentiation. Very little cell differentiation is truly autonomous in vertebrate organisms. The myriad cell phenotypes present in mammals, for example, must reflect a corresponding complexity in the timing, nature, and amount of inductive interactions. Whatever the nature of inductive stimuli may be, they emerge as a consequence of specific sequential interactions of cells during embryonic development.

The first embryonic cells, blastomeres, of mice and other mammals are all totipotent. During cleavage and early morphogenesis these cells come to occupy different positions in the three-dimensional embryo. Some cells are on the outside, some inside. The different environments of these cells cause the cells to express different patterns of metabolism in accordance with their own developing programs of gene function. These patterns of metabolism create new chemical environments for nearby cells and these changed environments induce yet new programs of gene function in responding cells. Thus, a progressive series of reciprocal interactions is established between the cellular environment and the genome of each cell. These interactions drive the cell along a specific path of differentiation until a stable equilibrium is reached in the adult. Thereafter little change occurs in the specialized cells and they become remarkably refractory to changes in the environment. They seem stably locked into the terminal patterns of gene function characteristic of adult cells. The genome seems no longer responsible to the signals that were effective earlier in development.

Of course, changes can occur in adult cells that lead to renewed cell proliferation and altered differentiation as seen in neoplasms, both benign and malignant, but such changes are very rare in deed when one considers the number of cells potentially available for neoplastic transformation. Possibly, mutations in regulatory DNA of dividing adult cells can occasionally lead to new and highly effective programs gene function that we recognize as neoplastic or malignant. However, most genetic changes in adult cells can probably lead to cell death since random changes in patterns of gene activity are not likely to be beneficial".

Brain Disorders, Other Than Cancers, Also, Can Be the Result of Dysfunctional Stem Cell, Cell-Cell Communication and Epigenetic Expression

John Torday stated it best when he said that a fundamental mechanism is needed for all normal development in metazoans:

"..., since the mechanism of cell communication itself is universal in biology, in keeping with a Kuhnian paradigm shift. This approach may even elucidate the nature and evolution of consciousness as a manifestation of the cellular continuum from unicellular to multicellular life. We need such a functional genomic mechanism for the process of evolution if we are to make progress in biology and medicine [148]".

Finally, the brain, which has multiple communicating regions, controls different operational functions by the extra-, intra- and gap junctional inter-cellular mechanisms of glial, oligodendrocytes, and neurons [83], can be altered during early development to give rise, not only to unconscious control of body functions, but, also, to altered awareness of becoming self-aware ("As a result of a thousand million years of evolution, the universe is becoming conscious of itself, able to understand something of its past history and its possible future"-Julian Huxley). By diurnal control of the integrated cell-cell communication process, via the feedback of light (possibly by the alteration in melatonin [133]), daily metabolic breakdown molecules, exposures to drugs, dietary factors, stress, etc. this homeostatic regulation of these three forms of cell communication can explain both normal development and health, but also many diverse diseases associated within various functional regions of the brain.

In general, cancer is usually viewed as an "old-age" disease. Therefore, while cancers in children are rare compared to adult cancers, their patterns of the types seem to be different than the adult cancers. From the teratomas to the other neuronal and lympho-reticular tumors, one might have characterized them as primitive-like. In addition, today, the "success-rate" of treating childhood cancers seems much better than the success rate of adult cancers. If during early development, the stem cells of the origin of childhood cancers are increased, possibly, due to an epigenetic alteration, not mutation of oncogenes or tumor suppressor genes, then exposures, postnatally, to massive amounts of normal growth factors of childhood, could lead to these childhood cancers.

To illustrate the potential role of epigenetics in linking a shared mechanism in three hereditary human syndromes that have both cancers and other chronic diseases, the Down syndrome, tuberous sclerosis complex (NCF) syndrome, the Hutchinson-Gilford Progeria syndrome and a genetic model of the autism spectrum disorder will used.

The human genetic syndrome, the Down syndrome, is a very unique syndrome that not only leads to birth defects, leukemia, predisposition to diabetes, cardiovascular diseases, premature aging, and, in those that live long enough, a high risk for Alzheimer's disease and possibly to autism-like diseases [150-152]. To classify these individuals, while they have a chromosomal mutation leading to trisomy 21, the underlying problem is not point mutations in any of the three copies of genes on chromosome 21, but it is due to altered gene regulation of those genes. In other words, this syndrome, brought about by the inheritance of three 21 chromosomes, causes abnormal epigenetic expression of those normal genes that can lead to a wide variety of chronic diseases. It is a syndrome caused by chromosomal mutation that causes epigenetic disruption of normal genes.

To further explore the role of prenatal exposures to agents that act epigenetically to alter, potentially, organ-specific adult stem cells in many organs, including the brain, the example of tuberous sclerosis complex might serve as an example [152]. Tuberous sclerosis complex (TSC) is a neurocutaneous, autosomal dominant genetic disease affecting approximately 1 in 6,000 to 10,000 live births (references in [152]). TSC causes highly variable, multisystem growth of benign tumors that cause diverse clinical problems (references in [152]). Abnormal brain growths are one of the most common features of TSC and lead to epilepsy, developmental delay, cognitive impairment, autism, behavioral problems, and hydrocephalus. While there is no direct evidence to date that exposure to epigenetic-acting endogenous or exogenous agents during in utero development could lead to multiple clinical pathologies after birth, this study seems to indicate that organ-specific stem cells were affected later in life by agents that affected either increases or decreases of these stem cells. The fact that benign tumors in the brain and autism shared some underlying mechanism is suggestive. In the example of a genetic model of the Autism Spectrum Disorder, (ASD) with the use of a human iPSC-derived neuron, it has been shown that either a deletion or duplication of a region of a ~600 kb locus harboring 29 annotated genes highly expressed in the brain deletion or duplication of this locus is associated with ASD [153]. Again, in this example a chromosomal mutation seems to set off an unregulated series of epigenetic dysregulation of gene expressions during development.

The last example of a human hereditary syndrome that is associated with pre-mature aging is another demonstration where an inherited mutation seems to upset the epigenetic regulation of normal genes. This syndrome seems to demonstrate a role of epigenetic mechanisms that might link the issues of stem cells, oxidative stress, gene expression changes and aging, but not in cancer or brain disorders during their short life span. In this example, individuals are born with a very rare point mutation (the affected gene- lamin A) [154]. While the numbers of these progeria patients are extremely low, any epidemiological observations related to the issues of this Review, i.e. cancer and brain -related disorders, are not available. However, the known molecular information, concerning the coded protein's effect on cellular behavior, as well as the developmental features of these individuals' short life-span, suggests an altered epigenetic event has taken place. At birth, these babies seem to have a normal appearance, i.e., no obvious birth defects. This implies that this mutation did not seem to have a major impact on the developmental processes in utero. Yet after birth and exposure to normoxia, rather than appearing to progress, developmentally, there is a stalling of the normal progression of all phenotypic childhood growth, such that, within a decade or so, a real degradation of physical attributes is seen, suggesting a pre-mature aging process had taken place.

One of the very interesting feature seen in the cells of these children is that the nucleus appears to be wrinkled [155]. This is here one might speculate that the inherited point mutated lamina gene starts to affect the epigenetic alteration of genes in their cells, particularly in the various organ-specific adult stem cells which are required to make bone, teeth, hair, muscles, etc. If the wrinkled nuclei, which provides the anchor for the microtubes connecting to the chromosomes, are rendered unable to regulate the genes on the chromosomes, then those adult stem cells would either die by apoptosis or pre-maturely terminally differentiate. It is well known that stem cells are normally found in low oxygen niches [156] and when exposed to normoxia, they differentiated or apoptosed. Since the embryo and fetus develop in a low oxygen uterine environment, it suggests that these adult stem cells function normally and divide symmetrically to produce all the tissues needed for normal development and birth. After birth and exposure to normoxia, the phenotype of the wrinkled nuclei now appears and its effect on normal gene expression takes it tole on the survival of these organ-specific adult stem cells. Without these stem cells, no growth of various tissues/organs cannot take place, nor can there be tissue replacement after normal wear and tear or wounding. In other words, this point-mutated gene, in the absence of normoxia in utero, has little or no measurable effect on development. Only after exposure to normoxia after birth, does this gene cause its effect on epigenetic regulation of the genome, particularly in the stem cells. If much of the brain differentiation occurred normally in utero, then most brain functions after birth in these individuals might appear quite normal. If this hypothesis has any merit, examining the shape of the nuclei of the various tissues in utero might be the test. Lastly, while one might predict, if adult stem cells can give rise to cancer and other brain-related diseases, one be able to determine if these progeria individuals would have a lower risk for cancers and brain disorders.

To put these three human genetic syndromes, that illustrate the role of either a gene or chromosomal mutation, into a perspective as to how they might cause dysregulation of gene expression, especially during development, to contribute to multiple pathologies, In summary, these three genetic syndromes (Downs, TSC and progeria), two of which predispose the individuals to birth defects, cancer and many chronic diseases, including brain dysfunctions, are the result of either a gene or chromosomal mutation that affects epigenetic mechanisms, especially during early development. The progeria syndrome might actually reduce the risk to cancers and brain disorders. Yet all three demonstrate how a gene or chromosomal mutation can affect epigenetic regulation of the remaining normal genome.

Microbiome and The Link to Multiple Pathologies Which Might Involve Understanding of The Potential Epigenetic Mechanisms to Explain Childhood and Adult Cancers and Neurological and Brain Dysfunctions

Recently, there has been an explosion of epidemiological correlative links between the microbiome and many normal and human pathologies [157]. It has been estimated that there are many more bacteria in the human being than the number of human cells [158]. Under these factual circumstances, it would seem illogical that there would be no physiological interaction between these bacteria populations and the human host. Given that these bacteria communicate with each other via various secreted oligopeptides, which have been termed, quorum sensing peptides [160], it calls into question whether these quorum sensing molecules can interact with various host cells and if so, how do they affect both potential beneficial physiological functions or potential pathological consequences. “Quorum sensing” is the term to describe how bacteria communicated to each other via “quorum-sensing peptides” to alert each other about the changing environment they find themselves. The evolutionary transition of single cell “quorum sensing” to the multicellular metazoan involved the genetic appearance of new kinds of signaling “Quorum sensing molecules”, such as growth factors, hormones, cytokines, and chemokines, in order to regulate, homeostatically, cell proliferation, differentiation, apoptosis and senescence [62,40,71].

In the context of this Review, the microbiome has been linked to the gut/brain axis [161]. However, the mechanism by which these microbial “quorum sensing” peptides might interact with the various human cell types in the many organs to either be beneficial or disease-causing is not yet known. In the case of either childhood or adult cancers, as well as neurological or brain diseases, the role of inflammation has been shown to be the physiological response to these diseases [162]. In the case of the bacterial quorum sensing peptides, the mechanisms are not yet known. Concerning some of the metazoan “quorum sensing” molecules, e.g. hormones, growth factors, cytokines, chemokines, they are known to bind to receptors (as well at high concentrations to work at receptor-independent fashion [162])

to induce oxidative stress intra-cellular signaling and cytokine production by immune cells. These cytokines can stimulate stem cell proliferation and to inhibit gap junctional intercellular communication [72,163]. Finally, if inflammation is the physiological factor related to cancers, either in the child or the adult, and if, as it has been recently shown that the microbiome has been linked, empirically, to all kinds of neurological or brain dysfunction [164], this might provide another example of a shared epigenetic mechanism, via an inflammatory mechanism, linking both brain cancers and brain disorders during development, through altered cell-cell communication mechanisms.

Conclusion

It is critical to explain the mechanistic origin of all diseases, including brain cancers and brain disorders, if a scientific basis for diagnosis, treatment and prognosis meets the criteria for "precision" and "personalized" medicine. This is particular relevant to the observations that childhood and adult cancer patterns and treatment responses are known to be very different. The biological basis for these observations must include, today, the likelihood that the single cell that can give rise to a benign or malignant cancer is a stem cell. Given that, after the fertilization of the egg, the inherited genome must constantly interact with the endogenous and exogenous environments throughout embryogenesis, fetal, neonatal, adolescent, mature and geriatric development. Alteration of the intrinsic genetic information by mutagenic mechanisms (e.g. "errors of DNA repair" or by "errors of DNA replication") or by alterations of gene expression at the transcriptional, translational or posttranslational levels via "epigenetic" mechanisms, particular during early development [165], could contribute to carcinogenesis or to various brain disorders. In the case of childhood cancers, teratoma-like tumors in early development, suggest that preventing organ-specific stem cells from dividing asymmetrically, by non-mutagenic means, would lead to teratoma-like tumors because the internal physiological milieu, influenced by potential microbial factors that can cross the blood/brain barrier, could favor this phenomenon. In adults, the organ-specific stem cell seems to be the "target" cell to start the "initiation", promotion, progression process of the multi-stage, multi-mechanism concept of carcinogenesis. The "initiation" of the single organ-specific adult stem cell seems to be due to a mutagenic or "irreversible" event, followed by a rather long promotion or "epigenetic" process, where by other additional mutagenic and epigenetic changes occurs to form, ultimately, an invasive, metastatic tumor. Since the teratoma-like tumors involve, primarily, at least initially, epigenetic events to the stem cells, they are most likely more easily treatable with agents that can induce epigenetic alterations of genes, whereas adult cancers that involve irreversible mutagenic events, seem to be more resistant to all kinds of current therapies, in that the sustaining cell of these adult tumors are the "cancer stem cells", which are resistant to both radiation and most chemotherapeutic agents.

Therefore, starting from the hypothesis that both childhood and adult cancer start from the single adult organ-specific adult stem cell, one should be able to conclude that(a) all cancers start from a single cell; (b) the operational process of carcinogenesis involves mutations (during the "initiation" phase); (c) epigenetic mechanisms (directly at threshold and non-cytotoxic levels and indirectly at cytotoxic levels) play a role during the promotion phase; (d) chronic inflammation (induced during the promotion phase) contributes to the mitogenesis of the initiated stem cells; (e) interruption of this promotion can be done by other epigenetic agents that can act as anti-oxidants; (f) normal stem cells and "cancer stem cells" do not have functional cell -cell communication (either because of non-expression of the connexin genes or non-functioning of expressed connexins, rendered non-functional by oncogenes); (g) all tumors and cell lines derived from these tumors are mixtures of "cancer stem cells" and "cancer stem cells; (g) normal stem cells can divide by either symmetrical and asymmetrical cell division and exist in a low oxygen microenvironment (niche), whereas "cancer stem cells" can under normal conditions of tumor growth divide only by symmetrical cell division; and (h) targeting the "cancer stem cell" is a necessity for the realistic treatment of cancer. In addition, since regulation of adult stem cell numbers and their differentiation into various brain functions is dependent on cell-cell communication, the link between these two very different diseases, brain cancers and brain disorders seems to be a shared underlying mechanism that involves epigenetic mechanisms. Modulation of these cell-cell communication mechanisms is an up-stream event that leads to modulation of intra-cellular communication to alter the ultimate down-stream event of molecularly- modifying the genome.

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Conflict of Interest

The author has no conflict of interest.

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