Journal of Stem Cell Research & Therapy

OPEN ACCESS Freely available online

Research Article

Human Adult Stem Cells as the Target Cells for the Initiation of Carcinogenesis and for the Generation of Cancer Stem Cells

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ABSTRACT

The inference to stem cells has been found in ancient myths and the concept of stem cells has existed in the fields of plant biology, developmental biology and embryology for decades. In the field of cancer research, the stem cell theory was one of the earliest hypotheses on the origin of a cancer from a single cell. However, an opposing hypothesis had it that an adult differentiated somatic cell could "de-differentiate" to become a cancer cell. Only within the last decade, via. the "cloning" of Dolly, the sheep, did the field of stem cell biology really trigger an exciting revolution in biological research. The isolation of human embryonic stem cells has created a true revolution in the life sciences that has led to the hope that these human stem cells could lead to basic science understanding of gene regulation during differentiation and development, stem cell therapy, gene therapy via. stem cells, the use of stem cells for drug discovery, screening for toxic effects of chemicals, and understand the aging and diseases of aging processes.

Keywords: Adult stem cells; Oct-4; Initiation; Promotion; Progression hypothesis of carcinogenesis; Re-programming

INTRODUCTION

While it might be argued that a single cell organism, such as a bacterium, is an immortal cell, during the course of biological evolution, new phenotypes emerged that pro-vided survival advantages when cells organized into a co-hesive society of cells to form a multi-celled organism. While temperature, availability of nutrients, pH, atmospheric factors, and radiation influenced the growth regulation of these single cell organisms, stability for the species was maintained by the genetic information that protected by a relatively error free DNA repair and DNA replication system.

In the multi-cell organism, a Faustian bargain, of sorts, was made for new adaptive features that allowed this collection of cohesive cells to survive to maintain the species. Of course, while most of the factors that controlled cell growth of the single cell organism are relevant for the individual cells of the multi cell organism, internal or endogenous growth control was needed to regulate the many cells within the multi-cell organism. Moreover, some cells gave up ordinary self-replication ability in order to provide highly specialized adaptive function for the survival advantage of the whole organism. Thus, the process of differentiation appeared, together with the mechanism that allowed asymmetric cell division to supplement the process of symmetrical cell division.

This unique feature of a cell's ability to proliferate either by symmetrical cell division (to increase the cell numbers of like-type cells) or by asymmetric cell division (to maintain homeostatic levels of daughter-like mother cell but to allow the formation of a differentiation of a specialized cell) is a hallmark of a multi-cell metazoan. In addition, as a consequence of this differentiation process was the induction of mortality of both the specialized differentiated cell and ultimately, the whole organism. A unique form of cell death, programmed cell death or apoptosis also appeared that aided in allowing the multi- cell organism to acquire new adaptive features. The transition of the single cell, fertilized egg to a larvae, pupae and butterfly, for example, required specialized cells at each phase of development (food acquiring genes/phenotypes) to give way to newer specialized cells that ultimately provided the end product of development of wing muscles for an adult butterfly to mate, and pass on the genes to maintain the species.

Clearly, while almost all the cells of the multi cell organism contain the total genomic information of the species, only a portion of those genes are expressed in each specialized cell. Therefore, the process to regulate, correctly, specific battery of genes from the total

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Received: February 02, 2021; **Accepted:** February 15, 2021; **Published:** February 22, 2020

Citation: Trosko JE (2021) Human Adult Stem Cells as the Target Cells for the Initiation of Carcinogenesis and for the Generation of Cancer Stem Cells. J Stem Cell Res Ther. 11:472.

genome must have emerged during this evolutionary transition from the single cell organ to the multi cell organism.

METHODS

In order that the individual, mortal, multicellular organism help to maintain the survival of the species to which it belonged, the formation of both germinal stem and somatic or adult stem cells was required. The relative genomic stability had to be maintained in the germ stem cells, with occasional mutations occurring, to give the species a reservoir of new genetic options to adapt to the inevitable environmental changes. Seen in this manner, the multicellular organism's germinal stem cells were immortal, while the mortal individual was only the transient carrier for these immortal stem cells.

The somatic stem cell also emerged during this evolutionary transition from the single cell immortal organ-ism to the mortal individual multicellular organism that carried immortal germ cells. In order to pass through its various development stages (embryo, fetus, neonate, adolescent, mature and geriatric stages), processes to provide the whole organism enough cells for growth, differentiation, as well as for wound-healing and death due to apoptosis, had to emerge. The development of a unique type of stem cell, which had the ability to selfrenew (the two daughter cells having retained the ability be a stem cell as the mother cell), as well as to divide asymmetrically for the production of one daughter to maintain "stemness", including maintaining immortality, and the other to be a 'transit-amplifying" cell, committed to have a finite life span that could differentiate, senescence or apoptosis.

In contemporary terms, there seems to be a number of stem cell types. The "totipotent" stem cell is the fertilized egg, meaning it can give rise to all cell types (approximately 200 in the case of the human being) and the re-producing individual with both the germinal and somatic stem cells. The germinal stem cell can give rise, ultimately, to either sperm or eggs. It resides in its special niche [1]. As the embryo starts to form from the fertilized egg, (blastomere, gastrula, etc [2]), the totipotent stem cell starts to restrict the daughter stem cells' ability to give rise to a whole individual, but still maintains the ability to give rise to all the other somatic cell types. These are "pluripotent" stem cells. As the embryo transits to the fetal stage, the micro environmental changes, which, in all likelihood, provides different signals to regulate different genes to adapt to this new situation. Illustrating this beautiful cybernetic relationship between selectively regulating specific genes out of the total genome by a cascading selfinducing sequence as development proceeds is the description of this process by C. Markert [3].

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 indeed 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."

As developmental processes and the internal micro environment must become more unique, the new adult or somatic stem cell, itself, is restricted further in its ability to be a pluripotent like stem cell. This new adult stem cell is referred to as a multi-potent stem cell. These cells, in turn, can give rise to another restricted ability to give rise to different specialized cells. Again, further development limits derivatives of these multi-potent stem cells to become bipolar stem cells, such as the "oval" cells of the liver [4]. Lastly, the final restriction of these bi-polar stem cells is a "unipolar" stem cell that only gives rise to a single differentiated progeny. The offspring of these stem cells that lose the ability to proliferate asymmetrically, but not symmetrically, are consider to be life-span limited (the Hayflick phenomenon [5]). These cells eventually senesce or die by terminal differentiation or apoptosis.

Overarching all of this is the critical idea that one of the most important evolutionary developments in the emergence of the multi-cell organism is the appearance of a gene or several genes that responds to micro-environ-mental triggered signals that direct the cell to divide either symmetrically or asymmetrically. This might be one of the most important genes to study [6], in view of the observation that, within the stem cell theory of cancer', dysfunction/disregulation of asymmetric cell division seems to be involved early in the carcinogenetic process [7].

In addition, the delicate function of maintaining the immortality of the genome for the perpetuation of a multicell species has to be done within a "mortal" individual consisting of 200 terminally differentiated cell types and some immortal germ and adult stem cells.

The state of understanding the restriction or differentiation of the toti and pluripotent stem cells follows a time's arrow course (i.e., only one way) or whether all their progenitor differentiated daughters can be "reprogrammed" to totally dedifferentiate back to the embryonic stem cell is still in a state of flux [8]. While there does seem to be solid evidence of transdifferentiation of some cells [white fat cells to brown fat cells [9]], the evidence that this process is yet complex in the laboratory and possibly limited *in vivo* because of developmental and aging factors.

The concept of a stem cell being immortal is also complicated by

current conceptual and experimental contradictory reports. One view has any stem cell (both embryonic and somatic/adult stems) is naturally immortal until it is induced to terminally differentiate or to become "mortal". Experimentally, the observation that these stem cells seem to demonstrate genomic instability after significant cell divisions [10]. This might be due to inevitable errors in replication of DNA, as the stem cells proliferate. On the other hand, this might be the consequence of in-adequate *in vitro* culturing conditions, such as growing the cells in an oxygen rich environment [11], on substrates and micro-environmental factors different from the natural niche microenvironment found *in vitro* [12].

However, these normal stem cells were shown, not only to meet the definition of what a stem cell should be (have selfrenewal and differentiation potential), but also that they could be neoplastically transformed. Historically, one must remember, only of few reports of the neoplastic transformation of human fibroblast and epithelial cells have been made.

The origin of the few that were claimed to have been neoplastically transformed were not identified as using immortalizing viruses, such as SV40 or human papilloma viruses or being transfected with hTERT.

In these reports, investigators recovered immortalized human cells from normal primary cultures of adult tissues. Many of these immortalized" cells could then be neoplastically transformed. All of this supports, on the surface, the idea that these normal human primary cell populations could be "re-programmed". Moreover, it tended to support the hypothesis that one must first "immortalize" a normal "mortal" cell in the primary culture before it could be neoplastically transformed.

Alternatively, since the normal adult cell is "immortal" until it is induced to mortalize or terminally differentiate, apoptose or senesce, it will remain immortal. If a virus, such as the SV40, human papilloma, or human hepatitis, blocks the immortal normal adult stem cell from terminally differentiating, apoptosing or senescing, it will remain immortal. It does not become "reprogrammed" to the stem cell state. In fact, it has now been blocked from normal programming of differentiation, apoptosing or senescing.

In a series of reports on the isolation and partial characterization of human breast stem cells, it was shown that these cells could differentiate into human breast epithelial cells, form true-like mammary structures, transit from a completely mutually exclusive set of genes in the stem cell state to another set in the differentiated state. Later after exposure to SV40, clones were obtained that were immortalized or more accurately, blocked from mortalization, which maintained most of the marker genes of the normal stem cells. After X radiation, a few clones were obtained that, again, maintained these critical stem cell marker genes and were weakly tumorigenic. After transfection of these weakly tumorigenic cells with the neuoncogene, clones of highly tumorigenic cells were isolated. Again, these cells maintained the critical set of expressed genes found in the original normal adult human breast stem cells. Much later, these, and other normal human adult stem cells were shown to express the Oct-4A gene and not express the connexin genes or have functional GJIC. In summary, these results demonstrate, directly, that the Oct-4A gene was not "reprogrammed" during this process of becoming "immortalized" and of becoming neoplastically transformed.

One addition implication of these findings is that the claim that viruses can cause cancer might have a logical foundation in these observations. If after exposure to nor-mal human organs, which contain adult stem cells, any virus that might infect an adult stem cell might prevent that stem cell from differentiating, apoptosing or senescing. In effect the virus has "initiated" this adult stem cell. As a result, this cell could live long enough to accrue addition changes to become a malignant cell.

An addition significant observation has been made with regard to the interpretation of iPS cells being the result of reprogramming of differentiated cells. In the study where mouse iPS cells were isolated from primary cultures of mouse heptocytes, a comment was made in the paper, namely, the mechanism of iPS cell induction, however, is unknown. Low efficiency of iPS cell induction suggests that their origins may be of undifferentiated stem cells co-existing in fibroblast culture. Most of them were also positive for Bgal, indicating that iPSHep cells were derived from hepatocytes or other albulmin expressing cells, but not from un-differentiated cells that do not express albumin. However, in the isolation of human liver stem cells, the liver stem cell, an undifferentiated cell, by definition, expresses not only Oct-4, but also the albumin gene and protein. This further provides evidence that the origin of these iPS cells was not the reprogramming of differentiate hepatocytes might be the so called cancer non-stem cells. But the selection of the adult liver stem cells.

DISCUSION

Adult stem cells, cancer stem cells and cancer non-stem cells

If the aforementioned hypothesis is correct, namely, that the adult stem cell is the target cell for initiating the carcinogenic process, then one might be able to test part of this hypothesis by looking a one of the markers for these adult stem cells, namely, Oct4A in spontaneous tumors. To begin, it is already known that all tumors lack functional GJIC, either because they never express their connexin genes or that the expressed connexins are rendered non functional by expressed oncogenes. In the case of initiation/promotion models, such as the rat liver studies, the lesions appear to express connexins and have functional GJIC, until exposed to tumor promoting chemicals, such as penobarbital, known to reversibly inhibit GJIC. On the other hand, there are tumor cells that do not express any connexins. Yet, when cell lines are derived from tumors and growth *in vitro*, the micro environment changes, as it does *invivo* in Figure 1.

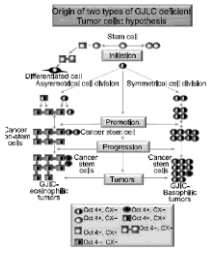

Figure 1: Diagram illustrating the potential origin of two types of non-gap junctional communicating cancer cells, either due to the original target cell being an adult stem cell that did not transcrip-tionally express its connexin genes (HeLa and MCF-7- type tumors).

Even in the case of Hela cells, cells that, when cultured, under certain conditions, have no expressed connexins or functional gap junctions. However when grown under an-other condition, such as cocultured with HL-60 leukemic cells or with normal fibroblasts, both cell types can be shown to be coupled by gap junctions. Even when one examines the promoted lesions of a rat liver, one can detect clones within clones, or in general, there are sub-populations within all tumors. The interactions, both by direct contact and by secreted factors, influence the growth of the whole tumor. This indicates that, as an initiated cell is promoted, soon, additional genetic/epigenetic changes occur due to micro environmental changes. Eventually, a single initiated cell accrues all the hallmarks need to invade and metastatize. During that process, the original adult stem cell, when initiated (blocked from asymmetric cell division or terminally differentiation), starts to grow. As the clone of initiated cells growths, the micro environment changes between the initiated cells and the neighboring normal cells [There will be stromal epithelial interactions, as well as interactions between the initiated cells and themselves in the interior of the tumor]. The induced intracellular signaling, caused by these micro environmental changes, is bound to alter gene expression.

The altered gene expression in these initiated cells could induce some genes that could induce apoptosis. That tumors contain cancer stem cells. These would be the cells that helped to sustain the long term growth of a tumor. When cells were isolated from tumors that were either able or not to perpetuate the tumor, a large number of "cancer stem cells" from many different types of tumors have been and are continuing to grow. With the demonstration that Oct-4 gene was considered a stem cell marker, not shown to be found in normal tissue, but found in various tumors, it was hypothesized that this Oct-4 gene was re-expressed during the carcinogenic process. This reflected the prevailing paradigm that a normal differentiated somatic cell had to be reprogrammed. However, since our laboratory had isolated many human adult stem cells from various tissues (kidney, breast, pancreas, mesenchyme, liver, intestine), we were able to demonstrate that all of these normal adult organ-specific stem cells expressed Oct-4A and did not express connexin genes or have functional GJIC.

Moreover, in tumors from these organ sites, all ex-pressed Oct-4A within the tumor and in cancer cell lines, such as HeLa and MCF-7. Oct-4 has also been shown in other cancer cell lines. This, in fact, suggests that primary cell lines, that eventually senesce or go through crises, do so because the few stem cells have been diluted out during subsequent passages and that the progenitor cells exhibit the Hayflick phenomenon. Immortal and cancer cell lines must, by definition, include stem cells that have been initiated or initiated and neoplastically converted to become cancer stem cells Figure 2.

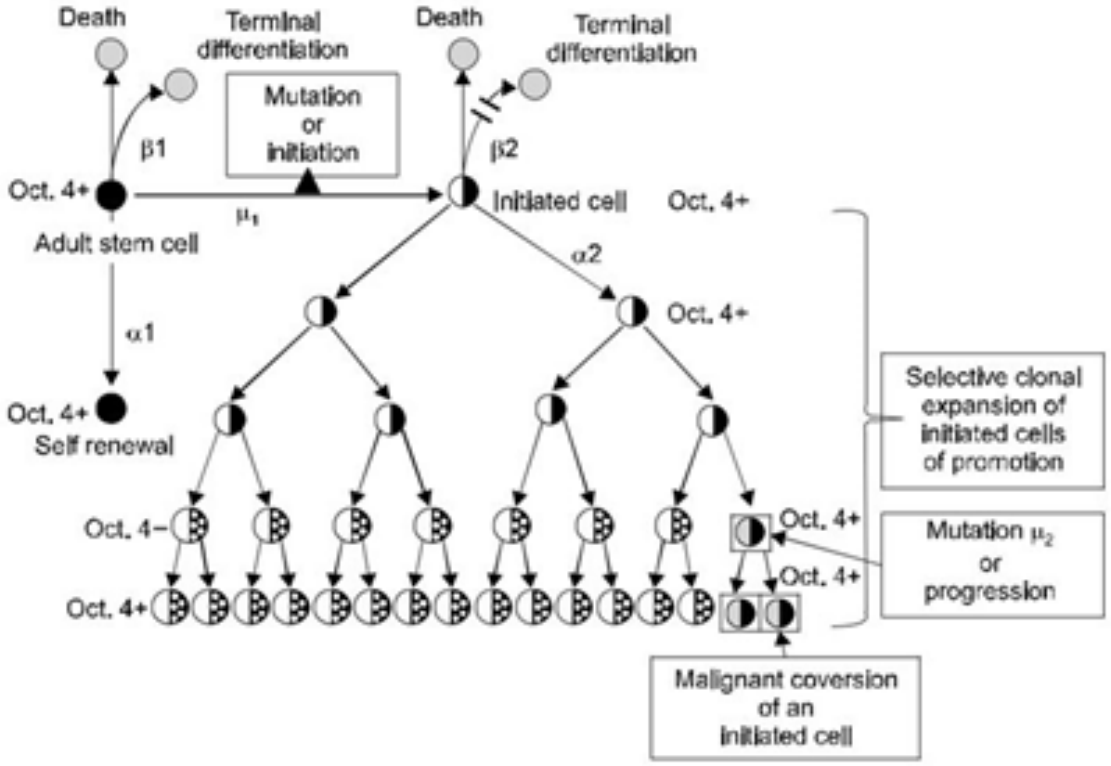

Figure 2 : In this diagram, a normal adult stem cell is shown dividing asymmetrically to form one daughter that is committed to ultimately terminally differentiate. The other daughter is designated to be identical to its mother adult stem cell (Oct-4). If that adult stem cell is exposed to some condition that prevents asymmetrical cell division, but does not suppress the Oct-4 expression, it is operationally an initiated cell. That is, if mitotically stimulated to divide, it divides symmetrically to form two initiated, non-terminally differentiated cell. Initiation is, then, defined as the process that prevents an "immortal" normal adult stem cell to terminally differentiate or become "mortal". These adult initiated stem cells are still Oct-4 positive or benign cancer stem cells. As these initiated Oct-4 cells are stimulated to proliferate and resist apoptosis, the growing benign tumor micro-environment changes, some of these initiated Oct-4 cells can partially differentiate into "cancer non-stem cells" [Oct-4 negative]. Eventually, additional stable mutational or epigenetic events occur, providing the benign Oct-4 + cancer stem cells to become invasive, metastatic "cancer stem cells".

In both cell culture and within the tumor, one would expect the micro-environment to change so as to induce, differentiatially, altered gene expression causing some of these Oct-4 cells positive cells to repress its expression. This would cause these cells to eventually cease to proliferate indefinitely.

Upon testing the hypothesis that the Oct-4A positive cells within a tumor were the "cancer stem cells", it was shown that Oct-4A positive cells were found in 100% of the 21 canine different tumor sites. Later, it was shown to be expressed in most of the human bladder tumors examined for Oct4. Still later, Oct-4 was observed in human oral cancers. What was also shown in all these tumors was the ratio of Oct4 positive cells to Oct-4 negative cells varied widely. Even when one examined the cancer cell lines, HeLa and MCF-7 cells, the population of cells exhibited a mixture of Oct-4 positive to Oct4-negative cells. The implications of this for both molecular/biochemical studies of cell lines derived from tumors or from the tumors themselves is that one needs to be cautious of the results because these cell line and tumors are not homogeneous. That especially relates to many DNA micro-array studies which would be the net effect of a mixture of cancer stem cells and cancer non stem cells.

Cell-cell communication and differentiation/growth control/apoptosis, role in chemoprevention and chemotherapy

If one starts with the premise that the adult stem cell is the target cell that starts the initiation promotion progression process of the multi-stage, multi-mechanism theory of carcinogenesis, strategies for the prevention and treatment of cancer seem fairly obvious. First, simply by increasing or decreasing the stem cell pool in any organ would, all other factors being equal after initiation, increase or decrease the probability of the initiation event from taking place. While it would be appropriate to minimize exposures to mutagens, such as protect oneself from too much sunexposure, it would decrease the risk to suninduced skin cancer. However, it is impossible to reduce to zero the risk to the initiation event. Every time a cell proliferates, there is a finite chance that an error in replication could lead to a mutation in a critical gene involved in the carcinogenic process.

That, then, leads to the importance of preventing the initiated stem cell from being promoted (by preventing these initiated cells from being expanded and/or being induced to die by programmed cell death or apoptosis). Since both normal adult stem cells and their initiated progeny are growth controlled either by secreted negative growth regulators or by gap junctional intercellular communication, and since most, if not all, tumor promoting agents block cell-cell communication between the initiated cell and the normal differentiated or neighboring sib cells, it would seem that the tumor promotion phase would be the most effective phase to intervene. By interfering with the tumor promotion phase, which, in the case of human beings, can take place over decades, would allow one to delay or even reverse the clonal expansion of the initiated cells to accrue all the hallmarks of a cancer cell.

Given that endogenous and exogenous factors can act as tumor promoters, and given that tumor promotion, caused by very different conditions (e.g., wounding, nor-mal growth, cell removal, cell death, drugs, pollutants, food additives, toxicants, microbial toxins, hormones, inflammatory factors, solid particles, etc.), it might seem that it would be impossible to prevent tumor promotion. In deed, tumor promoters can be species, gender, developmental stage-, cell type and organ specific. However, there are some universal characteristics of tumor promoters, namely, they seem to have threshold levels of action; exposure must be for long periods of time, given in regular exposures and in the absence of agents that are considered antipromoters. Also, one of the emerging observations that seems to link two different physiological processes (cell proliferation and the immune system) with the tumor promotion process is chronic inflammation.

The hypothesis seems to be that when, in an initiated tissue having an adult stem cell that is blocked in its ability to proliferate by antimitogenic factors, is exposed to an agentcondition that triggers oxidative stress in both cells of the immune system and the initiated epithelial or fibroblastic tissue, an interaction between the two can happen in Figure 3.

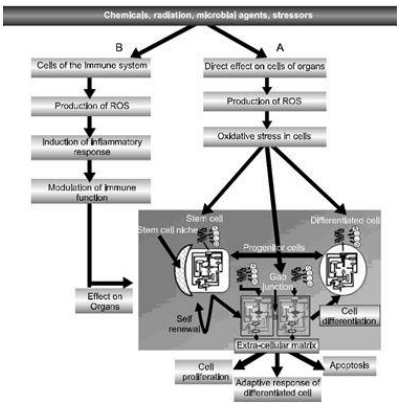

Figure 3: The diagram tries to incorporate a "systems" aspect of how a physical, chemical or biological agent could affect a multi-cellular organism. At non-cytotoxic concentrations or doses, an agent could simultaneously trigger oxidative stress in both the cells of the immune tissues and the epithelial/ endothelial/ stromal cells in various organs. Upon induction of Reactive Oxygen Species (ROS) and of oxidative stress induction of intra-cellular signaling in various cell types of the complex immune system, various cytokines would interact on tissues, containing the three fundamental cell types (adult stem cells, progenitor and terminally-differentiated cells). Given that these cells would have been exposed to the toxic agent and that they, also, would have reacted to the agent differentially because of their different physiological/phenotypic state, the interaction of all three types could be very different (e.g. the normal stem cells might be induced to proliferate asymmetrically; any initiated precancerous stem cell might proliferate symmetrically; the progenitor cells might be induced to proliferate symmetrically and to migrate, as in wound healing; and the terminally differentiated cell might adaptively respond or to apoptose) in response to the inflammatory signal.

Tumor promoters appear to be non genotoxic, yet they can induce oxidative stress. Contrary to common belief, while Radical Oxygen Species (ROS) can, in principle, damage any macromolecule in a cell, in the target cell at tumor promoting agent at non-cytotoxic levels and in an undifferentiated initiated stem cells, they can induce intra-cellular signaling leading to inhibiting GJIC and altering gene expression. Even a genotoxic agent, such as UV light, by killing a large number of cells in initiated skin, can cause compensory hyperplasia of any surviving initiated cell. Cytotoxic agents, such as the non genotoxic alcohol or carbon tetrachloride, can also induce compensatory hyperplasia to act as an "indirect tumor promoter".

The search for a universal chemoprevent agent might now be seen as an illusion. It has been shown that a dietary component, beta sitosteriol, could prevent the growth of initiated rat liver cells with expressed rasoncogene, but not the same type of rat liver cell expressing oncogenes, such as neu, src or even mycras.

In effect, tumor promotion prevents the initiated cell from terminally differentiating and from dying by apopto-sis. The accumulated initiated cells expand and increase the probability of additional genetic and epigenetic changes. Therefore, if oxidative stress is a major component of tumor promotion, then antipromoters or chemopreventive agents might be viewed by acting by antioxidant mechanisms. Evidence exists that many antipromoters have anti-oxidant properties. However, one must be careful in applying this observation in that some antioxidants can have pro-oxidant activity. Unless one understands the actual mechanism by which a chemo preventive agent works, unintended consequences could occur. The classic examples of this were the termination of the CARET and ATBC clinical intervention trials to reduce the risk to cancers.

Since caloric restriction has been shown to reduce many chronic diseases, one might hypothesize that this physiological phenomenon might reduce both the stem cell pools of certain organs, as well as prevent cell proliferation and possibly induce apoptosis of any initiated cells. Therefore, caloric restriction might act both to reduce the initiation of stem cells and to inhibit the promotion process. This might explain the relative low incidence of cancer in the survivors of the atomic bombs.

Barker hypothesis/nutrition and stem cell biology

To prevent or treat cancers, with the assumption that the adult stem cell is the target cell for initiating the cancer process, the old Barker hypothesis seems to be explained, mechanistically, with the stem cell theory. There are several excellent examples of this.

The prenatal exposures to the drug, DES, led to in-creased risk to vaginal cancers of the female offspring of mothers who took the drug during pregnancy.

If the DES exposure during pregnancy of a female fetus causes an increase in stem cell pool in the vaginal tissue, then during sexual maturation of the vaginal tissue, any initiated cell caused by abnormal proliferation might now be promoted by the sex hormones at this stage of development.

Another example is the study of the breast cancers in Japanese women who survived the atomic bombs of Hiroshima and Nagasaki. One explanation is that Japanese mothers' diets included lots of soy products and, in part, these women were calorically restricted. Human breast stem cells, having been isolated and characterized, have been shown to be induced to differentiate into progenitor breast epithelial cells by a major component of soy, namely genistein. Only the human breast stem cells, but not the differentiated progenitor breast epithelial cells, were capable of being neo-plastically transformed. Therefore, if the soydiet of pregnant Japanese women induced differentiation of the adult breast stem cells of the female fetus, as it has been shown in rodents, then after birth, there would be fewer breast stem cells for the development of breast tissue and fewer adult stem cells to be targets for initiating the breast carcinogenesis process.

Recently, in experimental pregnant rats exposed to the environmental pollutant, bisphenol-A, the male offspring after birth developed a high risk to prostate cancers, even though they were not exposed to this pollutant after birth. Even more extraordinary was the observation that if the pregnant rats were exposed to both bisphenol-A and dietary soy, the male rats had a dramatically reduced risk to prostate cancers, again even though after birth they were not exposed to either factor. This strongly suggests that the pollutant and dietary factors acted on the target cells for prostate cancer. One possible explanation is that bisphenol A caused an increase in the prostate stem cell pool in the male fetus. This would increase the risk for an initiation event. After birth, some factor, either endogenous or exogenous, could promote the prostate cancer. On the other hand, during development of the male, soy diet, containing antioxidants, such as Bowman Birk inhibitor or genistein might cause the prostate stem cell to differentiate, reducing the stem cell pool and reducing the risk for prostate stem cell initiation.

Recently, it was reported that there was a correlation of umbilical cord blood haematopoietic stem cell and pro-genitor cell levels with birth weight. This implied that there might be a prenatal influence on cancer risks. Possibly, the fact that the frequencies of childhood cancer types, which are, in general, different from the types of adult cancers, might also be related to this Barker hypothesis. In general, cancer is usually viewed as an "old-age" disease. Therefore, while cancers in children are rare compared to adult cancers, their types seem to be different than the adult cancers. From the teratomas to the other neuronal and lymphoreticular 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, initiation is increased due to enhanced errors of replication, or possibly, due to epigenetic alteration, not mutation of oncogenes/tumor suppressor genes, then exposures, postnatally to massive amounts of normal growth factors of childhood, could lead to the "promotion" of these stem cells. These tumors, if they are of non-irreversibly altered stem cells, are now exposed to agents that can cause them to terminally differentiate, they might be treated easier than the tumor cells of adults which were irreversibly initiated or mutated and then promoted over decades to accrue many more alterations in their genome to become an cancer stem cell.

In summary, based on the assumption that the stem cell pool in specific tissues can be modulated.

Decreased) during development of the fetus, and that the stem cell is the target cell for initiating the cancer process, dietary or pollutant/drug exposure of the fetus could dramatically increase or decrease the risk to cancer later in life. This could be the explanation of the Barker hypothesis. Therefore, implications for pre-natal care of pregnant women should be of high priority. It is

this fact that takes one's control of cancer risk out of the individual's hands. Only after one can, in part, control one's own behavior, can one have partial control to prevent the promotion of ones initiated cancer stem cells (which all human beings have in their bodies).

Mothers who give birth in the last 12 months was coded with the help of health extension workers and the sample size was allocated proportionally to all administrative sub-cities of Sodo town and two Sodo zurea kebeles, then by using systematic random sampling technique every 6th mothers were interviewed.

Stem cells and aging

With the recent focus on stem cell biology, stem cells as a target for diseases and stem cell therapy, it would seem that its possible role in the aging and diseases of aging would have been a predominant component of the theories of aging. However, only within the recent decade, have speculations that stem cells must play a role in the aging process appeared.

The classic dilemma in the aging field involved the issue that the aging and diseases of aging, such as cancer, are or are not independent processes. When one examines many genetic predispositions to cancer, such as xerodermaq pigmentosum or Downs, predisposition to aging also occurs in the skin, where ultraviolet the environ-mental trigger both skin cancer and aging of the skin, and predisposition to leukemia and high risk to Alzheimer's, respectively.

Exogenous agents that can induce cancers could also induce premature aging. In natural aging, we notice that the individual organs do not uniformly age. The individual that is an alcoholic is at high risk for liver cancer and aging of the liver function. The young persons, who ex-pose themselves to large amounts of sun light, will increase the risk for skin cancer and premature aging of the skin. A cigarette smoker induces pre-mature aging of lung function, while at the same time enhances the risk for lung diseases, such as lung cancer. With the reduced risk to aging and chronic diseases. In brief, In brief, the pre-mature or progressive loss of structure/function of cells/tissues/organs/organ systems is a common feature of aging and disease. Depending on the circumstances by which genetic and environmental/dietary agents interact, either or both the loss of efficiency in biological function (aging) or an appearance of clinical abnormality disease can occur.

If the hypothesis presented here is correct, namely, that the adult stem is the target cell for cancer and if the stem cell pool (increased or decreased) alters the risk to cancer, then a possible linkage can be made where the aging process and the cancer process (as a model for other stem-cell-dependent chronic diseases) share a common element, namely the adult stem cell. Since biologically the terminally differentiated cells must be derived from the transit-amplifying or progenitor cells and the adult stem cells, it should logically follow that reducing the stem cell pool would reduced the risk of cancer and be linked to the in-ability to expand tissue and repair.

The amazing recent discoveries of two genetic syndromes, namely the Hutchinson Gilford-progeria, pre-ma-ture aging syndrome and the Nieman-Pick type C neurological syndrome, have identified adult stem cells as being the center of both diseases. In the former, a mutated lamin A gene appears to cause abnormal functioning of all the adult stem cells of all organs. On the other hand, the organ-specific neuronal adult stem cell of the Nieman-Pick type C seems unable to differentiate properly in the brain. Even more dramatically, in both cases, exogenous agents seem to be able to circumvent the genetic dysfunction in the stem cells of both diseases.

There have been speculations that relationship between aging and cancer were the result of evolutionary forces. In essence, the consequences of unlimited cell proliferation would only enhance genomic instability, there-fore, senescence was a option a cell had to decrease the risk to cancer. Although it is generally assumed that a stem cell is immortal until it is induced to terminally differentiate, no one has yet demonstrated that a single embryonic or adult stem cell can proliferate without senescing at some point [remember, all current attempts to grow embryonic or adult stem cells *in vitro* are not done under the *in vivo* niche conditions, it has been shown that hypoxic and anti-oxidant conditions *in vitro* appear to prevent differentiation or early senesce of stem cells [10]]. While progenitor cells, such as human fibroblasts or epithelial cells have limited life spans *in vitro* under con-temporary conditions, the Hayflick phenomenon, then the shortening of telomeres, and genomic instability might be characteristics of only the progenitor or transit amplifying cells.

In summary, conceptually, if adult stem cells can be tar-gets for mutagens, cytotoxic or epigenetic agents that can alter gene expression in a tissue, depending on the gene and the number of stem cells affected, then a chronic dis-ease might manifest itself (diabetes, cancer, atherosclerotic plaque, cataract). On the other hand, if the stem cell pool is increased or decreased during pre-natal/postnatal development, altered risk to chronic disease in later life would be seen. By decreasing the stem cell pool in specific organs or in all organs later in life will hamper the functioning of that organ or individual.

CONCLUSION

In summary, there seems to be an important role in cell-cell communication in regulating, not only cell pro-liferation, cell differentiation and apoptosis of normal stem and progenitor cells, but also of the initiated cell. Interference of cell-cell communication by all the agents and conditions which are associated with tumor promo-tion has been documented. Tumor promotion is that process that allows the initiated cell, which can not normally divide by asymmetrical cell division and does not normally apoptose, to clonally expand, allowing addition genetic changes to become a malignant, metastazing cell. Prevention of the down regulation of cell-cell communication by tumor promoters and the restoration of cell-cell communication in tumor cells would be the strategy for chemoprevention and chemotherapy, respectively.

AKNOWLEDGEMENT

The author has no conflicting financial interest.

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