“Destined to Die”, Neural Stem and Progenitor Cells as Possible Seedbeds for Cancer: A Hypothesis and Theoretical Model

Kumar Mallik M*

Department of Laboratory Medicine

*Corresponding Author:
Kumar Mallik M
Consultant Cytopathologist, Department of Laboratory Medicine, Mubarak Al Kabeer Hospital, Hawally, Kuwait
Email: mrimmym@yahoo.com

Received on: January 23, 2017 | Accepted on: January 24, 2017 | Published on: February 14, 2017


Copyright: © 2017 Kumar Mallik M. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY) (http://creativecommons.org/licenses/by/4.0/) which permits commercial use, including reproduction, adaptation, and distribution of the article provided the original author and source are credited.

Published by Scientific Synergy Publishers

Introduction:

The ability to resist apoptotic and non-apoptotic cell death is considered to be a hallmark of cancer because all cancers share this characteristic [Hanahan and Weinberg, 2011]. How this particular hallmark facilitates the accumulation of oncogenic mutations without triggering apoptosis during the process of initiation and progression of the neoplasm and how it protects cancer cells from succumbing to anti-neoplastic therapies are well known [Wong, 2011]. Many of the molecular mechanisms which contribute towards the empowerment of cancer cells with enhanced survival capabilities are well characterized [Allison et al, 2012, Wong, 2011]. Cancers develop as cancerous mutations accumulate. Some of these mutations contribute towards apoptotic resistance exhibited by different cancers. However acquisition of mutations indicates damages to the DNA. Such damages provoke apoptotic responses [Nowasheen et al, 2012]. Therefore cells which serve as origins of neoplasms should already have heightened survival capabilities in order to survive the accumulation of mutations. The hypothesis and model presented in this article is an attempt to envisage a common mechanism through which certain cells may acquire increased apoptotic resistance and thus become ideally suited to serve as the seedbeds of cancers. The cell of origin of cancers has been a subject of intense speculation and debate with most of the attention being directed towards the multipotent stem cells and the oligopotent progenitor cells [Visvader and Lindeman, 2012]. An oncogenic mutation might initiate a neoplastic process whose further development and subsequent progress depend upon the accumulation of further genetic and epigenetic aberrations [Hanahan and Wienberg, 2011]. Cell proliferations and apoptosis are often closely related. Both during physiological and pathological conditions some of the cells in proliferating compartments undergo apoptosis [Al Enezi, 2004].

In light of the above mentioned scenario, the hypothesis presented here is centered on cells which are present in a proliferating cellular compartment but are destined to undergo apoptosis. The article hypothesizes that if one of the above mentioned cells was to face an apoptotic roadblock it would be unable to complete the apoptotic process. As consequence it would survive amongst the population of proliferating cells as one which was destined to die but survived referred to WDDS cell in this article. The molecular changes which the cell encounters before encountering the road block could be equated with a cellular near death experience which might significantly alter the molecular circuitry of the cell. These cells, as a result of the above, might become more resistant to apoptosis which could serve them well for the purpose of becoming the seedbeds of cancer development. In order to substantiate the feasibility of existence of such a phenomenon it is essential to identify a situation where a proliferation associated apoptotic process might get aborted due to an apoptotic roadblock, leading to the generation of the hypothetical population of cells which “were destined to die but survived”. Dissecting the available knowledge related to the molecular machinery which underlies the apoptosis that occurs concurrently with neural progenitor cell proliferation [Bieberich et al, 2003] provides with a prospect of analyzing a situation during which the apoptotic process might face a roadblock which might lead to the generation of the above mentioned WDDS cells. The apoptosis in the proliferating neural progenitor cells during murine brain development depends on an asymmetric distribution of Prostate apoptosis response proteins [Par-4] and Nestin. Although there is a rise in ceramide concentration in all the cells during the proliferative process and elevated ceramide levels are necessary for cell
death to occur, following the asymmetric cell division, only those cells which receive Par-4 proteins die while those which receive Nestin survive [Bieberich et al 2003]. Par-4 protein was first described as an apoptosis inducing protein in prostatic carcinomas [Sells et al 1997] but since then their roles as an apoptotic modulating protein have been demonstrated in a wide range of biological and pathological conditions and a variety of molecular mechanisms underlie their role in apoptosis [Hebbar et al 2012]. Importantly, Par-4 protein needs to gain access inside the nuclei in order to perform its pro-apoptotic functions. However in situations with hyperactivity of Akt protein, a particular post-translational modification of the Par-4 protein occurs, which prevents it from entering the nucleus and this abrogates its ability to induce apoptosis [Goswami et al 2005].

Hyperactivity of Akt, following PTEN [Phosphatase and Tenascin homologue] mutations is a common occurrence in many cancers. These mutations commonly occur in a wide range of tumors including brain tumors like glioblastomas [The cancer genome atlas research network 2008]. Neural stem cells [NSCs] and neural progenitor cells [NPCs] are both considered as entities which might serve as origins of various brain tumors [Walters et al 2010]. From the behavioral and conceptual angle NPCs have more limited self-renewal capabilities as compared to NSCs and are oligopotent as compared to the multipotent NSCs [Seaberg and Van Der Kooy 2003]. In light of the cancer stem cell [CSC] theory the above paradigm acquires profound importance since CSCs have been shown to be critical components of brain tumors [Stiles and Rowitch 2008]. Cancer stem cells have self-renewal and multi-differentiation potential along with greater abilities to resist apoptosis which make them ideally suited to serve as the seedbeds for tumor recurrence [Allison et al 2012].

Putting all the above mentioned facts, a theoretical model is being proposed which constitutes a scenario wherein a PTEN mutation or any other genetic alteration creates a hyperactive Akt status amongst a population of neural stem/progenitor cells. The resulting Akt hyperactivity would prevent Par-4 proteins from inducing the apoptotic process amongst the proliferating cell population and this might lead to the generation of a population of cells with stem cell properties which were destined to die but which managed to survive; [WDDS] cells. The events which might be triggered as a result of the above have been envisaged on the basis of the knowledge pertaining to the interaction between Par4 protein and p62 protein. The p62 protein is a vital protein interaction partner of Par4 [Moscat et al 2009]. It serves as a crucial signaling hub in a wide range of cellular functions. Its role in modulating the process of oncogenesis has been demonstrated in various cancers [Moscat and Díaz Meco 2012]. The article speculates that the binding of Par-4 to p62 in a cell which was destined to die might be able to alter the cells’ molecular machinery, since p62 is a vital signaling hub. The model presented here is not an attempt to speculate upon the possible existence of a mechanism involving the initiation of oncogenic process within the neural progenitor cell population during embryogenesis. However, since examples of close analogy are known to exist between embryogenesis and oncogenesis [Monk and Holding 2001], the model presented here may be studied as a paradigm of a situation in which an apoptotic roadblock could initiate a sequence of events driven by molecular interactions that might facilitate the process of oncogenesis. In the following sections, firstly the available knowledge based on which the basic tenets of the hypothesis and theoretical model have been constructed will be presented before describing them. In a subsequent section, some experimental strategies which might query the various aspects of the model will be put forth followed by a section on discussion.

Available knowledge based on which the basic tenets of the hypothesis and the theoretical model has been constructed.

Neural stem cells and neural progenitor cells: Neural stem cells have unlimited self renewal potential in vivo and in vitro as well as the potentiality to differentiate into all three neural lineages whereas the progenitor cells have limited capacities for self renewal and ability to differentiate into one restricted lineage [Seaberg and Van Der Kooy 2003]. Both have been shown to posses the potential to initiate brain tumors [Walters et al 2010].

The role of asymmetric distribution of PAR-4 protein in apoptosis during neuronal progenitor cell proliferation: Apoptosis occurs during neural progenitor cell proliferation, wherein, following an asymmetric cell division, one daughter cell dies while the other survives to further proliferate or differentiate [Kuan et al 2000] [Sommer and Rao 2002]. Bieberich et al have shown that during the E12-E16 stage of brain development in mice, the levels of brain ceramide and prostate apoptosis response protein-4 [PAR-4] are elevated with the concurrent presence of numerous apoptotic cells in the sub ventricular and ventricular zones [Bieberich et al 2001]. PAR-4/ceramide induced apoptosis is thus the predominant mechanism through which active cell death occurs in the developing mouse brain. In a later study the same group of authors has established an elegant mechanism through which the fate of proliferating neural precursor cells is decided by an asymmetric cell division during which the asymmetric distribution of PAR-4 and Nestin occur [Bieberich et al 2003]. Although there is an increase in ceramide biosynthesis in all the cells, some cells express PAR-4 without expressing Nestin, while the others express Nestin and not PAR-4. Thus there are two groups of cells; PAR-4 positive, Nestin negative and PAR-4 negative, Nestin positive. Using TUNEL staining for identifying apoptotic cells, the authors demonstrated that the PAR-4 [+] , Nestin [-] cells undergo apoptosis while the PAR-4 [-], Nestin [+] cells survive [Figure 1].

The pro-apoptotic effect of PAR-4 protein and the role of AKT in regulating its pro-apoptotic effect: The PAR-4 gene was first identified as one which is up regulated during apoptosis of prostate cancer cells [Sells et al 1994]. The gene encodes for a multi domain protein comprising of 343 amino acids which can induce apoptosis in different ways depending upon the cell, the situation and the apoptotic stimuli. Inhibition of NFKB signaling pathway is one of the frequently utilized mechanisms by Par-4 protein in this regard [Hebbar et al 2012]. PAR-4 is a cytosolic protein which needs to get translocated to
the nucleus in order to induce the apoptotic process [Hebbar et al 2012]. Endogenous Akt was shown to be a binding partner of PAR-4 through co-immunoprecipitation experiments performed on human prostate cancer cells PC3 [Goswami et al 2005]. Akt binds PAR-4 at its Lucien zipper domain and phosphorylates it on its S-249 [Seine 249 residue]. This prevents the nuclear translocation of PAR-4 and its apoptosis inducing effect. The binding of Akt to PAR-4, and the phosphorylation of its S-249 residue is essential for the inhibitory effect of AKT-1 in PAR-4 induced apoptosis. [Figure2] [Goswami et al 2005] [Hebbar et al 2012]. It was also shown that 14-3-3 proteins, also bind to PAR-4 in an AKT dependent manner and contributes towards the effect. [Goswami et al 2005].

The interactions between PAR4 and p62 protein: The p62 protein [also called Sequestosome 1], is a critical signaling protein. It utilizes PBI as an important protein protein interaction module to form a complex with PAR4 and atypical protein kinase c ζ [Moscat et al 2009]. A ternary complex is formed between PAR-4, PKC ζ and p62 in which there is a direct interaction between PAR4 and p62 [Chang et al 2002]. In fact p62 inhibits the PAR-4 mediated inhibition of PKC ζ. Since PKC ζ is supportive of NFkB signaling, the PAR-4- PKC ζ interaction inhibits it and contributes towards its pro apoptotic effects. p62 inhibits this interaction and promotes NFkB signaling. The above mentioned ternary complex appears to play a crucial role in the fine tuning of apoptosis-survival balance. The significance of this becomes multifold when one considers the fact that p62 is a multi-domain protein and these domains allow it to interact with a wide array of other proteins and thus act as a signaling hub involved in a wide range of biological functions like receptor endocytosis, cell growth, mitosis, autophagy, protein degradation and control of the levels of reactive oxygen species. A number of signaling pathways like mTOR and NFKB also utilize this hub [Moscat and Diaz-Meco 2009]. Needless to say, p62, play a critical role in cell survival, proliferation and oncogenesis. The regulation of ROS levels is crucial for the self-renewal and proliferation of neural stem cells [LaBelte et al 2011]. Since p62 is important for ROS regulation through its interaction with Keap and NRF2 proteins [Taguchi et al 2011], it is possible that p62 might have a role to play in stem cell/ progenitor cell self-renewal and cancer stem cell bio dynamics. Since cancer is a disease which involves fine adjustments in wide range of biological processes to prevent the cell from undergoing apoptosis, the alterations at the p62 signaling hub occurring as a result of dysfunctional interactions with protein partners like PAR 4 might have very significant effects in the process of oncogenesis.

PAR-4 and resistance to therapy in gliomas: In a recent article, Zhuang et al have shown that PAR-4 mediated apoptosis is important for the Temozolomide induced killing of gliona cells and association with prion proteins.PAR-4 inhibits this process and promotes chemoresistance to Temozolomide. [Zhuang et al 2012]. This indicates a potential connection between the pro-apoptotic role of PAR-4 proteins during neural progenitor cell proliferation and its possible effect on drug tolerance mechanisms to Temozolomide. It also brings about an intriguing element of functional paradox with Par-4 having the capability of acting both in a pro-apoptotic and anti-apoptotic manner.

Akt hyperactivity in brain tumors: A number of brain tumors show hyperactivity of Akt. In glioblastomas, for example, mutations in the PTEN gene can occur in 36 % of cases leading to Akt hyperactivity. The others changes which could also lead to hyperactivity in Akt are mutations in PI3K (15%) and amplifications in AKT gene in 2%. [The Cancer Genome Atlas Research Network 2008]. In the light of the above findings it is tempting to envisage a possible sequence of events which might occur if a neural stem cells/progenitor cell undergoes a PTEN mutation leading to AKT hyperactivity leading to abrogation of the ability of Par-4 protein to promote apoptosis.

The hypothesis and the model

The hypothesis which is being proposed is as follows; [Figure 3]. The apoptotic process, which affects some of the cells among a population of proliferating cells might face a roadblock, potentially leading to the generation of a population of cells which were derived from a cell or cells which "were destined to die but survived"[WDSS] cells. Assuming that these cells go down the apoptotic pathway for certain duration of time and subsequently survive, it is possible that their molecular machinery gets significantly altered in a way which provides them greater ability to resist apoptosis i.e. Greater survival ability. Such ability would provide the cell with an advantage because it would enhance its chances of resisting potentially apoptosis triggering oncogenic events during the process of initiation of cancer. This would make these cell ideally suited for serving as seedbeds of cancer. In order to study the feasibility of such a phenomenon a biological situation has been selected and analyzed from a theoretical perspective to generate a theoretical model to speculate on the possibilities which might arise as a result of an apoptotic process which might get aborted due to some pre-existing molecular anomaly which could have resulted from a prior mutation.

The platform on which this model has been built is a population of proliferating neural progenitor cells during the process of mouse brain development. Some of these cells undergo apoptosis. Since the PAR-4 protein is essential for this apoptosis, preventing the PAR-4 protein from performing its apoptotic function might act as an apoptotic roadblock which could lead to the generation of a population of “were destined to die but survived” [WDSS] cells. The sequence of possible changes has been described below.

If a neural progenitor cell undergoes a mutation, like a PTEN mutation that leads to hyperactivity of the AKT protein a sequence of events might occur which has been outlined in figure 4. Asymmetric cell divisions occur during neural progenitor cell proliferation and it is the asymmetric distribution of PAR4 proteins and Nestin between the daughter cells which determines their fate. The cell receiving PAR4 undergoes a ceramide mediated apoptosis, whereas the one which receives Nestin survives. The exact mechanism of portioning out these proteins into the two cells is unknown. In case a neural stem/progenitor cell suffers a mutation like a mutation in PTEN gene, it should experience the effects of AKT hyperactivity. One of the effects of AKT hyperactivity is the phosphorylation of the PAR-4 protein at the seine 249 residue which prevents it from gaining access into the nucleus, which is necessary for it to induce apoptosis through
its interference with NFKB signaling. 14-3-3 proteins bind to PAR-4 and sequester it within the cytoplasm. Since PAR4 mediated signaling is necessary for the death of neural cells, the above sequence of events will produce a population of PAR4 positive cells which were destined to die but did not because of reasons stated above. These has been referred to as “were destined to die but survived” [WDDS] cells. PAR4 has a number of protein interaction partners. p62 is one of them. The reason for highlighting its relation to the p62 protein is because p62 is an important signaling hub with critical influence on an array of biological functions and signaling pathways. It is unknown whether the WDDS cells have any mechanism through which the excess PAR-4 protein could be inactivated. If not, PAR-4 is likely to bind to p62 and form a ternary complex comprising of p62, PAR-4 and PKCζ. It is known that p62 antagonizes the pro-apoptotic effect of PAR-4 which the latter achieves by inhibiting PKCζ. However in this scenario PAR-4 is unable to act in a pro-apoptotic way because of reasons mentioned above. It is possible that as a result of this abnormal binding of PAR-4, the biological functions in which p62 serves as an important signaling might get altered. These functions involve the participation of the p62 hub in NFKB signaling, MTOR signaling, cell growth, mitosis, autophagy, proteosomal degradation, cell survival and regulation of the levels of reactive oxygen species. This could alter the fine tuning of various biological mechanisms, possibly allowing accumulation of mutations without triggering apoptosis and these could be crucial in the oncogenic pathway. The different tenets involved in the construction of this hypothetical model could be investigated through experimental approaches and strategies. Some of these have been outlined below.

**Experimental strategies to study the feasibility of the underlying hypothesis and the model**

The experimental strategies which are being proposed below attempt to find the answer to the following set of questions.

i) Is the PAR-4 protein able to trigger apoptosis amongst neural stem/progenitor cells which have hyperactive Akt?

ii) In case a hyperactive Akt status prevents PAR-4 from triggering apoptosis is it possible to isolate these PAR-4 positive neural stem/progenitor cells, and set up separate cultures of PAR4 and negative cells in PTEN wild type and PTEN mutant mice? [See below]

iii) Are there any differences between the above groups of cells with respect to their proliferation, clonogenicity, differentiation and ability to transform to transformed and neoplastic cells?

iv) Is there any association between PAR-4 proteins and p62 in these cells?

v) Are the p62 associated cellular processes different in the above cells?

vi) Is the PAR-4 protein able to trigger apoptosis amongst neural stem/progenitor cells which have hyperactive Akt?

During E12-E18 of mouse brain development the levels of ceramide and PAR-4 proteins are elevated. [Bieberich et al 2001]. On the other hand PTEN can be conditionally deleted in different parts of the embryonic mice brain using the Cre-LoxP technology. [Groszer et al 2001] PTEN deletion is just complete around E14.5. [Groszer et al 2006]. By crossing Pten conditional knockout mice with the Nestin-Cre line, it was possible to generate mutant mice with increased brain size and similar to macrocephalic phenotypes found in humans with inherited PTEN mutations. The increase in size is due to increase in cell proliferation, increase in cell size and decrease in cell death. In the proposed experiments it should be possible to generate neurosphere cultures from PTEN mutant and PTEN wild type mice as indicated in the studies above. TUNEL staining may be used to determine the proportion of apoptotic cells amongst the cells constituting the neurosphere. The AKT phosphorylation status in these cells may also be compared by lysing the cells and subsequently immunoblotting with antibodies against Akt phosphorylated at specific residues which is indicative of their activity [Oteagi et al 2006]. With help of TUNEL staining the proportion of apoptotic cells within the two populations can be quantified and compared. The level of endogenous ceramide within the neurosphere cultures is determined and the dependence of the apoptosis on ceramide is queried using a ceramide synthase inhibitor like fumosin [Bieberich et al 2003].

Following this immunofluorescence microscopy may be performed for TUNEL, PAR4, Nestin, p62 and with the help of immunofluorescence overlays the co-expression of these proteins in the cells may be determined. Then it may be determined whether the asymmetric distribution of Par-4 and Nestin occurs in the above proposed set up and whether the Par-4 positive cells survive amongst the PTEN mutated Akt hyperactive population.

ii) In case a hyperactive Akt status prevents Par-4 from triggering apoptosis, is it possible to isolate these PAR-4 positive neural stem/progenitor cells and culture them?

Laser capture microdissection [LMD] technique may be used in culture cells to isolate the populations of cells chosen according to their immune profile [Mustafa et al 2012]. Similarly in the proposed experimental set up LMD could be used to isolate the following groups of

a) Par4 positive, PTEN positive [wildtype mice]

b) Par4 positive, PTEN negative [mutant mice]

c) Par4 negative, PTEN negative [mutant mice]

d) Par negative, PTEN positive [wildtype mice].

The hypothesized WDSS cells should be in the PAR4 positive, PTEN negative group. The Par 4 Positivism, PTEN negativism and the hyperactivity of Akt protein should be confirmed from cellular lysates of these cells using immunoprecipitation techniques with appropriate antibodies.

iii) Are there any differences between the above groups of cells with respect to their proliferation, clonogenicity, differentiation and ability to transform to transformed and neoplastic cells?

In the proposed experimental setup the dynamic properties of proliferation, clonogenicity and differentiation capabilities are to be studied in the different cell populations. Queries may also be made with regard to the transformation potential of the
different groups of cells. For example, attempts may be made to transform the neural stem/progenitor cells with the help of retroviruses containing the constitutively active mutation of epidermal growth factor receptor EGFRvIII as described by Ligon et al on INK4/ARF double negative neural stem cells [Ligon et al 2007]. Using such a method it might be possible to detect differences between the groups of cells with respect to the ease or difficulty or to that matter feasibility of them being transformed. In case there is transformation in the population of cells, the tumorigenous capabilities may be studied by injecting them into the brains or subcutaneous tissues of severe combined immune deficient mice.

iv] Is there any association between PAR-4 proteins and p62 in these cells?

In the course of the hypothesis a great deal of importance has been directed towards the possible interactions between PAR4 and P62 and how this interaction could influence the biological activities in which p62 plays crucial roles. These are regulation of cell size, mTOR pathway, autophagy, regulation of levels of reactive oxygen species [ROS] and NFkB activity among others. The following investigations could throw a significant amount of light on the concerned activities in the proposed set of experiments. The references in parenthesis indicate that different groups who have employed this methods to gain insights into various biological and pathological scenarios

a] Compare the localization of p62 as cytosolic speckles and aggregates which is indicative of the abilities of p62 in cellular functions of protein aggregations and proteasomal degradations as well as response to hypoxia [Moscat and Diaz Meco 2009] [Ratanen et al 2013]

b] Compare the differences in leucine induced increase in cell size [Duran et al 2011]

c] Correlation between p62 and S6Kinase1 [S6K1] levels and comparing the phosphorylation of S6K and 4EBP1 to estimate the activity of the mTOR pathway. [Duran et al 2011]

d] Compare the autophagic response to leucine depletion by estimating the accumulation of conjugated forms of LC3. [Duran et al 2011]

e] Comparison of the levels of endogenous ROS between the cell population using ROS sensitive dyes like DCFDA, hydroethidine and HPP-ARP [Taguchi et al 2011]

f] Quantify and compare the NFkB activity. The estimation of reporter gene activity may be utilized to evaluate the NFkB signaling activity status in these cells. [Widera et al 2006]

Discussion

Cancer cells have heightened survival capabilities [Hanhana and Weinberg 2011] and the cancer stem cells are more resistant to apoptotic stimuli as compared to other non-stem neoplastic cells [Allison et al 2012]. It is known that the above cancer hallmark facilitates the process of neoplastic initiation and progression and is crucial for cancer stem cells to survive anti-neoplastic therapies [Hanhana and Wienberg 2011]. However the underlying mechanism/s which uniformly empowers neoplastic cells from all cancers with survival capabilities, from the time of its initiation through its progression are unknown.

The hypothesis and theoretical model proposed here is an attempt to present a possibility which might be able to explain the above phenomenon. In the current article it has been hypothesized that cells which survive an apoptotic process due to a pre-existing apoptotic roadblock among a population of proliferating cells might be more resistant to subsequent apoptotic stimuli as compared to other cells. In an attempt to construct a model to show how the hypothesized phenomenon might work, the population of proliferating cells which has been utilized to build a theoretical model is the one consisting of proliferating neural progenitor cells where the apoptosis determinant is the Par-4 protein [Bieberich et al 2001 and Bieberich et al 2003] and the roadblock is a hyperactive Akt status [2005]. Non-neoplastic proliferations occur throughout the life of an organism and these proliferations could be physiological or pathological by nature. Also apoptosis of some of these proliferating cells do occur [Alenzi 2004]. If one of these apoptotic cells was to face an apoptotic roadblock which prevents it from completing this process, it might survive and according to the proposed hypothesis even have greater survival capabilities than the others in resisting subsequent apoptotic stimuli which could facilitate the process of neoplastic initiation in these cells.

The neural progenitor cells have been chosen as an example because the molecular determinants of the apoptotic process are known. It is also possible to theoretically analyze the effects of a possible roadblock which might obstruct this apoptotic process. In no way is it an attempt to try and pin-point the cell of origin or oncogenic mechanisms which are associated with any tumor in particular although progenitor cells have been implicated in the pathogenesis of oligodendrogliomas [Persson et al 2010]. It is rather a theoretical analysis of a possible sequence of events in a situation in which at least some of the initial events have been experimentally established. Neurogenesis continues to occur during adulthood in mammals in the subventricular zone of the lateral ventricle and the subgranular layers of the dentate gyrus of the hippocampus [Reynolds and Weiss 1992, Alvarez-Buyalla 2004]. Although an apoptotic regulatory process involving asymmetric distribution of Par-4 has not been described in adult neurogenesis other yet undiscovered mechanisms might be in place since apoptosis occurs during adult neurogenesis [Sierra et al 2010]. Moreover many of the cellular mechanisms evident during embryogenesis may get re-initiated during the process of cancer development. [Monk and Holding 2001].

In this model, the molecular events which might occur before the apoptotic roadblock comes into effect are unknown. Apart from the asymmetric distribution of Par-4 and Nestin between the two daughter cells which determines which of the two is destined to die, no other molecular changes are yet known. Nestin in itself is known to show pro-survival effects under certain circumstances through its interactions with the pro-survival protein bcl-2 [Piras et al 2011] but the effect of its absence in “WDSS cells” is currently beyond the scope of available knowledge. On the other hand the model is unable to demonstrate, any specific end to end sequence of molecular events which shows how the so called “WDSS cell” might carry an advantage over the other normally proliferating cells in being the preferred sites for the neoplastic process to begin.

The model has been constructed by translating and integrating knowledge derived from completely different
cellular systems. The effect of hyperactive Akt on preventing Par-4 mediated apoptosis has been studied and demonstrated on prostate carcinoma cells [Goswami et al 2005]. Whether a similar mechanism blocks the pro-apoptotic effect of Par-4 protein in neural progenitors requires to be investigated. It is known that a hyperactive Akt decreases the rate of apoptosis in proliferating neural stem cells [Groszger et al 2006] but there is no evidence as yet to show that Par-4 protein and Akt interactions could modulate this process.

It should also be noted that Par-4 knockout mice do not develop with any brain abnormality [García-Cao et al 2003]. This indicates that some other protein could replace Par-4, functionally with regard to its pro-apoptotic role during the embryologic neurogenic process. However the model is based on a situation where the downstream effects have been envisaged based on the presence of Par-4 and possible downstream effects based on its protein interaction partnerships with p62. The hypothesis is based on the premise that the “near death” experience encountered by the destined to die cells makes them more resistant to apoptosis. Although the possible interaction of Par-4 with p62 protein opens up a myriad of theoretical possibilities related to the perturbation of a crucial cell signaling hub [with cell survival being one of the functions which is regulated through this hub] the model is unable to show how this interaction could actually translate into a situation which provides the cell with enhanced capabilities to withstanding genetic and epigenetic changes without undergoing apoptosis and accumulating them in the process of neoplastic development. Moreover the hypothesis is an attempt to envisage a condition which not only explains why apoptotic resistance is a hallmark prevalent in all cancers but also to show how this facilitates the initiation of cancers through the accumulation of mutation. However in order to construct the model an apoptotic roadblock which commonly occurs as a result of a mutation [PTEN in this case] has been utilized. Indeed it is possible that this lone mutation might not have initiated an apoptotic response in the first place but by creating an apoptotic roadblock in a cell which was destined to die, alter the molecular circuitry which allows the accumulation of oncogenic mutations without triggering apoptosis.

It also needs to be seen what an excess of Par4 bound to p62 and PKCζ can do to the entire signaling hub in which p62 is a nodal point. The biological functions in which this hub participates in are varied, but of particular interest is its role in survival responses, mTOR signaling and autophagy [Lowe et al 2004, Moscat et al 2009, Moscat et al 2012, and Duran et al 2011]. In addition this hub is also important for regulation of ROS [Rantanen et al 2013]. Recently ROS has been shown to regulate a number of stem cell properties in the neural stem cell population [La Belle et al 2011]. Par-4 protein is indeed a pro-apoptotic protein but at the same time we need to know what its effect on neural stem/progenitor cell population might be when its pro-apoptotic potential is blunted. Its role in a cell’s molecular machinery is often context dependent [Hebbar et al 2012]. A noteworthy role of Par-4 protein which has been recently described is its role in mediating resistance to Temozolomide in glioblastomas, [Zhuang et al 2012] an intriguing new finding in view of the general pro-apoptotic role of this protein. A number of experimental strategies have been put forward to investigate the various tenets of the hypothesis. The hypothesis has been constructed on the basis of assumptions from varied cellular contexts and thus it is essential to test out the different tenets of the hypothesis and the theoretical model which has been proposed. Recent advances in laser capture micro-dissection technology could be of great help to isolate the so called “WDDS” cells and compare them with the other cells. Tumor recurrences continue to frustrate the efforts directed towards the achievement of effective management strategies in most cancers. The ability to resist therapy mediated apoptosis is the reason behind most tumor recurrences. In spite of the criticisms which might be put forward against some of the tenets of the models, the hypothesis and theoretical model is an attempt towards the development of a unified concept to explain this cancer hallmark in a novel manner with the hope of generating interest within the research community to pursue this paradigm through well planned experimental strategies.

References: