

Review Article**Tumor relapse, history, implication and future direction****Subrot Sarma^{1*}**¹Department of Biological Sciences and Biosciences, Lab of System Biology and Immuno-Engineering, Dibrugarh, Assam, India***Corresponding author:** Subrot Sarma, Department of Biological Sciences and Biosciences, Lab of System Biology and Immuno-Engineering, Dibrugarh, Assam, India; E-mail: subrot@gmail.com*Received Date: 12-06-2019**Accepted Date: 10-10-2019**Published Date: 18-11-2019**Copyright: © 2020 Subrot Sarma***Abstract**

Considering the extent and prevalence of the Tumor relapse, it requires the urgent attention for identifying factors involved in the relapse process and thus affecting the life span of the patients. Sensitization (SS) is a process defined on the basis of converting the Drug-Resistant Tumor Cells (DRTC) to the Drug Responsive State (DRS). The present article tries to specify and re-define the existing literature regarding the sensitization process along with its correlation to the adjuvant treatment- First correlating the sensitization adjuvant/process with approaches other than the radiotherapy/ chemotherapy which should be investigated in details in the future. The DRTC are defined on the basis of cell cycle dynamics of G0/quiescent cells state, understanding the cell biology of G0-G1 transition could become the basis of new approaches for making the cells in the DRS- In this regard noble point proposed in this article is investigating the factors involved in forcing the static cells -G0/quiescent cells- DRTC to G1 phase (drug-sensitive) - new way of looking at the sensitization process. One way to go about it is to compare with yeast genomics, like in yeast- a new hypothesis predicting different states of G0 is being proposed in the mammalian system which should be studied in details and also factors involved in the G0- G1 transition in the upstream and downstream of the genetic pathway. The third approach which should be the centre of the future research is comprehensive -coupling and un-coupling the process of SS and Anti-Tumor Therapy (ATT). Coupling approach is where agents for SS and ATT is one step process while uncoupling agents are different agents used for the former as well as for the later in two step process. This is very important as understanding this process would increase the efficacy, specificity, efficiency as well as eliminating the side effects of the sensitization process and anti-cancer therapy and ultimately affecting the life span of the tumor patients.

Keywords: Anti-Tumor Therapy; Quiescence; Cell Cycle dynamics; Coupling drug agents**Introduction**

In the year 2018, according to the World Health Organization data, the number of deaths due to Tumor has reduced

drastically due to the improved health care management scheme [1]. Although the conventional goal in terms of Tumor treatment has been focused on the treatment of primary Tumor, the recurrence of Tumor state after the primary treatment has not got the attention it deserves in the management of the diseases. Broadly the process of Tumor therapy could be divided into two phases (sensitization process and actual anti-Tumor therapy) [2, 3]. For the convenience of this readership, in the present review, sensitization is the process with the help of which cells in the G0/quiescent cells (drug resistant cells) of the tumor state are forcefully converted to enter the cell cycle by artificial means in the laboratory condition or in the clinical set. The most important question which has been addressed in this review in the Tumor treatment management is the dynamics of the relapse of Tumor and the survival rate associated with the solid tumor. The present review is only focused on solid tumor and non-tumor Tumor types are beyond the scope of this review (e.g. blood Tumor) which doesn't exclude the possibility of taking help from the understanding the cell cycle dynamics of blood Tumor and could be extrapolated to the understanding of solid tumor biology. Considering the extent of the health and economic burden associated with the Tumor management specifically dealing with the tumor relapse/ recurrence, it is of urgent need that research and development should be focus on improving pre-therapeutic sensitization process of the tumor treatment. This also calls for the up- gradation based on the advent of new biomedical techniques in the approach for the treatment of the tumor focusing on the sensitization process.

The relapse of the solid tumor is associated with resistance to the various therapeutic strategies both individual as well as in combination [4]. In the cell biological level, partly this resistance could be correlated with the heterogeneous nature of the solid tumor [5]. This heterogeneous nature of the solid tumor could be explained on the basis of cell cycle dynamics (quiescence cells), cell types (Tumor Stem Cell), mutation as well as molecular complexity of the tumor cells with its microenvironment [6]. Before discussing potential differential sensitization approaches used, it's very important to understand the biology of the tumor tissue and its diversity. The critical factor which might play a very important role in the effective elimination and re-

ducing the extent of relapse of the solid tumor would be dependent on the characterization, available knowledge regarding tumor biology and future focus of the research question in the present context.

Adjuvant treatment

Any therapeutic process which can minimize the extent of the relapse of the cancer is defined as adjuvant cancer therapy or which has been described in this review as sensitization process. Adjuvant treatment has been described in terms of breast cancer treatment and the prognostic indicators include size of the tumor and presence of the estrogen receptor which is used widely in the field [7]. Tamoxifen citrate, chemotherapy and radiotherapy are few approaches which have been used extensively along with adjuvant treatment in the breast cancer treatment [8]. For example, recurrence risk reduced to 47% with 10 years treatment in case of breast cancer [8]. It of note to understand that most of the literature available on process of adjuvant treatment for the tumor therapy relies on only radiotherapy and chemotherapy. This should be taken into consideration and emphasis should be on studying the correlation of how adjuvant treatments performs with respect to the other types of post-sensitization therapies like Immunotherapy, hormonal therapy etc.

Spatio-temporal position of the cells located in the Tumor tissue

The difference between a normal cell and the Tumor cell is that in the case of the later cells, the mechanism controlling their proliferation is consistently switched on whereas in the case of former, there is switched on and off mechanism [9]. It has been reported that depending on the stage of differentiation (growth of the tumor) of the tumor, there is difference in the way the cells are arranged in the cell cycle stage like e.g., 30% of the cells in the center of the Tumor are in G0/G1 and 70% of cells are in S/G2/M [9]. So the extent of the relapse of Tumor could be minimized by targeting the appropriate location within the tumor tissue depending on the stage of development of the tumor as well as the specific physical location of the cells to be targeted in the tumor tissue.

Molecular Heterogeneity of the tumor tissue

Differential cell cycle position within the Tumor tissue [9]

Stage of the Tumor- Depending on the stage of Tumor, primary Tumor or migrating cells of the tumor (still in primary site but in state of transition), the success of the chemotherapy would be determined. Cells in the primary site (non-migrating cells) are mostly in G₀/G₁ and are hence chemo-resistant whereas cells in the secondary site are mostly in the S/G₂/M phase and are chemo-sensitive [9]. It is very important to note that the distinguishing feature which makes the transition between cells in the G₀ phase and inside the cell cycle falls into two categories -an irreversible process – defined as senescence and reversible process defined as quiescence and part of discussion focuses in the later [10].

Now the heterogeneity (G₀ vs S/G₂/M) of the tumor tissue has to be taken into consideration while designing the therapeutic approach or precisely the sensitization process. An effective strategy would be to force the migration of the static cells to migratory pattern before the chemotherapy process initiates so that the percentage of the chemo-sensitive cells is increased drastically before the actual anti-tumor therapy. In this regard, the existing knowledge of the migrating cells and the appropriate microenvironment for its migration pattern including various critical factors like extracellular matrix protein (ECM), ECM degrading enzymes as well as Tumor cell migrating associated stromal cells could be used in an artificial set up for testing the possibility of forcing the cells into the cell cycle from the quiescent cells and subsequently transitioning the chemo-resistant cells to chem.-sensitive cells.

Differential property of the cells in the vicinity and in the proximity of the blood vessels

The microenvironment of the tumor tissue compromises many aspects including the process of excessive angiogenesis which may play a critical role in the effectiveness of the treatment [12]. Reports specifically related to Kaposi's sarcoma which are in phase I/II clinical trials showed that certain anti-angiogenic factor-like TNP-470, an analog of fumagillin has been tested successfully for renal cell carcinoma, brain Tumor, breast Tumor, cervical Tumor and prostate Tumor [13]. The type of the anti-therapeutic approach and its success would be determined based on the ability of the Tumor cells to grow after it can assimilate

and the requirement for the maintenance of the tumor environment. From the cell cycle dynamics perspective, the differential nature of the cells adjacent to the blood vessels and far away in terms of majority of cells near to the blood vessels in the proliferating stage might give a better perspective about how to go about targeting the specific cell types taking blood vessels as a potential anatomical landmark and focusing the sensitization process on the cells which are far away from the blood vessels as they are potentially more chemo-resistant and sensitization process could be applicable and be effective in a location specific manner.

Tumor Stem Cell (CSC) and Drug resistance

Cells within the tumor tissue having the ability to renew and are resistant to therapeutic methods and are the slowly proliferating are the one which are responsible for its recurrence and relapse after the anti-Tumor therapy. Classical quiescence cells and CSC share one unique property which is resistance to anti-Tumor therapy as well as responsible for relapse of the tumor. The distinction and classification is not well understood as CSCs are also type of cells in the quiescent state so there is still confusion regarding the distinction and similarity between them. Understanding the already available data on both quiescent cell biology and CSCs with respect to the molecular and genetic factors would be something one can investigate in the in the near future. After the identification of the CSCs there was a rapid interest in the field to identify molecular markers specifically associated with the tumor type which has been reported which includes CD133, CD44, ABCG2, ALDH, ABCB5, CD90 covering multiple organs like Brain [14](Cheng et al., 2009), Prostate [15], Pancreas [16], Melanoma [17], Colon, Liver, Lung, Ovary [18]. CSCs are known to be specifically showing resistance against drugs like paclitaxel, docetaxel etc [19, 20]. But the most important aspects which is relatively well understood for the possible mechanism associated with multi-drug resistance are epithelial to mesenchymal transition [20], Transporters associated with cell membrane – ABC (ATP-binding cassette; [21], Hypoxia and ROS [22, 23]. The field of CSC biology is quite diverse, broad and extensive which is beyond the scope of this review to describe The mechanism documented above associated with the drug resistance of

the CSCs is specifically associated with the chemotherapy and radiotherapy. Since the present review discusses sensitization process of the drug resistant quiescent G0 cells from the cell cycle perspective for the anti-Tumor therapy, it would be interesting to look at the diversity of the CSCs in terms of different cell types within CSCs. CSCs are drug resistant and slow proliferating cells (mean they are stem cells) which would indicate they are inside the cell cycle but they are drug resistant cells whereas quiescent cells are not inside the cell cycle but they are drug resistant. Combining the information available out of literature both from CSCs and quiescent cell biology, the hypothesis which could be proposed is that the quiescent G0 cells in the human subject not only consists of singular G0 phase but different stages of G0 (G01, G02, G03 etc) which have been reported in the case of yeast [24] whose mechanism is not well understood. With each stage of G0, their response to the sensitization process as well as subsequent actual anti-Tumor treatment would differ having either unique gene signature or having gradient of expression with one specific gene or combination of genes which should be investigated in the future. This model would fit with the hypothesis as there are differential response of the tumor tissue to various different types of sensitization agent and anti-Tumor agent. One important aspect in the management of Tumor therapy is that in most cases the drug resistance tumor cells are defined on the basis of their resistance to the chemotherapy and radiotherapy. It's not very clear how other types of known therapy would affect the drug response in the both sensitization and anti-Tumor procedure.

Future investigation should focus on the appropriate sensitization process and other alternative anti-tumor treatment and potential mechanistic correlation of CSCs resistance to the treatment apart from chemotherapy and radiotherapy. It's a statistical research question how using alternative available sensitization technique and anti-tumor agents might have an implication in the CSCs for its ability to response to the treatment if it makes any difference in terms of percentage of cells involved in the process of recurrence of the tumor gets affected. Recent developments in the field of CSCs have to change the traditional view of CSCs being under-proliferative but being hyper-proliferative and it looks like the CSCs are more plastic

than it was appreciated [25] which makes the classical definition a bit complicated. So more work is needed in order to classify and distinguished CSCs and other known quiescent cells. The only consistent criterion which defines the CSCs is its (CSCs) ability to induce tumor in a non-tumor tissue when transplanted to other tissue [26] which was documented in the literature.

Genomic approach from G0 to G1

The genomic complexity is relatively well conserved between yeast *Schizosaccharomyces pombe* and human although species -specific differences exist in terms of cell cycle dynamics [24]. It has been suggested that at least 1000 genes are involved in the maintenance of quiescent state out of which atleast 300 are housekeeping genes as shown in the study performed in *Schizosaccharomyces pombe* [27].

The differences in the G0 to G1 transition has been explained on the basis of gene expression pattern. In a gene manipulation study using both over-expression and knocking out the expression of the c-Myc gene in the untransformed cells [28] in the cell lines. A slight external variation in the expression level of a c-Myc gene can alter the rate at which the transition process takes place. In another study with In vitro analysis a deleted form of hepatocyte growth factor induces the expression of c-Myc having a role in G1-S transition but no role in the G0-G1 transition [29] which might indicate alternative pathways involved in this process. This study was done in the untransformed cells and this could be used as a possible sensitization approach for transitioning the quiescence cells to the G1 phase before the actual anti-tumor treatment could be initiated. Factors like the type of tissue involved as well as possible manipulation in the hierarchy of c-Myc expression pathway both upstream and downstream and its associated genetic factor components should be taken into consideration for the G0-G1 transition (sensitization). Some of the genes have been identified quiescent fibroblast cells which played a very important role in the G0-G1 transition which belongs to the family of JUN, FOS, Zing Finger proteins, Nuclear hormonal receptors, etc [30]. Mirk/Dyrk1B is another important kinase that has been shown to play an important role in the quiescent pancreatic cells and their down-regulation by ROS affects the level

of G1 cyclins which helps in the transition from quiescence to proliferative state [31]. Additionally, in the case of colon Tumor, Mirk's role has been described in terms of differences in its level of expression determines if the cell would be in a quiescent state or in the G1 phase of the cell cycle. The pathway involves retinoblastoma protein p130/Rb2, E2F4 and CDK inhibitor p27kip1 [32]. As reported in this paper when the levels of Mirk are altered, the cells can be forced to enter the cell cycle which could be used as an effective strategy for conversion to the G1 phase and enter the cell cycle from G0 state.

Cell motility and G0-G1 transition

The cell motility is one of the most important criteria which makes the quiescent cells is less motile as compared to the cells in the cell cycle. Another set of genes that played a very important role in the transition of the G0-G1 phase cells are growth arrest-specific (Gas) genes which are highly expressed in the quiescent cells. The down-regulation of these genes led to the transition from the quiescent state to the G1 state and enters the cell cycle [33] which is part of the microfilament system. The phosphorylation of tyrosine residue is followed by the activation of Serine/threonine-protein Kinase such as PKC. An actin cross-linking protein such as MARCKS which is a myristoylated alanine-rich Kinase substrate whose activity is inhibited by the process of phosphorylation of the PKC along with calmodulin interaction [34, 35]. The most important thing which needs to take into consideration is that the expression of MARCKS is high during the G0 phase and it gets down-regulated during the transition to the G1 phase [36]. The modulation of the cytoskeleton proteins affecting the motility of the cells could be exploited in the future which could be used as a potential strategy to tackle forcing cells from the G0 phase to enter the cell cycle.

Another important gene that has been reported to play an important role in the entry of quiescent cells into the G1 phase of the cell cycle is alfalfa cyclin gene, termed *cycMs3* in yeast [37]. The gene is not expressed in the G0 phase of the cell cycle in yeast at least in the mRNA level but was found to be expressed in a higher level when the cells are forced into the G1 phase of the cell cycle via external growth factors. The mammalian homolog for the gene could be an important drug target for the sensitization

process which should be investigated in the laboratory as well in the clinical setup. Before that comparative expression analysis across species has to be taken into consideration in a spatio-temporal manner along with the sequence homology of the gene in two species before testing it as a potential sensitization agent.

Among others, one important regulator of G0-G1 transition is Retinoblastoma protein (Rb) protein considered to be a master regulator in terms that absence of Rb expression forces the cell into enter the cell cycle irrespective of presence of external growth factor signaling [38, 39]. The genetic factors like p130/E2F-4, p107 plays an important in this transition out which p130 helps maintain the cell in the quiescent state, expressed highly by virtue of down-regulating the target genes of E2F-4 [40]. Although Rb protein is very well studied gene with respect to the cell cycle check points, its role in the sensitization process needs additional work as the pathway is so diverse and complex and still deciphering the factors related to the pathway is still under investigation.

The microenvironment of the growth arrest G0 cells

The cell cycle dormancy or being in the quiescent state has two mechanisms in the balance of proliferation as well as apoptosis. Hypoxia is a condition when the cells in the tumor state are deprived of oxygen. It is not only the intracellular signaling pathway that is responsible for the dormant state but the surrounding micro-environment also makes the critical decision of being in a dormant state or not. In this condition, the tumor cells are in the low survival phase and often followed by a metastatic condition which is beyond the scope of this review. It has been suggested that hypoxia induces resistance to chemotherapy and radiotherapy treatment as it favors the dormant state. Many factors have been identified like Forkhead Box M1 (FOXO1), LOXL2, Hypoxia inducing factor (HIF-1) in different tissue-specific cell lines which plays an important role in the transitioning the dormant state to the metastatic state [41,42,43, 44]. One more pathway which has been implicated in the exit of dormancy is the down-regulation of LIFR:STAT3: SOCS3 signaling pathway [45]. It is important to mention that most of the exit from the dormancy state to the proliferative state is directly or indirectly related to the ERK MAPK/p38 MAPK pathway [46]. The above-mentioned factors have been used for understanding the

basic biology of Tumor in the laboratory set up. These factors could be tested for the potential applied during the process of sensitization before the actual anti-Tumor therapy initiates and thus indirectly affecting the process of relapse of Tumor.

Virus, tumor and its correlation with G0-G1 transition

The process of sensitization in the management of Tumor therapy responsible for relapse of the tumor after treatment is one of the most important aspects which are the focus of the present review. The origin of the recurrence and relapse of the solid tumor initiates with the drug resistant quiescent as well as Tumor Stem Cells (CSC) [47]. There are lots of reports in the literature which describes the mechanism, genetic factors and signal transduction pathways involved in quiescent cell biology as well as of CSC [48]. Although CSC are type of slow replicating quiescent cells, understanding the correlation, similarity and differences between quiescent cells and CSC is still open for investigation and discussion and for sake of simplicity in this review, the drug resistant quiescent cell property is concentrated in this report.

In the normal cell, virus once gets infects the host cell, it responds by triggering its immune defence system by virtue of releasing cytokines in the form of interferon pathway (INF)[49] but the same host defence immune response is nullified in case of tumor cells with defective INF pathway [49,50]. If the tumor cells are only focused, within the tumor cells the virus can affect differentially depending on the type of virus which can either arrest the cells in G0-G1 transition or can promote the G0-G1 transition [51].

For example, depending on the genes encoded by the viral genome it could either have a growth arrest or it could help the transition from the G0 phase to the G1 phase. Genes encoded by Influenza A Virus (IAV), etc can induce growth arrest while other viral encoded proteins induce the cells to enter the cell cycle like MT-5 protein and HBx protein encoded by Hepatitis virus. The downstream factors and the mechanism are relatively well understood [52]. The oncolytic affect using virus induced tumor therapy been used extensively studied and been used in the clinical setup with relative success using multiple alternative pathway and using different molecular mechanisms [53, 54, 55]. Now from the management of tumor therapy

perspective, comprising both sensitization process as well as actual tumor therapy programme, it's those viruses are of importance for the present context whose function has been documented for targeting specifically the quiescent drug resistant tumor cells (G0 phase cells) for the sensitization process as a biomarker and drug target before the actual anti-tumor therapy. For e.g., in Breast Tumor- two adenoviruses Ad5/3-Δ 24 and Ad5.pk7-Δ 24 which are identified based on expression of CD44+CD24-/low CSCs (using the promoters Cox-2 viruses and MDR [56]. For development and innovation of new sensitization agent for the Tumor therapy in the form of virus, it's very important to understand differential implication of different types of virus in the host cell. The potential biomarkers or drug target for tumor therapy having two steps - sensitization of the tumor cells (transition of G0 to the G1 cells) and Anti-Tumor therapy (cytotoxicity or killing of tumor cells), the agent (in this case virus) used in this two steps- either have coupled activity in terms of G0-G1 transition and cytotoxic activity (activation of apoptosis programme) or individually function as G0-G1 transition agent only or cytotoxic agent only (by activation of immune response) depending on the genetic diversity and function of the viral genome. Genetic manipulation of the viral genome based on the requirement as a transitioning agent as well as having the ability to kill the drug resistant tumor cells should be the focus of the future investigation in the field of Tumor therapy. Every individual once in a life time might have been infected with different types of virus and out of which many people doesn't have any clinical issue with it.

In order to get the insight into the tumor biology as well as host-parasite dynamic, in the laboratory showed some interesting result- it has been shown that human herpes virus 8 (Herpesviridae) once infects both mouse and/or human cell lines remain dormant by the function of interferon gamma. But once a parasite infects these cells, the immune response to helminthic worm presence releases interleukin 4 which inhibit the function of interferon gamma which blocks the interferon gamma function and initiation of viral replication takes place in the host cell and increases the chances of tumor generation [57]. These was just an example of how this double infection (viral/bacterial) occurring in the nature could use in the laboratory condition or in clinical set up for forcing the drug resistant

quiescent tumor cells to enter the cell cycle using these combination for potential sensitizing agent. Care should be taken for devising the strategy in the gene manipulation level so that the artificial drug generated have got all the possible gene fragments required for the sensitization process (G0-G1).

Also it would be a trial and error experiment whether if the said combinational approach of using potential sensitization drug using the necessary elements from the both virus /bacteria has any differential response in the tumor tissue. As the tumor tissue is very heterogeneous in nature, it would be worth studying if exposure to this potential drug as a sensitization agent affects specifically the G0 cells or not and also ask if this addition to the tumor tissue increases the number of G0 cells converting to G1 phase cells. Similarly there are reports which described the use of different bacterial agents for using it as an anti-tumor agent which includes *Listeria*, *Clostridia* and *Salmonella* [58, 59, 60]. These amazing works by the pioneers in the field have managed to make use of the naturally occurring phenomenon applied into clinical biology of anti-Tumor biology. Using this already available information future work should focus on the sensitization process in terms of effect of bacteria on its own or in combination in forcing the cells to enter cell cycle from drug resistant quiescent state. The responsiveness of the different types of cell presents in the tumor cells if any after adding the potential Sensitizing agent (bacterial on its own or in combination) should be studied in detail for its effectiveness and feasibility as a sensitization drug.

Other factors involved in the Cell Cycle progression from the quiescent state

Micro RNA (mi RNAs) and cell cycle progression

Micro RNA (mi RNAs) are a distinct class of regulatory RNA molecules which works in the post-transcriptional level involved in the process of proliferation, cell fate specification, etc [61]. Specific miRNA like MiR-15a has been implicated in the regulation of G0-G1 progression by targeting specific cyclin-dependent kinase (CDKs) D1 (CCND1) and E (CCNE) [62, 63] in the specific cell culture condition [61]. The process of sensitization could be made more efficient by virtue of using specific miRNA targeting genes (e.g., highly expressed genes only in the G0 phase of

the cell cycle) in the signal transduction pathway whose down-regulation would transition the G0- phase cells to the G1 phase before the actual anti-Tumor therapy starts. One more miRNA (miR-16) has been implicated when over-expressed down-regulates the target gene (CDK6) and maintain the cells in the G0 phase of the cell cycle. This study was done with a patient suffering from lymphoma. Pharmacological or genetic inhibition of miR-16 or up-regulation of CDK6 could be used as a potential strategy to convert the quiescent cell to enter the cell cycle during the sensitization process in case of non-lymphoma [64]. Although the above study was done in the case of lymphoma, it would be worth exploring this possibility for the sensitization process in other types of the tumor first in the laboratory set up and then if successful into the clinical trials.

Taking help of Yeast Cell Cycle biology for application in the human subjects for clinical trials

Yeast biology in terms of cell cycle dynamics is well understood and can be easily correlated to mammalian system as most of the classical studies of cell cycle have been performed in yeast in terms of its signaling pathway and molecular mechanism associated with it [24, 65, 66, 67]. The quiescent cells have atypical characteristic like nutrient deprivation and only a subpopulation of it manage to enter G1 phase of the cell cycle (others undergoing cell death) which implies existence of more than one type of G0/quiescent cells atleast in the yeast in the cellular level [68, 69]. It is of importance to note that there are reports which also suggest the same concept of existence of subtypes and /or different G0 states of G0 phase cells based on the differential response to the external signaling mechanism for its decision to enter cell cycle or not [70,71,72]. In the yeast, it has been shown that due to the activation of different metabolic pathways (e.g., glycolytic pathway and Oxidative pathway), the level of carbon source increases in the form of acetyl -CoA driving the histone stimulation and subsequent activation of gene amplification required for entry into the g1 phase of the cell cycle [73, 74]. This has been demonstrated in the yeast and if the same mechanism could be applied in the mammalian system (which should be investigated in details), then increasing the carbon source as a potential sensitization step before the actual treatment starts would drastically increases the quan-

titative conversion of G0 cells into G1 phase. It might not be valid for the sensitization process for all types of tumor but would be restrictive depending on the type of tissue under consideration but still worth of investigating in the future experiments.

Another pathway which plays an important role in the making the decision of entry and exit to the cell cycle is the TORC1 pathway where its activation led to the transition from G0 to G1 phase of the cell cycle in the yeast [74, 75]. Generally the studies done in the yeast are comprehensive and with evidence regarding the involvement of different factors which contribute to the transition of quiescent cells to the proliferative state [76].

Biology of the quiescence cells and its transition in the yeast cells has been used to understand the basic mechanism of cell cycle check point and specifically G0-G1 transition and latter one can be used as a blue print for the future biomarker platform for using in sensitization process for Tumor therapy before the actual Tumor treatment. The potential of above factors as potential biomarkers for the sensitization process in the clinical set up in the human subject before the Tumor therapy would be something needs further study and detailed analysis.

Discussion

Other important critical factors which has not been discussed in this review are Immunotherapy [77,78], Anti-Tumor phytopharmaceuticals [79,80], Epigenetic factors [81], Signal transduction pathway like Wnt/Beta Catenin pathway, Bmpr1a, Noggin [82,83] etc. Advances have been made in the field of Tumor therapy in the recent decade with the subsequent amplification and spreading of the occurrence of the disease due to both genetic and environmental factors [84]. Based on the data reported regarding the relapse rate of different types of tumor, it is of urgent importance that the process of sensitization gets the necessary attention in terms of biomedical research in both laboratory and clinical setup. The disease management of Tumor therapy is of utmost importance in the present scenario. The data on relapse percentage for different types of tumor are as follow-for bladder it is 50% [85] relapse rate, for glioblastoma it is 100 % [86], kidney 13% [87, 88, 89], pancreas 36% within one year [90]; thyroid 30% [91, 92] etc. As the above data emphasize the importance

and frequency of the relapse in the various types of tumor, the management of the tumor therapy involving the process of sensitization has to come in the forefront of the tumor therapy. As described earlier presence of alternative pathway indicating differential response to the microenvironment of the quiescent cells (angiogenesis, hypoxia, adipocyte etc) in both gene and cellular level might show presence of different types of quiescent state and/or different types of quiescent cells. Those tumor cells which are in the G0 phase of the cell cycle either enters G1 phase and/or a part of the cells undergo apoptosis [93] or a part remains in the quiescent state. The heterogeneous nature of the G0 phase or different state of G0 has to be understood in the single cell level which has got a lot of technical difficulties in the laboratory as well as in the clinical set up. Statistically it's the maximum number of cells converting to G1 phase from G0 will eliminate or reduce the extent of the relapse of the tumor. So identifying the genetic as well as non-genetic factors which are responsible for giving unique signature to those G0 cells destined to enter the G1 phase could be the target of the sensitization process in a tissue specific manner before the actual anti-Tumor therapy initiates. Here in this review the various factors involved in the G0 -G1 transition in the different species (microbe, yeast, Virus, Bacteria, mammalian sample, human subject etc), different types of tissue (breast, brain, pancreas, thyroid etc) has been described. The factors include different types of biomolecules ranging from the receptors, extra-cellular signaling factors, intra-cellular signaling factors, nuclear receptors, nuclear/cytoplasmic proteins, cytoskeleton proteins, transcription factors etc [94]. Two ways one can go about tackling this problem. First approach which should be focus of the future investigation is testing and extrapolating the already identified factors in one species to the human clinical subjects if not being tested till now and using it as a potential biomarker for the process of sensitization which can be used as a drug target. The future studies should focus on studying both qualitative as well as quantitative factors responsible for transition of G0 phase to enter the cell cycle and could be proposed as potential biomarker in the sensitization process. This might include unique gene expression pattern (G0 or G1 unique genes), regulation of gene expression pattern (high or low level), microenvironment (hypoxic,

adipocyte, p H), of G0 phase cells promoting or inhibiting the transition process. Secondly, it calls for the detailed analysis of understanding quiescent cell biology in the single cell level. It is a long journey starting from understanding quiescent cell biology to cross-species comparison of cell cycle dynamics, analysis in the molecular and cellular level of G0 cells in the laboratory as well as in the clinical set up. Although practically it is almost impossible to eliminate 100% relapse state of the tumor after Tumor therapy but investigating combinational approach for the sensitization process with factors already documented in the literature can be used as a alternative testing therapy specifically for the sensitization process as a potential drug target. The future studies will be relevant in the statistical level (reducing the extent and rate of tumor relapse in percentage) and hence extending the life span of the Tumor patient after Tumor therapy. The ultimate aim of the sensitization process during cancer therapy is improving the survival time of the patient along with increase in the period of diseases free condition after the tumor initiates.

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