

## Quantum Stem Cell in the Infinity Loop: A New Concept for Our Understanding of the Normal State and Cancer

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**Abstract: Problem statement:** The scientific community is in need of more rigorous understanding of the mechanism of initiation of mitosis. The complete understanding of the initiation sequence may allow knowledge of the normal and disease states, including cancer. This understanding and knowledge would open the way for developing curative treatment of cancer. This article proposes a mechanism of initiation of mitosis based on preservation of maternal DNA and presents evidence in its support. **Conclusion:** This will be compared to the governing biology of the stem cell compartment. The implications for understanding and treatment of cancer will be described.

**Key words:** Stem cell, cancer stem cell, histone code, apoptosis, micro RNA, hypoxia

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### INTRODUCTION

Cells in the stem cell compartment may be resistant to conventional therapies for cancer due to their differences in imprinting and gene expression as an adaption to survive in their unique hypoxic microenvironment. The genes that may have normally induced apoptosis in normoxic conditions may be silenced or other antiapoptotic genes may be over expressed. Apoptotic gene expression patterns should be characterized in cancer cell lines in hypoxia, compared to normoxia and compared to cancer stem cells. Given that the cells in the stem cell compartment have adaptively changed their imprinting pattern, they may be selectively susceptible to therapy including plasmid constructs with proapoptotic genes linked to specific promoters more active in these target cells. Better characterization of the metabolic pathways induced by various treatments in cells in the stem cell compartment could lead to new therapeutic strategies.

The attempts of the scientific society in the last several decades at understanding disease states have enjoyed an ever increasing sophistication with the advent of new technologies. However we have frequently continued to misunderstand the true state of the cell and the universal laws that govern its sheer existence. The main theme of this article is a new way of approaching the definition of the normal state.

Currently, we are still in the dark as to what mechanism(s) trigger(s) the mitosis, or how a normal cell “thinks” in this regard. In cancer therapy, this lack of fundamental understanding is akin to searching in the light for a key that we have lost in the darkness. Since

the time of inception the genome has continued to adopt new and different mechanisms for protection of its integrity while simultaneously pursuing evolution to higher levels of complexity. Maybe evolution is a genius balance of these two major principles. During the multi cellular era, paramount to an isolated cell was to obtain the means of survival by sharing its genetic machineries in a reciprocal fashion with neighboring cells. 3.8 billion years later this is forbidden and yet the smooth pace of evolution continues. This mixing of genomes continued until the level of its complexity established automata which can be defined as a state of self sufficiency and independence of the genome to acquire higher levels of complexity internally rather than with external exchange. At the same time, the cell started to build multiple echelons of barriers to prevent the foreign genome from penetrating into its genetic machinery, including double stranded RNA, single stranded DNA and most importantly genomes with discrepant patterns became forbidden from getting incorporated into the self genome. Apobec family of genes is a pattern recognizer and acts as a gate keeper and does not allow discrepant tandem repeats to get in. Why has the ingenious of the system selected pattern as the key mechanism to protect its genomic integrity (Holmes *et al.*, 2007; Takaori-Kondo, 2006)? Probably because pattern is the simplest and most descriptive way to recognize such differences and could be translated into the histone code and its interconnecting and trans talk mechanisms such as microRNA patterns.

Another fundamental question that has not been asked let alone being answered so far is if tandem repeat pattern differences such as aaaaaaa-tttt could

prevent foreign DNA from entry, then why this and other pattern differences between paternal and maternal DNA following fertilization get ignored? Paternal genes with different patterns of tandem repeats and other pattern signatures are allowed to dock in the vicinity of maternal genes despite their potential to invade and change maternal pattern signatures. Why during embryogenesis the cell continues to silence segments of its own genome/self patterns as it moves on in the process of organogenesis? This paradox cannot be resolved with the conventional way of thinking. One could arbitrarily define a pre-self recognition era which is limited to the time interval taken by fertilization. I propose that despite the fact that these two totally different genomic signatures seem to have consolidated by creating a 2n chromosome cell; they continue to perceive the inherent differences in the patterns of their tandem repeats or other as yet unidentified sequences/signatures. This consolidation and yet separation is one way of defining the quantum way of thinking and acting of the cell. In quantum mechanics in Schrödinger's famous cat in the box experiment: The cat is neither alive nor dead though it is alive and dead at the same time. In light of the fact that it is the maternal genome that has been approximated by the paternal genome and in anticipation of imminent infiltration of paternal genome into maternal sequences, immediately after formation of zygote the pattern dissimilarity recognition genetic machinery which perceives such differences in pattern even when they are separated by a distance in the space would through its connection loops with signal transduction elements and cell cycle machinery initiate mitosis in an attempt to minimize or ideally zero down such differences., This machinery is different from the family of genome whose job is to recognize pattern dissimilarity of the invader genome having infiltrated into that of the host.

I propose that this machinery is inherently present in the germ cells as a defensive mechanism against invasion by foreign or even neighboring germ cells and is awaiting our discovery. Thus, with each round of mitosis we should expect a decrease between the dissimilarity of paternal and maternal DNA patterns, i.e.: Paternal DNA becomes more maternal and that could potentially lead to perturbation in the paternal histone code and microRNA profile. Perhaps this is why the mitochondrial DNA is originating from maternal line only and paternal mitochondria get destroyed. This lends support to the existence of the above mentioned sensor mechanism through which this critical machinery is safe guarded against major turbulences. I predict that if we do single cell DNA, microRNA or histone code profiling of the

mitochondria through multiple rounds of mitosis we would either see no changes or infinitesimally small changes in these profiles, as mitochondrial DNA is not in conflict with that of foreign DNA It is the maternal DNA itself; and it should indeed undergo mitosis by signals through the nucleus. If we isolate mitochondrial DNA (mitochondria) from the cell, it would be very difficult to imagine that they could initiate mitosis on their own. If the mechanism of initiation of mitosis is indeed the cell's attempt to minimize the difference between the paternal and maternal DNA patterns of tandem repeats and other signatures, i.e., making paternal DNA patterns more maternal, then one might imagine that the cells that are dormant in each organ should have the most maternal DNA patterns, up to the level of exhaustion of this mechanism. Those cells should have achieved this goal to the maximum capacity of the system. for that reason, I propose that the hyperplastic stem cell compartments are comprised of such cells, which are well protected from invaders in their hypoxic environment; only when minor perturbation in paternal DNA patterns in these cells make them less maternal as a result of ongoing manipulations by agents such as viruses or spontaneous mutations, they undergo mitosis to achieve minimization of such differences. If the mitoses were asymmetrical it would replenish the Transit Amplifying Cells (TACS) which through multiple rounds of mitosis and finally differentiation lead to organogenesis, thus at the point of exhaustion of this mechanism organogenesis happens! This defines the infinity loop in the sense that when and where one expects demise of the system through discontinuation of mitosis that system would make a major leap towards organogenesis and maintenance of homeostasis. If mitosis of the stem cell follows symmetrical pathway it would lead to restoration of the normal size of the population of the stem cell compartment, again stabilization of the system is achieved in the face of destabilizing events. Signals from TACS and stem cell population sensor mechanisms should decide about symmetrical versus asymmetrical versus apoptosis or migration of stem cells to other organs and sites including the peripheral blood or quiescence. One also could envision the incessant rounds of mitosis and pathological expansion of the stem cell compartment as a manifestation of an unfulfilled attempt to narrow the gap between maternal and paternal DNA patterns created by some ill genetic or environmental events. I propose that if we do single cell microRNA or histone code profiling of cancer stem cells and compare them with such patterns of normal stem cells we would find a more paternal pattern in cancer stem cells that would

not dissipate and might indeed become more paternal as the process of malignancy advances to higher stages.

A more fundamental question is the reason for the sheer presence of stem cell compartment in each organ. This is where we need to refer to the universal laws governing macro cosmos, which extend themselves into the micro cosmos. By dissecting these principles one could see major parallelism between them. The known universe has originated from zero geometry, infinitely hot and dense (Hawking's radiation) expanding to its very end in no time in the form of bubble(s). This has probably preceded the Big Bang and generation of about 300 small black holes per 1 light year. There are certain areas connecting the bubbles where time and space do not exist (cosmic strings) through which one could traverse from one end to another in no time. The breakdown of symmetry has been proposed to have led to the formation of galaxies which in many universes have a central blackhole; some others do not have black holes in their center because of Fineman's law (sum over histories). Some say that our known universe came into existence following collision of two massive black holes. The cell comes into existence following collision of one sperm and one ovum (fertilization), which contains highly dense and compact genetic material: Six picograms of genetic material carrying three billion nucleotides in six micrometer diameter. The massive pace of enlargement of embryo is also similar to the massive pace of expansion of the universe following its birth, the universe is old after the first 3 min so is the human embryo after the first 3 months. The breakdown of symmetry leads to the formation of galaxies, the breakdown of symmetry of embryo also leads to the formation of organs. The stars die in 4 major ways: Black hole, white dwarf, super nova and neutron stars; the cell also dies in four major similar ways: Apoptosis, senescence, necrosis and autophagy (Henriquez *et al.*, 2008). Perhaps a Creator has set a series of laws that act as the foundation of creation of universe, a universe that would lend itself to the formation of life based on the same fundamental laws and principles. It is the understanding and dissection of these laws that would enable us to understand the normal state in the bio universe/ the universe of living organisms and that understanding would pave the way to understand the disease states including cancer. In case of cancer our focus should be on mapping the microRNA and histone code profile of the cancer stem cell and comparing that with the same pattern of normal stem cell counterpart and then decipher the mathematical difference and zero down that difference with gene delivery, microRNA delivery or epigenetic modification methodologies. We should also re-examine the mechanism of our

occasional success in examples like germ cell tumors and Hodgkin lymphoma; most probably in these instances we are dealing with non-stem cell (like) disorders such as uncontrolled proliferation of TACS. Understanding of the hypoxic environment in which the stem cell compartment resides is also of great significance in our final perception of biology of cancer and our design of treatment modalities. This environment has created a sanctuary site that the neighboring cells would not be able to penetrate (Brahimi-Horn *et al.*, 2007). Indeed our misunderstanding of the depth of this concept can misguide us in our current design of related treatment modalities. We should not forget that the response of the stem cell compartment in hypoxia is totally different from that of the TACS. Today we can see that many groups are developing targeted therapies against HIF mediated pathways including VEGF (Achen and Stacker, 2008; Kim *et al.*, 2007). Indeed many times we are targeting the TACS rather than the stem cell compartment, which naturally would not lead to cure. Current approaches might indeed promote further expansion of the stem cell compartment through time. Clearly if the stem cell compartment would employ the same response to hypoxia, e.g.: Upregulation of VEGF, it would lose its stem cell like identity by promoting creation of new vasculature and bringing in more oxygen! In this regard we should reconsider our strategy. Again one could see major resemblance between hypoxia as a strong barrier against penetration into the stem cell compartment and black holes in galaxies that are shielded by enormous gravity, so much so that whatever that gets into their event horizon would get annihilated. By the same token any cell approaching the hypoxic environment of the stem cell would die of hypoxia. The TACS born out of the asymmetrical division of the stem cells are rapidly expelled into the normoxemic environment.

The lack of major success in cell mediated immunotherapy may be due to the fact that the most sophisticated cell delivery mechanisms available today would not survive in the hypoxic environment of the stem cell compartment. The chances for success in this regard would increase if the delivered cells could survive the hypoxia, i.e.: Would have stemness capability. It is also amazing that oxygen on which life depends (electron transport system), has also been employed in the bio universe to kill other forms of life (germs) which could potentially destroy the life of complex structures through superoxide and other mediators of the oxidative damage. Thus, oxygen is playing a wide spectrum of functions: At 21 percent it perpetuates life, at single digit concentration it protects

our stem cell compartment and at superoxide level it protects us against invaders. We need to grasp a deeper understanding of the many faces of oxygen and its role in normal physiology and cancer and employ those mechanisms towards generating new therapy. For example if we could generate and propagate hypoxia resistant cells, we could potentially shuttle them into the stem cell compartment as mentioned above, or if we could deliver oxygen generating machineries such as cyanobacteria into cancer stem cell compartment we could hope that we could destroy them. We also need to develop a deeper understanding of the stem cell compartments based on the above general principles. These compartments are hyperplastic rather than plastic in nature, they not only govern the homeostasis of each organ but also communicate with one another through inter organ communication network and help keep the balance by replenishing one another's population deficiencies and insufficiencies. They connect between and among different universes of organs in a way similar to cosmic strings in the macro cosmos. That is why at times we could see that a hematopoietic stem cell is the source of lung cancer and another time a patient with breast cancer could present with rectal mass and rectal bleeding. On occasion the stem cells of the transplant recipient's donor organs such as liver could migrate to the recipient's lung and cause lung cancer and at other times the stem cells from organ recipient's lung could lodge in the donor's organ such as kidney and lead to renal cell carcinoma. So by the token of these real life examples the conventional walls of wisdom would get tumbled and replaced by a quantum sense of understanding of the stem cell that resides in the infinity loop. By separating and engineering a hematopoietic stem cell we could replenish any other organ's diseased stem cells, vice versa.

We could now ask that as the laws that govern the micro bio cosmos are the extension of the laws that govern the macro cosmos with their rules of birth, evolution and death being the same, where do the DNA damage and response mechanisms fall in this regard?, Is there a parallel. We have learned that DNA can get damaged in five major pathways: (1) oxidation, (2) alkylation, (3) radiation, (4) mismatch, (5) double strand break (Altieri *et al.*, 2008; Hazra *et al.*, 2007). In order to understand such similarities we need to grasp an understanding of the dynamics of the birth engine of the macro cosmos in which infinitely large number of universes are constantly being born, of which our known universe is only one. One might immediately get reminded of collision of matter and anti matter galaxies and the ensuing massive outburst of energy as a kind of

mismatch! Under the blue print of the above principles we should start to ask ourselves what the real meaning and mechanisms leading to point mutations, amplifications, translocations, deletions, insertions, monosomies, hyperploidy, aneuploidies are and what are the stem cell compartments and on occasion TACS (transit amplifying cells) trying to achieve by evolving into such anomalies?. As the stem cell compartments are made of cells whose paternal signatures are the most maternal (to the maximum capability and the limit of exhaustion of the system), any perturbation that could make the stem-(like) cell paternal signature less maternal or more dangerously so maternal signature more paternal could, based on the specificities of those circumstances and inciting agents lead to one or more than one of the above mentioned aberrancies in an attempt to reverse the situation back to baseline. In other words these anomalies are constructed and employed by the stem cell compartments to close the generated gap by the ill mechanisms and return to baseline. Many times the stem cell compartment could achieve its goal, except for the disease states that show up on clinical grounds which probably are exceptional examples of failure. That is why we frequently see that certain malignancies are associated with specific aberrancies; e.g.: Inversion of chromosome 16 in AML (M4), 9: 22 translocation in CML and Philadelphia ALL (Kavalerchik *et al.*, 2008). In case of CML this employed translocation which leads to the activation of a transmembrane tyrosine kinase and the ensuing rapid proliferation, not only cannot minimize the difference between the paternal and maternal DNA pattern differences (achieving the base line condition), but through time leads to additional anomalies such as beta-catenin activation which is responsible for blast crisis (Eisenmann, 2005). Thus, if we understand the language of the system and come to know how the stem cell thinks we can refer to individual disease based anomalies and by analyzing them through computational biology methodologies we can come up with an understanding of the nature of the specific molecular insult in each specific disease. That is to say that by analyzing and understanding of the meaning of the product (the molecular and genetic aberrancies), we could come to recognize the nature of the reactants (molecular pathogenesis of that specific disease), simply because these genetic and epigenetic anomalies are the prescriptions written and the mechanisms employed by the stem cell compartment to handle a specific molecular insult. One might ask, why in certain solid malignancies there is no specific translocation or mutation that could repeat itself in the vast majority of the patients? The simple answer to that is in the

redundancy of different kinds of molecular insults driving the system into a specific disease pathway, which then leads the stem cell compartment to construct and employ different anomalies as a remedy, which clearly fails in clinical disease examples. However in the vast majority of cancers we could see up-regulation of a (transmembrane) kinase which takes the cell into incessant rounds of mitosis and by the same token about 50% of all malignancies have mutated p53 interfering with apoptosis and many times this will lead to an ill attempt by the insulted stem-(like) cell to restore the deranged maternal-paternal DNA pattern difference to its base line minimum and this indeed opens the window of opportunity on other ill and malignant mutations and creates a full blown malignant phenotype (Feng *et al.*, 2008). By using this blue print I would like to address several real life disease examples starting with BRCA1 and BRCA2 mutations that are associated with very high risk of breast and ovarian cancer (Pasche, 2008). These two proteins are part of a big network of proteins involved in DNA double strand break repair, among the many other functions they are involved with. One could ask why the cancer should predominantly happen in these two organs. The short answer is that based on the above proposed blue print, the stem cell compartment of these two organs is exclusively dependent on these 2 proteins and their related pathways to minimize the paternal-maternal pattern differences that could have inadvertently increased as a result of any perturbation in the micro environment or the genome. In other words, tissue specificity is dictated by the addition of stem cell compartment to the gene products of interest to achieve the correction/minimization of the pathologically increased maternal-paternal pattern gap. Indeed BRCA1 is essential in the formation of normal branching of the breast ducts and ductules, i.e.: At the point of exhaustion of minimizing the paternal-maternal pattern gap during embryogenesis, as mentioned above BRCA1 is employed by breast stem cells to conduct the task of organogenesis. Homeologous recombination is another intriguing concept that I would like to address in this context. Following double strand DNA break one strand is recruited to fill the gap/and replace the lost bases. I propose that a double strand DNA break could be divided into active or internal which is the one employed by the stem cell compartment and affecting the paternal strands and passive or external imposed on the system by exogenous factors such as ionizing radiation which could randomly affect either maternal or paternal strands. Under normal conditions the stem cell compartment would do its best to cover the gap with maternal strand derived DNA, though in disease

states including cancer this could get reversed. Thus when the break happens in the paternal strand, following repair the paternal strand becomes more maternal. That is why homeologous and non-homeologous end joining could prove detrimental to the cell and indeed in mismatch repair deficient models which are highly predisposed to malignancy there is a significant increase in the incidence of the last two mechanisms of repair. On occasion when break happens in maternal strand, NHEJ could be the preferred option over the catastrophic homeologous recombination and using the paternal strand to fill the gap, i.e.: Making maternal strand more paternal (catastrophe), especially if apoptosis is also blocked leading to closure of the exit mechanism.

I would also like to briefly touch on the role of telomeres in cancer. The length of telomeres act like the mileage on a car in a reverse fashion, telomere length would send signal to the stem cell compartment as to how many rounds of mitosis it has undergone and how many more rounds it is allowed to go through before becoming vulnerable to major catastrophic events. Under normal conditions before telomere length decreases to a critically short level the stem cell would undergo apoptosis before it could get hit by a catastrophic event. The fact that cancer stem cells have a long telomere denotes the significant role that blockade of this message to stem cell compartment could play in prevention of persistent rounds of mitosis which would eventually lead to catastrophic malignant event(s), so the long telomere length in cancer cell could be a reflection of a summation of events leading to cancer rather than a cause and effect phenomenon as many currently contend. At the end I would like to touch on myelodysplastic syndromes, as this unique group of disorders might have a unique message for us in the sense that the stem cell compartment rather than undergoing repeated rounds of mitosis to minimize the inappropriately widened paternal-maternal strand pattern gap as a result of ill events (genetic, environmental or combination of them) is afflicted by premature and inappropriate apoptosis as well. This deprives the MDS stem cells of the opportunity to achieve that goal and because of increase in apoptosis rate of TACS, the stem cells are pushed back into perpetuation of their immature/blast like phenotype and further asymmetrical division and through time would out number the other cell types in the bone marrow and whatever other number of genetic lesions get employed by stem cell compartment to overcome this problem would only make things worse and eventually take the stem cell compartment into a full blown leukemic phase. The fact that Imids would reverse the

cytogenetic abnormality and the disease process as well, in almost half of the 5q- or deleted +/- other accompanying complex cytogenetic abnormalities strongly point towards the microenvironment aberrancies as the source of the problem in those specific patients. This lends support to the proposed blue print, in the sense that if we hit the right target, the diseased clone would vanish and normal phenotype will replace the diseased one.

### CONCLUSION

We need to move fast and prove the validity of this blue print by single cell microRNA and histone code profiling of embryonic (stem) cells during different phases of embryogenesis and compare them with that of the paternal and maternal related patterns. We also need to generate the same blue print of cancer stem cells and create mathematical models for these differences and by using nanotechnology deliver/correct the pattern signature differences for each malignancy. Addressing different disease states with that kind of understanding would enable us to open an unprecedented window of opportunity to cure cancer as well as other pathological conditions and design new prevention and treatment modalities.

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