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The Common Genesis of All Cancers

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Abstract

It is a commonly held belief nowadays that cancer originates in tissue-specific adult stem cells. Most of the tissues in human body have adult stem cells at their base. The difference between embryonic stem cell and adult stem cell is that whereas the former, through a carefully orchestrated cellular program of development genes, can give rise to terminally differentiated cells of all types, the later can repair the terminally differentiated tissue by giving rise to cells of few types specific to the tissue. In a majority of tissues the adult stem cells are relatively quiet, swinging into action only on signals of damage or injury to tissue. One of the exceptions of this is the adult stem cell of intestinal epithelium, which is continuously in action as the differentiated cells of intestinal epithelium are continuously shed into the lumen. The adult stem cells have the property of self-renewal: they can undergo asymmetric cell division to give rise to two distinct daughter cells one of which is the exact copy of mother stem cell and the other is a partially differentiated progenitor cell or progeny, and symmetric cell division to give rise to two identical daughter cells which are exact replicas of mother stem cells. The progenitors further undergo cell division to yield terminally differentiated cells having specific morphologies and functions. The rates of self-renewal, apoptosis and differentiation of adult stem cells and their progenitor cells is very tightly regulated to achieve homeostasis, i.e. steady state where in the number of adult stem cells, progenitor cells and terminally differentiated cells attain a constant value. It has been suggested that cancer results by multiple mutations in adult stem cells and or progenitor cells which disturbs the balance between rates of self-renewal, apoptosis and differentiation leading to unsteady state. Though adult stem cells of different tissues are different from each other, the similarity in their fates and properties both under normal conditions and carcinogenic conditions strongly suggest that there must be a common genesis of all cancers, at least of those organs that have adult stem cell in their lineage. Through this review I investigate the possibility of common genesis of all cancers.

Keywords: Carcinogenesis; Cancer stem cells; Self-renewal; Apoptosis

Introduction

Is there a genesis of cancer common to all cancers? This is a burning question if we dream of a single unique preventive therapeutic against all cancers. This is what ideally all researchers on carcinogenesis around the world aim at. Having a preventive therapeutic specific to the type of cancer does not help, at best what we can achieve with this effort is prevention of recurrence of a particular cancer type in a patient once he/she has been cured of that cancer type. In recent years the research on carcinogenesis has focused on adult stem cells [1]. It is the occurrence of multiple mutations cumulated over multiple stages in adult stem cells and progenitor cells that lead to their transformation to cancer stem cells (CSC) [1]. CSC by them is not cancer but in most of the cases it is CSC that initiates tumors [2]. CSC has the same self-renewal capability as the normal stem cell but its proliferation, apoptosis and differentiation is aberrant and thereby gives rise to cancer through a mechanism which is yet unclear. However, I have a belief that this mechanism is unique, i.e. common to all cancers. The reason for my belief is the similarity in fates and properties of adult stem cells and progenitor cells of all tissue types under both normal and carcinogenic conditions. In order to understand this mechanism I review five different types of cancers of five different organs respectively. They are leukemia, colon cancer, pancreatic cancer, liver cancer and breast cancer. After carefully doing the above said review, I finally propose a hypothesis that CSC fools homeostasis of the tissue microenvironment to transform into cancer. Based on my hypothesis I also propose a possible single unique preventive therapeutic against all cancers, however, this proposal is not without serious challenges. A part of my work may seem speculation, but this speculation is necessary to open new frontiers in cancer research.

Leukemia

Leukemia is the cancer of the blood. However, there is not only one type of blood cancer but there are many depending upon the lineage of blood cell affected and the characteristic of aberration in morphology and functioning of cancer cells more popularly referred to as the leukemic blast. All mature terminally differentiated cells of the blood are generated from Hematopoietic Stem Cells (HSCs), residing in Bone Marrow (BM), in a hierarchical fashion [3]. The cell division of HSC gives rise to two types of Multi Potent Progenitors (MPPs), either Common Myeloid Progenitor (CMP) or Common Lymphoid Progenitor (CLP). The CMP on further cell division give rise to following mature cells of the blood: megakaryocyte, thrombocyte, erythrocyte, mast cell, basophil, neutrophil, eosinophil, monocyte and macrophage. The CLP on further cell division give rise to following mature cells of the lymphatic system: natural killer cell or large granular lymphocyte, T lymphocyte, B lymphocyte and plasma cell. The lymphatic system is different from the blood. The lymphatic system is a part of the circulatory system connected with the heart, however it is different from blood vessels: arteries and veins. The lymphatic system comprises of its own network of vessels called the

lymphatic vessels in which flows the fluid consisting of mature cells generated from CLP. This fluid is called lymph. Blood capillaries connect with the lymphatic vessels and thus complete the circuit with the heart. The lymphatic cells are primarily responsible for the immunity of organism.

The cancers of both the myeloid line of cells and the lymphoid line of cells generated from HSC are known as leukemia or blood cancer though the lymphatic cells are different from blood cells. Some of the leukemia's are acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic myelomonocyticleukemia (CMML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), T cell lymphoblastic leukemia (T-ALL), non-Hodgkin's lymphoma (NHL), etc. [3-5].

In this review I will discuss the genesis of blood cancers of myeloid line of blood cells, specifically AML and CML, and not the blood cancers of lymphoid line of cells generated from HSC. There is no particular reason for this choice. The stem cell origin has been both postulated and shown experimentally for myeloid leukemia's [6]; the hypothesis states the existence of Leukemic Stem Cells (LSCs), having same features as HSCs, in myeloid leukemia's which initiate and support the leukemic blast. It is the occurrence of multiple mutations in multiple stages in HSC or MPP leading to the loss of homeostatic balance between proliferation, apoptosis and differentiation of these cells (HSC or MPP) that give rise to LSCs [3,7]. M. Ryan Corces-zimmereman and RavindraMajeti in the work [7] has pointed towards the evolutionary nature of leukemia stating that the first mutation of a sequence of multiple mutations leading to leukemia occur many years before the actual onset of disease as is the case with many other cancers also [8]. Over a period of time the HSC or MPP accumulate multiple mutations retaining in every step of evolution the capability of self-renewal and the capability to give rise to differentiated progeny. Suppose that up to N number of mutations the HSC or MPP retain the ability to produce mature blood cells of proper morphology and function, the cancer has still not set in. Merely acquiring the property of self-renewal (in case of MPP) and retaining it (in case of HSC) is not enough to cause cancer; with sequentially undergoing mutations, if at a certain step, say, N+1 the differentiated progeny of HSC or MPP is not identifiable with any of the known mature blood cells but instead has an aberrant morphology and aberrant function, the cancer has set in. And hereafter the multiply mutated HSC or MPP is no longer called the HSC or MPP but is referred to as the LSC. This sequence of mutations leading to leukemia cannot be a random one, it needs to be unique for a particular type of leukemia identifiable with the morphology and function of the particular leukemic blast. What happens after the above mentioned N+1th mutation that give rise to cancer is the subject matter of this review and is discussed in "Conclusions and Discussion" section.

A very popular hypothesis of the deregulated expansion of cancer cells is up-regulation of cell proliferation and the loss-of-function mutation of apoptotic genes in LSC [5]. However, if we consider the existence of LSC as an essential element in the genesis of cancer and also consider that the apoptotic genes are definitely mutated in leukemia, there should be no apoptosis at all of the leukemic blasts derived from LSC, and also of the LSC. But experimental results [4] show otherwise. Did profiling of the rate of proliferation and the rate of apoptosis of BM cells in different leukemia and found that there is considerable apoptosis of the leukemic cells though the rate is less than the proliferation rate. With this result I challenge the above hypothesis of deregulated expansion of cancer cells; though a few apoptotic genes may be mutated in the course of sequence of mutations leading to leukemia but not all. Interestingly, another experiment [9] also shows that the leukemia cells have a lower proliferative rate than normal HSCs. This proliferation is of the LSC and not the leukemic blast [6]. Hence, normally the LSCs in full blown cancer are rare. I will include all of these features in my hypothesis of common genesis of all cancers as I state it in "Conclusions and Discussion" section.

Another proof that challenges the hypothesis that the apoptotic machinery of cell is mutated in leukemia comes from the study of dynamics of cell numbers of LSC and the leukemic blast. Initially when leukemia is about to set in, there is not a single cell of the leukemic blast in blood. Because cancer will set in when the leukemic blast is populated, initially LSCs must undergo uncontrolled proliferation giving rise to large number of their own copies which thereafter undergoes aberrant differentiation into progeny which is the leukemic blast. This is so because the cells of leukemic blast do not renew [6]. Once there is adequate population of leukemic blast in the blood which can drive itself through uncontrolled proliferation, the LSC is quiet and has very less numbers of itself [6,9,10]. This means that after the uncontrolled proliferation of LSCs there is widespread apoptosis of it to restrict its numbers to few.

We will now touch upon the characteristic of the LSC of AML, AML LSC and the LSC of CML, CML LSC. The leukemic cells of AML obtained from patients show a hierarchical cellular organization with a few quiet cells, probably the AML LSC, capable of self-renewal, occupying the apex of this hierarchy [11]. This hierarchical structure is similar to that of healthy blood cells with HSC at the top. Another study indicates that at an early stage of disease LSCs are rare (i.e. their frequency in blood is low), but, however, if the patient after undergoing chemotherapy shows relapse (i.e. AML comes back) there is a 10 to 100-fold increase in LSC frequency [10]. The CML LSC shows features similar to AML LSC. It is CML LSC which is also responsible for drug resistance and relapse on treatment with Bcr-Abl tyrosine kinase inhibitors, it is notable that CML is caused by a chromosome translocation that generates the Bcr-Abl oncogene [12].

Colon Cancer

Colon is the name given to large intestine. The intestine (both small and large) is a long tubular structure with the inside hollow space known as lumen. Overlooking the lumen are millions of crypt-villus structures which have a lining of single sheet of epithelial cells on the outside [13]. The crypt-villus structure is a folded finger like structure protruding into the lumen. The top third of it is known as the villus and the bottom two-third constitutes the crypt. The villus harbors the terminally differentiated epithelial cells which performs the key functions of an intestine. The top of the crypt is occupied by the multipotent progenitor cells. Below the progenitor are the adult stem cells. And at the very bottom below the stem cell population is Paneth cells- another terminally differentiated cell originating from the stem cell. The stem cells undergo asymmetric cell division to give one daughter cell which is the exact copy of the mother cell and another partially differentiated cell which is the multipotent progenitor. The progenitors further undergo cell division to give rise to any one of the following four terminally differentiated epithelial cell lineages: enterocytes, goblet cells, endocrine cells and the Paneth cells [14]. The enterocytes, goblet cells and endocrine cells make up the villus.

The other name for colon cancer is Colorectal Cancer (CRC). Colon cancer has also been hypothesized to be a stem cell disease [1]. This

hypothesis is natural because the functional units of intestine also originate from a consistent population of adult stem cells maintained near the base of the crypt. Like leukemia this cancer can also be assumed to develop over years or decades, taking this much time to accumulate multiple mutations in a sequence spread over time starting from the first mutation in colonic stem cell and or its progenitor [14]. This set of mutations cannot be a random one as I already stated above in section Leukemia, but a definitive one to produce finally the aberrantly differentiated cell with aberrant morphology and aberrant function. Amongst these set of mutations, apart from the mutations in genes necessary to cause aberrant morphology and functioning of intestinal epithelial cells, may also be included the mutations in genes that lead to deregulated proliferation and apoptosis of Cancer Stem Cells (CSC). A popular consensus amongst scientists particularly those engaged in studies on carcinogenesis is that for the genesis of cancer the apoptotic genes be necessarily mutated. But I do not agree with this consensus. The reason for my disagreement is the stem cell nature of disease. If it is so that the cancer cells arise from a relatively small population of CSCs which have accumulated mutations over years, the mutations in apoptotic genes should lead to the zero apoptotic status of CSCs and cancer cells. It is not so sure let us look at one experimental study [15]. In this study the researchers found the spectrum of apoptotic index (AI) in terms of the percentage of cells undergoing apoptosis to the total number of epithelial cells of intestinal lining involved in the experiments, designed and executed separately for the left colon, right colon and sigmoid rectum. The subjects/patients involved were the ones with previous history of large adenomas in the colon, they were called high risk; and the controls which were called low risk. Let us consider the data for right colon and left colon. The mean AI for right colon patients is close to 2.2% whereas that for controls it is close to 2.7%. For the right colon the mean AI reduced by only 18.5% in a high risk group vis-à-vis the low risk group. This is proof enough that the reduction in apoptosis once the disease (colon cancer, more specifically adenoma here) had occurred is not significant so as to raise alarm. The mean AI for left colon patients is close to 1.25% whereas that for controls it is close to 2.75%. For the left colon the mean AI reduced by 54.5% in a high risk group vis-à-vis the low risk group, which again is not a significant reduction. Let us analyze this result in terms of absolute number of epithelial cells undergoing apoptosis. On average small intestinal crypts contain 250 cells [1]. If we assume the same number for colon crypts and assume that out of the million (1,000,000) crypts present in colon a third is found each in left colon, right colon and sigmoid rectum, the 1.25% AI for left colon translates in absolute number to 1 million 41 thousand 6 hundred sixty six cells undergoing apoptosis, which by itself is a huge number and cannot be considered insignificant. We can safely assume the similar profile of AI to exist in colon at the time when colon cancer is fully developed in the patient and progressing, i.e. we consider here the sample of patients with high risk representative of the patients with fully developed cancer. This result is similar to the one obtained for leukemia [4].

Though the imbalance is created on progression of cancer, i.e. relatively higher proliferation rate than apoptosis, the absolute number of cancer cells undergoing apoptosis is mind-boggling and calls for a deeper investigation than the general consensus that in the genesis of cancer inhibition of apoptosis plays an important role. I will say that the apoptosis is not inhibited in cancer cells but the resistance to apoptosis is increased in cancer cells so that a few cells undergo apoptosis compared to the number of cells undergoing proliferation. How this imbalance occurs need deeper and more precise research to exactly pin-point the mechanism of apoptosis in cancer cells. However, I have a proposal for the possible clue to creating the above mentioned imbalance. The key events taking place in the genesis and or progression of cancer is the up-regulation of proliferation and down-regulation of apoptosis. If you look for the "List of Signaling Pathways" in Wikipedia, it will enlist 17 signaling pathways operative in human cell. Each of these signaling pathways is a complex network involving dozens of molecules and is important for some of the normal activities of cell including proliferation and apoptosis. Given that all these 17 pathways operate inside the same cell, there is every possibility of cross-talk also amongst these 17 signaling pathways. So the permutation and combination of these pathways and their complex networks give rise to a mind-boggling number of both intracellular and extracellular mechanisms that control cellular activities including proliferation and apoptosis. So it is expected that biology is not simple, more specifically it is not linear, so that we could not predict easily the output of variation in the concentration of a particular molecule in terms of a particular cellular activity. This situation is same if we linearize a particular non-linear system and obtain n simultaneous equations in n unknowns, where this n is a very large number. Now if in this system we perturb a particular coefficient, it is not easy to predict the variation in solution of these equations. Only computer can calculate that, in this sense computer is GOD for this system of equations. Similarly, there is every possibility for the existence of GOD (central controlling authority of all the 17 signaling pathways in human cell) which knows very-well the effect of perturbation in the concentration and or deletion of particular molecule on the cellular activities. I propose that this GOD is glucose metabolic pathway. This pathway sits at the top of these 17 signaling pathways.

Mason EF, Rathmell JC shows that the key mechanism by which the cell growth and death is regulated is glucose metabolism. However, it also shows that the glucose metabolic pathway is downstream of cell growth pathways including proliferation [16]. This work says that the presence of growth signals and or molecules in the niche of cell up-regulate the uptake of glucose. However, I do not agree with this conclusion of the work. The reason for this observation by the work could be that there exists a closed positive feedback loop between the two pathways. In fact my hypothesis is that the glucose metabolism sits at the top of all these 17 signaling pathways in the human cell, and that in turn these pathways exercise control over the glucose metabolism also through closed positive or negative feedback loop. My belief is that once the organism has taken in glucose as food material, this glucose is made available to all the cells of body and glucose metabolism is active in all the cells which are exposed to the concentration of glucose above a certain minimum threshold value. This is so because energy released by the metabolism is needed not merely for proliferation and differentiation but all the other activities of cell including mere survival and maintenance of the internal machinery. Some might argue that this is a chicken and egg situation (Which came first?). I have a simple way out of this dilemma- the first life forms on earth originated in nutrient rich fluid instead of it being other way round, i.e. the life form did not came first by some other mechanism and then showed its control on nutrient uptake. The same relationship is expected to be copied in the cell of an organism. The glucose metabolic pathway sitting at the top of proliferation pathway does not mean that all the cells undergoing metabolism proliferate. For example, in the Wnt signal pathway (Wnt is known to cause proliferation), proliferation will take place if the Wnt ligand is present in the microenvironment of cell and simultaneously if the energy released by the glucose metabolism is in excess of that required for survival and maintenance. Thus there is

two-step control over proliferation: firstly by the glucose metabolic pathway sitting at the top and secondly by the presence of appropriate molecules in the niche of cell. Additionally it is naturally the energy release by the glucose metabolism that causes the transcription of Wnt gene into Wnt glycoprotein and its subsequent secretion from the cell in which it is produced. Thus at least in this way Glucose metabolism is sitting upstream of Wnt signaling pathway if not in the way in which I proposed. More on this in the "Conclusions and Discussion" section. Meanwhile, I discuss below two of the signaling pathways, Wnt and TGF-beta, implicated in the genesis and progression of colon cancer, to give an idea of the complexities involved and thereby stress that the mechanisms of control in biology are non-linear.

Wnt signaling pathway derives its name from the ligand Wnt which when it binds to the trans-membrane receptors Frizzled (Fz) and corecptor Lrp5/6 (LDL receptor related proteins 5 and 6), the complex Wnt-Fz-LRP5/6 is formed [14,17]. What we are discussing here is the Wnt canonical pathway. There exists the Wnt non-canonical pathway also but that we do not discuss it here. Wnt pathway is also known as the Wnt/β-catenin pathway because the Wnt-Fz-LRP5/6 complex blocks the formation of complex of glycogen synthase kinase 3β (gsk3β), APC tumor suppressor protein and axin. It is notable that the gsk3β/APC/axin complex phosphorylates β-catenin, bound to E-cadherin inside the cell but outside the nucleus, and the phosphorylated β-catenin undergoes degradation through an E3 ubiquitin ligase dependent pathway [1]. Therefore, the presence of un-phosphorylated β-catenin in the cell is dependent upon the formation of Wnt-Fz-LRP5/6 complex; and this un-phosphorylated β-catenin accumulates inside the nucleus. A natural question that arises is that if there is any way other than the absence of Wnt ligand to block formation of Wnt-Fz-LRP5/6 complex. Yes, there is, and it is possible by the secreted protein Dickkopf1 (Dkk1) [17]. Once inside the nucleus the free β-catenin forms complexes with members of the Tcf (T-cell factor) and Lef (lymphoid enhancer factor) transcription factor family. The final result of this cascade is the expression of Wnt-responsive genes Myc, Ccnd1 and Axin2. In mice in which the transcription factor Tcf4 is deleted, which means that the Wnt-responsive genes are blocked from transcription, the colonic crypts are not formed and there is no proliferation [14]. Therefore activation of the Wnt pathway has been directly co-related with proliferation. Activation of β-catenin/TCF complex has been shown in colon cancer [18,19]. Thus there are at-least a dozen molecules involved in the Wnt canonical signaling pathway that include molecules either aiding the formation of a particular complex or inhibiting it, and it is hard to predict the final outcome of over-expression or under-expression of any one of these molecules, more so because there is every possibility that in this cascade each molecule may positively or negatively regulate the expression of some other molecules in the cascade and thus have a final positive or negative effect on the Wnt signaling pathway. The experiments need to be designed to accurately find such relationships, it is not enough to knock out one gene and observe the outcome because during the sequence of mutations leading to cancer the most probable effect of mutation in one particular gene may be the over-expression or under-expression of the protein corresponding to that gene.

TGF-beta signaling pathway derives its name from the family of TGF-beta ligands [20], which when binds to either serine/threonine kinase receptor1 (STK1) or serine/threonine kinase receptor2 (STK2) or both [14,20], forms a TGF-beta/STK1/STK2 complex. TGF-beta normally block cell proliferation and promotes apoptosis [1,14]. However, it is involved in the regulation of a variety of cellular processes including stem cell maintenance, stem cell function, differentiation and apoptosis [20]. The TGF-beta/STK1/STK2 complex activates the intra-cellular family of SMAD proteins. There are 8 proteins in the SMAD family- SMAD1 to SMAD8, each having a different role. However, the downstream target of the activation of these SMAD proteins is the transcription of key cell cycle checkpoint genes including p21, p27, p15. These genes lead to growth arrest upon activation. Colon cancer has been shown to be initiated and driven forward by synergism between TGF-beta and Wnt signaling pathways, where in the downstream target molecules of Wnt signaling is activated, simultaneously, along with the repression of the downstream target molecules of TGF-beta signaling [1,21]. A further complexity in this TGF-beta signaling network is that SMAD proteins functions also by interacting with multiple other signal transduction pathways, suggesting a cross-talk between these multiple signal transduction pathways and TGF-beta signaling network. There is evidence of a definite cross-talk between TGF-beta signaling pathway and Wnt signaling pathway [14]. The control over proliferation and apoptosis may be deregulated not merely by mutations in Wnt pathway and TGF-beta pathway but also by the relative concentrations of downstream target proteins of the Wnt pathway and the TGF-beta pathway. I am forced to make this hypothesis because if really it were so that colon cancers are driven by the loss-of-function mutations in TGF-beta signaling molecules, then all the cancer cells including the Cancer stem cells must be inhibiting apoptosis. This is not so, a few numbers of cells do undergo apoptosis and this number is significant when compared to the number of cells undergoing apoptosis in healthy cell. We have already discussed it earlier in the context of the experimental study [15].

Pancreatic Cancer, Liver Cancer, Breast Cancer

The pancreatic, liver and breast cancers too are stem cell diseases like Leukemia and Colon cancer. The same arguments and discussion as done for the stem cell nature and genesis of Leukemia and Colon cancer, under sections Leukemia and Colon cancer respectively, hold for these three, and therefore to avoid monotony we do not further discuss these three cancers. However, adequate references are provided [22-30].

Given the stem cell nature of most of the cancers with almost similar characteristics, there is every possibility that there exists a common genesis of all cancers. It is of utmost importance to accurately speculate/predict/hypothesize this genesis, if we have to beat the demon called cancer. To understand this importance let us take the example of the deadliest of the cancers-pancreatic cancer. Sanguinarine is a very promising toxin against pancreatic cancer which works by inhibiting self-renewal capacity, cell proliferation, pluripotency, etc. of pancreatic cancer stem cells [25]. Besides, more than a dozen phytochemicals have been discovered to date to target pancreatic cancer stem cells: curcumin, resveratrol, tea polyphenol EGCG (epigallocatechin-3-gallate), crocetinic acid, sulforaphane, genistein, indole-3-carbinol, vitamin E δ-tocotrienol, Plumbagin, quercetin, triptolide, Licofelene and Quinomycin [24]. Both papers show the magnitude of research effort that has gone in to prevent and cure pancreatic cancer [24,25]. But the grim truth is that the pancreatic cancer is still the deadliest of all cancers with a very poor prognosis. This calls for the exact prediction of the genesis of cancer, so as to come up with a concrete preventive and curative therapeutic. I exactly do this in this review article.

Conclusion

In most of the cases of cancer the cause of a cancer is a pre-cancer single mutation in the otherwise healthy adult stem cell or multi-potent progenitor. This single mutation, however, does not directly give rise to cancer but over a period of time multiple mutations occur in a sequence in multiple stages in the cell that initially had only single mutation, and thus a pool of small number of highly mutated cells are formed that have the same capacity of self-renewal as the healthy adult stem cell called the Cancer Stem Cell (CSC). CSCs do not always arise from adult stem cells and or multi-potent progenitors only, sometimes the mature differentiated cells also give rise to CSCs by undergoing a sequence of successive mutations that confer it the property of self-renewal, like, for example, in liver. It is the CSC that initiates tumor and maintains the cells of the cancer blast. What is the gap between CSC and initiation of tumor, i.e. exactly what happens between the establishment of CSC and onset of cancer is the primary focus of this review. It is not possible to know this, or capture this moment, by any experiment. The limitation is Heisenberg's uncertainty principle (HUP). According to HUP, the more accurate we are in freezing a particular quantum system/particle in time the more uncertain we are in determining its energy, and the more accurate we are in determining the energy of a particular quantum system/particle vice versa. In conducting experiments to find out what is happening inside the biological cell, we are dealing with quantum world. So, if we freeze the cell at the moment just before the onset of cancer and just after the establishment of CSC, we lose information regarding the expenditure of energy, i.e. the occurrence of cellular processes, inside the cell. If, however, we serendipitously observe the cellular processes occurring at the moment just before the onset of cancer and just after the establishment of CSC we will not know that these cellular processes are of that very moment. Based on the knowledge of stem cell nature of most of the cancers, I propose the following hypothesis without proof about the exact mechanism that leads to the onset of cancer from the establishment of CSC. A natural question that arises is: When we cannot design the experiment to capture this moment, how will we validate the hypothesis? My answer to this question is simple: Based on the proposed hypothesis we can design the possible preventive and curative therapeutic against cancer, which, if it works, will validate the hypothesis.

Hypothesis

Just after the establishment of CSC, the CSCs begin to both proliferate and undergo apoptosis aggressively. It is the large scale of apoptosis of highly mutated stem cell that fools the homeostasis of organism, and henceforth the homeostasis is unable to detect that these highly mutated stem cells are defective and cannot take any corrective and or immunology based action against these highly mutated stem cells (the highly mutated stem cells by themselves have a sense that they are defective and hence program their own death which is called apoptosis, but the otherwise healthy cells surrounding the highly defective mutated stem cells do not have a sense that these stem cells are defective because they, the stem cells are undergoing self-eradication- this is meant by the phrase fooling of homeostasis). Because the highly mutated stem cells are undergoing apoptosis in large numbers the repair mechanism of these cells are triggered to take corrective action by up-regulating the glucose metabolism pathway (GMP) and these cells thereby evolve into strong cells which have increased resistance to apoptosis.

There are works in partial support of a part of my hypothesis. Works in Bursch et al., and Schulte-Hermann, et al., show that Preneoplastic lesions in liver of rat have enhanced apoptotic rate than otherwise normal cells in liver, and that proliferation rate exactly balances the apoptotic rate [31,32]. Preneoplastic is the state of cells some time before the initiation of tumor, benign or malignant. The above mentioned observation is exactly what time before the cancer lesions come into existence is not clear (because of HUP), the only known sense of timing is that the cancer blast cells have not yet formed. However the claim of my hypothesis is that this observation of enhanced and balanced apoptotic rate and proliferation rate is exactly at the time just before onset of cancer and just after establishment of CSC.

The mechanism of the enhanced apoptosis of proliferating CSCs just before the onset of cancer is not clear. However, it can be conjectured that the intrinsic cue of the cell of it being highly mutated and thus defective, somehow activates the cell-intrinsic pathways of apoptosis. The next question concerning above hypothesis- Why is up-regulation of GMP the key component in the act of fooling of homeostasis by CSCs? Glucose metabolism *via* the pentose phosphate pathway has been directly linked with nucleic acid synthesis (NAS) inside the cell [33]. On cellular demands for repair the pentose phosphate pathway show increased utilization; and increased rate of nucleic acid (RNA and DNA) synthesis is important in controlling the mechanisms of repair, growth and reproduction [33]. In the hypothesis the enhanced apoptosis of CSCs is interpreted as damage done to the cells which the cells respond as demand for repair, and hence the up-regulation of pentose phosphate pathway in these cells. The mechanism by which the pentose phosphate pathway is up-regulated in response to the demand for repair is not clear, and henceforth must constitute an active area of research.

Promising Preventive and Curative Therapeutics Based on the Hypotheses of this Paper

The best prevention against cancer of all types will be to identify the defective stem cell when only the pre-cancerous single/first mutation has set in, and kill it. An ideal way to kill this pre-cancer stem cell would be to deprive it of glucose. Now there are two challenges to this strategy:

(a) How to selectively deprive only this stem cell, of glucose?

(b) How to identify this singly mutated stem cell?

The primary force driving tumorigenesis is the up-regulation of GMP in CSCs and other cancer cells. So the best cure for cancers of all types will be to deprive the cancer specific cells, i.e. the CSCs and cells of the cancer blast, of glucose. Another route will be to treat tumor cells with depressants of pentose-phosphate pathway. Two of the best known depressants of pentose phosphate pathway are ethanol-alcohol dehydrogenase and sodium metabisulphite [33]. A strategy needs to be devised for these two chemicals to target only the tumor cells. A brilliant alternative to this chemical approach is to follow a strict dietary regime where the patient reduces intake of glucose. This dietary regime is that the patient switches to fluid-only nutrition: fresh fruit juices and fat-free soups of vegetables. Both the fresh fruit juice and soup must be strictly homemade. I have heard that in some parts of the world expert nutritionists treat the cancer patients like this, but I do not have any documented proof of this. While discussing Leukemia and Colon Cancer at length, I have pointed out that post onset of cancer still a significant number of cells undergo apoptosis though its

rate is less than the proliferation rate. This means that despite the establishment of cancer in the human body, there are some pathways of apoptosis which are conserved, i.e., not mutated. The doctors must find out these conserved pathways/mechanisms of apoptosis in each individual cancer patient, and then treat that cancer patient by up-regulating this/these pathways in the tumor cells. This is an attractive curative therapeutic against cancer.

After a sequence of successive mutations in adult stem cells, multi-potent progenitor or even mature differentiated cell in some cases a constant pool of small number (3 here) of Cancer Stem Cells (CSCs) is formed. These three CSCs undergo proliferation to give 6 more cells which are copies of itself (Actually the number of cells after proliferation will be much larger than 6. I have drawn only 6 here because of the limitation of space). All the six cells which originate after proliferation undergo apoptosis, so that the proliferation rate and apoptotic rate are exactly balanced. This enhanced apoptosis of proliferating CSCs is interpreted as damage done to the cells which the cells respond as demand for repair, and hence the up-regulation of glucose metabolic pathway in these cells. Also the enhanced apoptosis of proliferating CSCs fools the homeostasis into believing that nothing is wrong with these CSCs and hence cannot take any corrective and or immunology based action against these highly mutated stem cells. The result is that the resistance to apoptosis is increased and the blast of cancer cells with aberrant morphology and aberrant function is established (Figure 1).

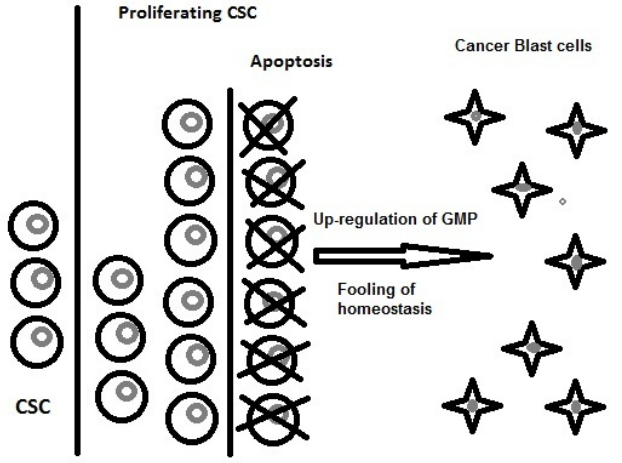

Figure 1: The common genesis of all cancers.

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